CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202293Orig1s026

Trade Name:	FARXIGA
Generic or Proper Name:	dapagliflozin
Sponsor:	AstraZeneca Pharmaceuticals LP
Approval Date:	May 8, 2023
Indication:	FARXIGA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated: • To reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression. •To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure. •To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors. •As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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APPROVAL LETTER

NDA 202293/S-026

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 and received July 8, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Farxiga (dapagliflozin) tablets.

This Prior Approval supplemental new drug application provides for the following new indication: to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit in adults with heart failure.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

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

The SPL will be accessible from publicly available labeling repositories.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable as heart failure with preserved ejection fraction is not a diagnosis that is clearly distinguished in children.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[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.

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

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
05/08/2023 02:26:33 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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) 05/2023

---------- INDICATIONS AND USAGE ----------
FARXIGA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated:
- To reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression. (1)
- To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure. (1)
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors. (1)
- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of use:
- Not for treatment of type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients. (1)
- Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action. (1)
- Not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for the treatment of kidney disease. FARXIGA is not expected to be effective in these populations. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Assess volume status and correct volume depletion before initiating. (2.1)

eGFR (mL/min/1.73 m^2)	Recommended Dose
eGFR 45 or greater	To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control. For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	10 mg orally once daily
eGFR less than 25	Initiation is not recommended; however, patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.

---------- DOSAGE FORMS AND STRENGTHS ----------
- Tablets: 5 mg and 10 mg (3)

---------- CONTRAINDICATIONS ----------
- History of serious hypersensitivity reaction to FARXIGA. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- *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. (5.1)
- *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 2, 6 1)
- *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 ----------
- Most common adverse reactions (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.

---------- DRUG INTERACTIONS----------
See full prescribing information for information on drug interactions and interference of FARXIGA with laboratory tests. (7)

---------- USE IN SPECIFIC POPULATIONS ----------
- *Pregnancy* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation* Not recommended when breastfeeding. (8.2)
- *Geriatrics* Higher incidence of adverse reactions related to hypotension. (5.2, 8.5)
- *Renal Impairment* Higher incidence of adverse reactions related to volume depletion. (5 2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FARXIGA (dapagliflozin) is indicated:

- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.
- To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure.
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.
- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

- FARXIGA is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.1)]*.
- FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.
- FARXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FARXIGA is not expected to be effective in these populations.

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 (5.2)]*.

Assess volume status and, if necessary, correct volume depletion prior to initiation of FARXIGA *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.5, 8.6)]*.

2.2 Recommended Dosage

See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table 1: Recommended Dosage

eGFR (mL/min/1.73 m^2)	Recommended Dose
eGFR 45 or greater	To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control*. For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	10 mg orally once daily*.
eGFR less than 25	Initiation is not recommended; however, patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.

* FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.
hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney 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)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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)]*. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been

reported in patients taking FARXIGA. FARXIGA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

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

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

5.2 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.

5.3 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:

- Ketoacidosis in Patients with Diabetes Mellitus *[see Warnings and Precautions (5.1)]*
- Volume Depletion *[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, in patients with heart failure, and in patients with chronic kidney disease. 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 2 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

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
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

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

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

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

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

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

FARXIGA 10 mg was also evaluated in a larger 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 (5.2)]*.

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=2684 (1.5%)	n=2655 (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=7116 (0.8%)	n=66511 (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

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

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

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

‡ OAD = oral antidiabetic therapy.

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

Genital Mycotic Infections

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 2). 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 Warnings and Precautions (5.1) and 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. These changes in serum creatinine and eGFR generally occur within two weeks of starting therapy and then stabilize regardless of baseline kidney function. Changes that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Warnings and Precautions (5.2)]*. In two studies that included patients with type 2 diabetes mellitus with moderate renal impairment, the acute effect on eGFR reversed 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 (5.1)]*.

DAPA-HF and DELIVER Heart Failure Studies

No new adverse reactions were identified in the DAPA-HF and DELIVER heart failure studies.

DAPA-CKD Chronic Kidney Disease Study

No new adverse reactions were identified in the DAPA-CKD study in patients with chronic kidney disease.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval 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

Table 5: Clinically Relevant Interactions with FARXIGA

Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia may be increased when FARXIGA is used concomitantly with insulin or insulin secretagogues (e.g., sulfonylurea) *[see Warnings and Precautions (5.4)]*.
Intervention	Concomitant use may require lower doses of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention	Monitor serum lithium concentration more frequently during FARXIGA initiation and dosage changes.
Positive Urine Glucose Test	

Table 5: Clinically Relevant Interactions with FARXIGA

Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. 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 (5.2) and Adverse Reactions (6.1)]*.

In the DAPA-CKD, DAPA-HF and DELIVER studies, safety and efficacy were similar for patients age 65 years and younger and those older than 65. In the DAPA-HF study, 2714 (57%) out of 4744 patients with HFrEF were older than 65 years. In the DELIVER study, 4759 (76%) out of 6263 patients with heart failure (LVEF >40%) were older than 65 years. In the DAPA-CKD study, 1818 (42%) out of 4304 patients with CKD were older than 65 years.

8.6 Renal Impairment

FARXIGA was evaluated in 4304 patients with chronic kidney disease (eGFR 25 to 75 mL/min/1.73 m^2) in the DAPA-CKD study. FARXIGA was also evaluated in 1926 patients with an eGFR of 30 to 60 mL/min/1.73 m^2 in the DAPA-HF study. The safety profile of FARXIGA across eGFR subgroups in these studies was consistent with the known safety profile *[see Adverse Reactions (6.1) and Clinical Studies (14.3 and 14.4)]*.

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). Patients with diabetes and renal impairment using FARXIGA may be more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion. 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 (2.2)]*.

Efficacy and safety studies with FARXIGA did not enroll patients with an eGFR less than 25 mL/min/1.73 m^2 or on dialysis.

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)]*.

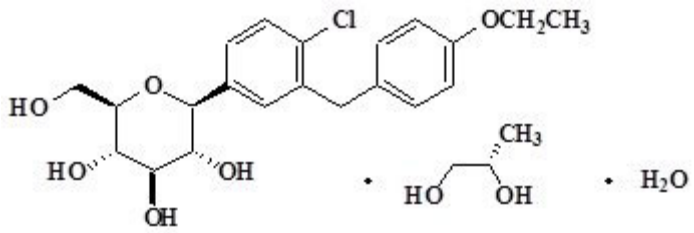
10 OVERDOSAGE

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, an inhibitor of the sodium-glucose co-transporter 2 (SGLT2), 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 $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$ 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 thereby promotes 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

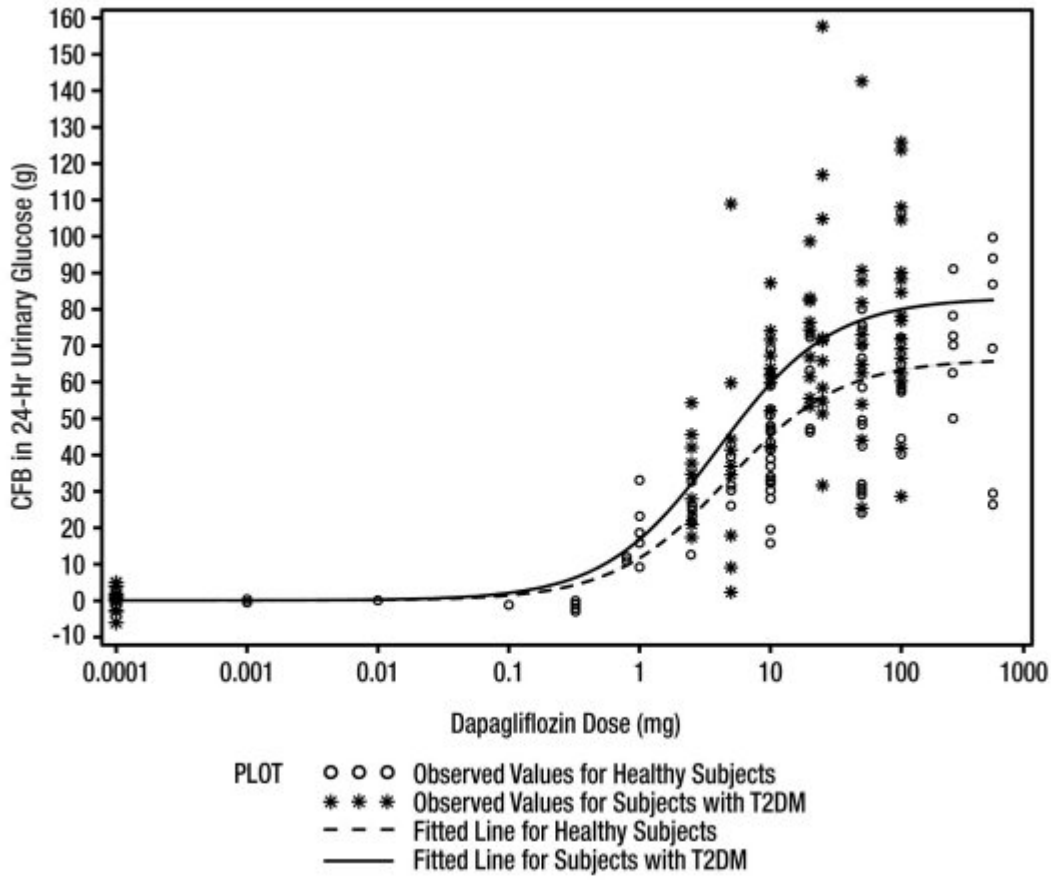
afterload of the heart and downregulation of sympathetic activity, and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback.

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%, 100%, and 200% higher, respectively, as compared to patients with type 2 diabetes mellitus with normal renal function. There was no meaningful difference in exposure between patients with chronic kidney disease with and without type 2 diabetes. 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 (2.2), Warnings and Precautions (5.2), 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 6 shows the effect of coadministered drugs on the pharmacokinetics of dapagliflozin. No dose adjustments are recommended for dapagliflozin.

Table 6: 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 7 shows the effect of dapagliflozin on other coadministered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

Table 7: 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 7: 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 8).

Table 8: 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 8: 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 9 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 9: 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)		

Table 9: Results at Week 24 (LOCF[*]) in an Active-Controlled Study of FARXIGA Initial Combination Therapy with Metformin XR

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.

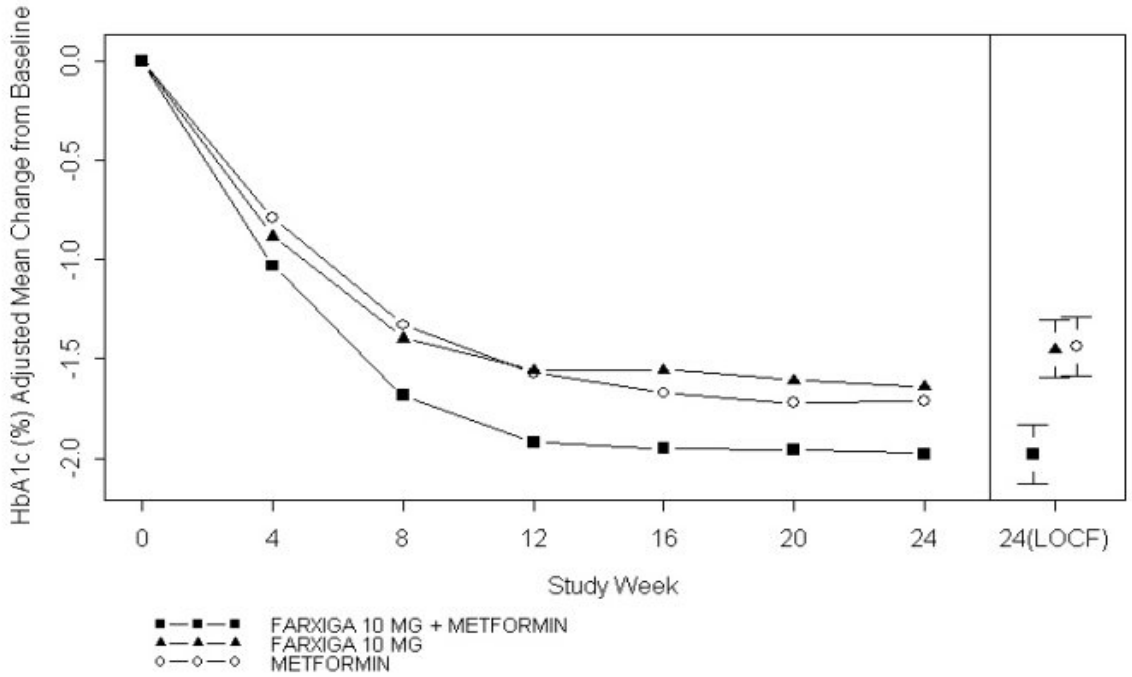
‡ Least squares mean adjusted for baseline value.

§ 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 10).

Table 10: 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 10: 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 11 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 11: 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.

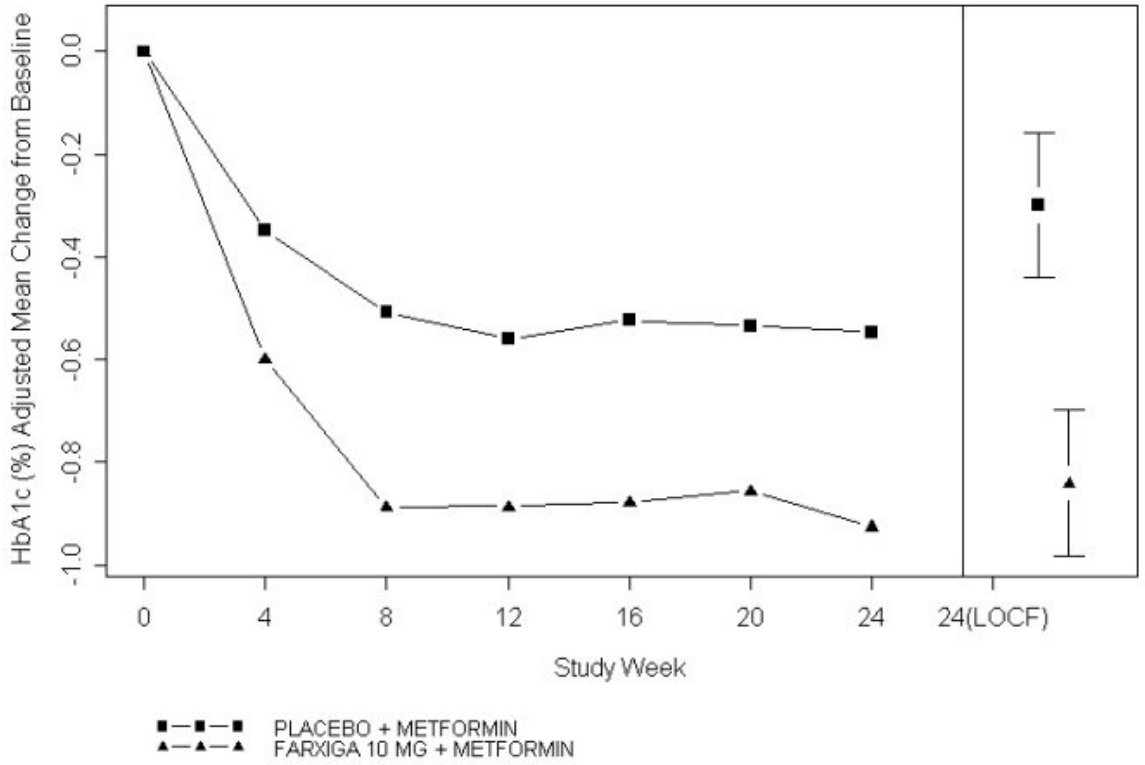
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ 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 12). 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 12: 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 post-baseline 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 13). 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 13). 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 13) 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 13). 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 13); 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 13: 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 13: 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=140[Þ]**	**N=141[Þ]**	**N=139[Þ]**
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 13: 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]	

Table 13: Results of 24-Week (LOCF*) Placebo-Controlled Studies of FARXIGA in Combination with Antidiabetic Agents

Efficacy Parameter	FARXIGA 10 mg	FARXIGA 5 mg	Placebo
Body Weight (kg)			
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 14).

Table 14: 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 cardiovascular (CV) outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either established CV disease 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 CV disease and 10186 (59.4%) did not have established CV disease. 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 antihyperglycemic 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 if non-inferiority was demonstrated, to test for superiority on the two primary endpoints: 1) the composite of hospitalization for heart failure or CV death, and 2) MACE.

The incidence rate of MACE was similar in both treatment arms: 2.30 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% CI of (0.84, 1.03). The upper bound of this confidence interval, 1.03, excluded the pre-specified non-inferiority margin of 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 15 and Figures 4 and 5).

Table 15: 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)

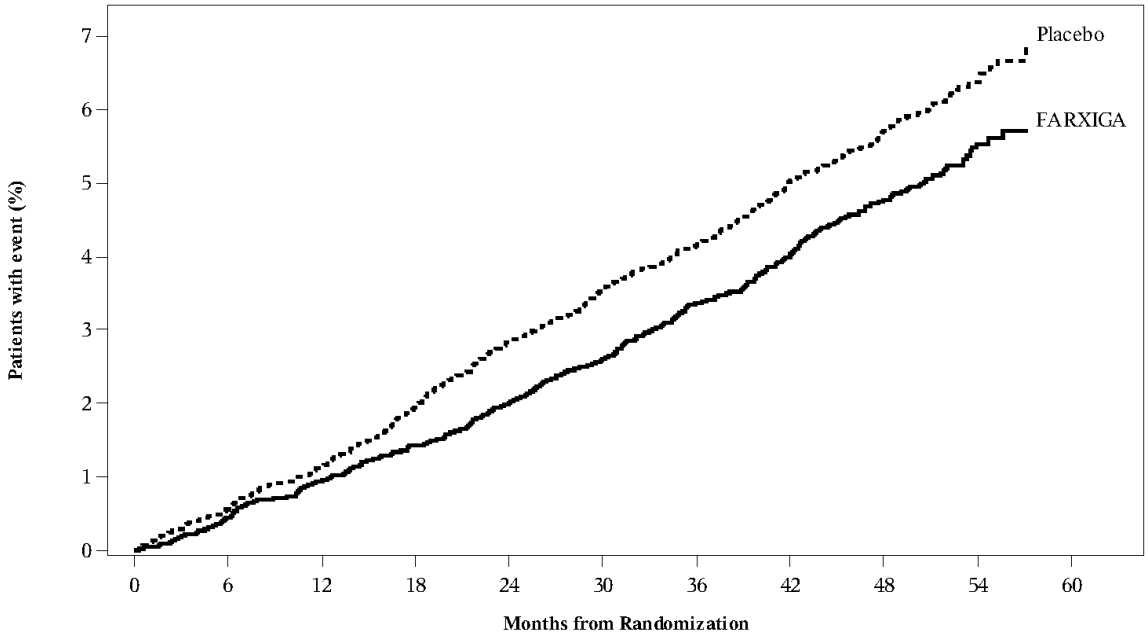
N=Number of patients, CI=Confidence interval, CV=Cardiovascular, MI=Myocardial infarction.

* Full analysis set.

† p-value =0.005 versus placebo.

‡ Total number of events presented for each component of the composite endpoints.

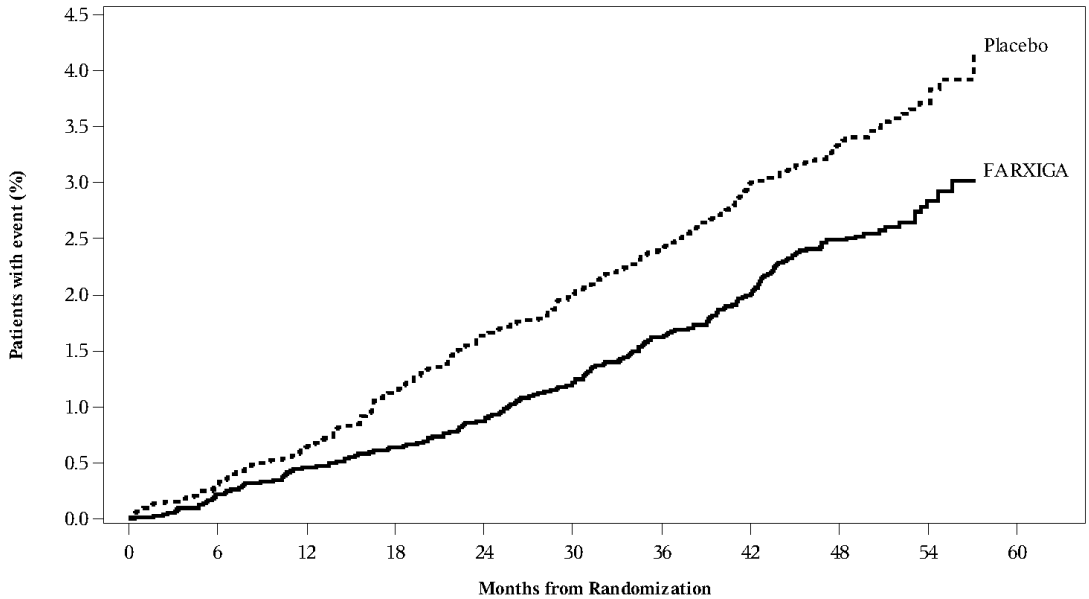
Figure 4: Time to First Occurrence of Hospitalization for Heart Failure or CV Death in the DECLARE Study



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 Chronic Kidney Disease

The Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD, NCT03036150) was an international, multicenter, randomized, double-blind, placebo-controlled study in patients with chronic kidney disease (CKD) (eGFR between 25 and 75 mL/min/1.73 m^2) and albuminuria (urine albumin creatinine ratio [UACR] between 200 and 5000 mg/g) who were receiving standard of care background therapy, including a maximally tolerated, labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). The trial excluded patients with autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis, or ANCA-associated vasculitis and patients requiring cytotoxic, immunosuppressive, or immunomodulatory therapies in the preceding 6 months.

The primary objective was to determine whether FARXIGA reduces the incidence of the composite endpoint of ≥50% sustained decline in eGFR, progression to end-stage kidney disease (ESKD) (defined as sustained eGFR <15 mL/min/1.73 m^2, initiation of chronic dialysis treatment or renal transplant), CV or renal death.

A total of 4304 patients were randomized equally to FARXIGA 10 mg or placebo and were followed for a median of 28.5 months.

The mean age of the study population was 62 years and 67% were male. The population was 53% White, 4% Black or African-American, and 34% Asian; 25% were of Hispanic or Latino ethnicity.

At baseline, mean eGFR was 43 mL/min/1.73 m^2, 44% of patients had an eGFR 30 mL/min/1.73 m^2 to less than 45 mL/min/1.73 m^2, and 15% of patients had an eGFR less than 30 mL/min/1.73 m^2. Median UACR was 950 mg/g. A total of 68% of the patients had type 2 diabetes mellitus at randomization. The most common etiologies of CKD were diabetic nephropathy (58%), ischemic/hypertensive nephropathy (16%), and IgA nephropathy (6%).

At baseline, 97% of patients were treated with ACEi or ARB. Approximately 44% were taking antiplatelet agents, and 65% were on a statin.

FARXIGA reduced the incidence of the primary composite endpoint of ≥50% sustained decline in eGFR, progression to ESKD, CV or renal death (HR 0.61 [95% CI 0.51,0.72]; p<0.0001). The FARXIGA and placebo event curves separate by Month 4 and continue to diverge over the study period. The treatment effect reflected a reduction in ≥50% sustained decline in eGFR, progression to ESKD, and CV death. There were few renal deaths during the trial (Table 16, Figure 6).

FARXIGA also reduced the incidence of the composite endpoint of CV death or hospitalization for heart failure (HR 0.71 [95% CI 0.55, 0.92], p=0.0089) and all-cause mortality (HR 0.69 [95% CI 0.53, 0.88], p=0.0035).

Table 16: Treatment Effect for the Primary Composite Endpoint, its Components, and Secondary Composite Endpoints, in the DAPA-CKD Study

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**FARXIGA 10 mg N=2152**	**Placebo N=2152**	**Hazard ratio (95% CI)**	**p-value**
Composite of ≥50% sustained eGFR decline, ESKD, CV or renal death	197 (4.6)	312 (7.5)	0.61 (0.51, 0.72)	<0.0001
≥50% sustained eGFR decline	112 (2.6)	201 (4.8)	0.53 (0.42, 0.67)	
ESKD*	109 (2.5)	161 (3.8)	0.64 (0.50, 0.82)	
CV Death	65 (1.4)	80 (1.7)	0.81 (0.58, 1.12)	
Renal Death	2 (<0.1)	6 (0.1)		
≥50% sustained eGFR decline, ESKD or renal death	142 (3.3)	243 (5.8)	0.56 (0.45, 0.68)	<0.0001
CV death or Hospitalization for Heart Failure	100 (2.2)	138 (3.0)	0.71 (0.55, 0.92)	0.0089
Hospitalization for Heart Failure	37 (0.8)	71 (1.6)	0.51 (0.34, 0.76)	
All-Cause Mortality	101 (2.2)	146 (3.1)	0.69 (0.53, 0.88)	0.0035

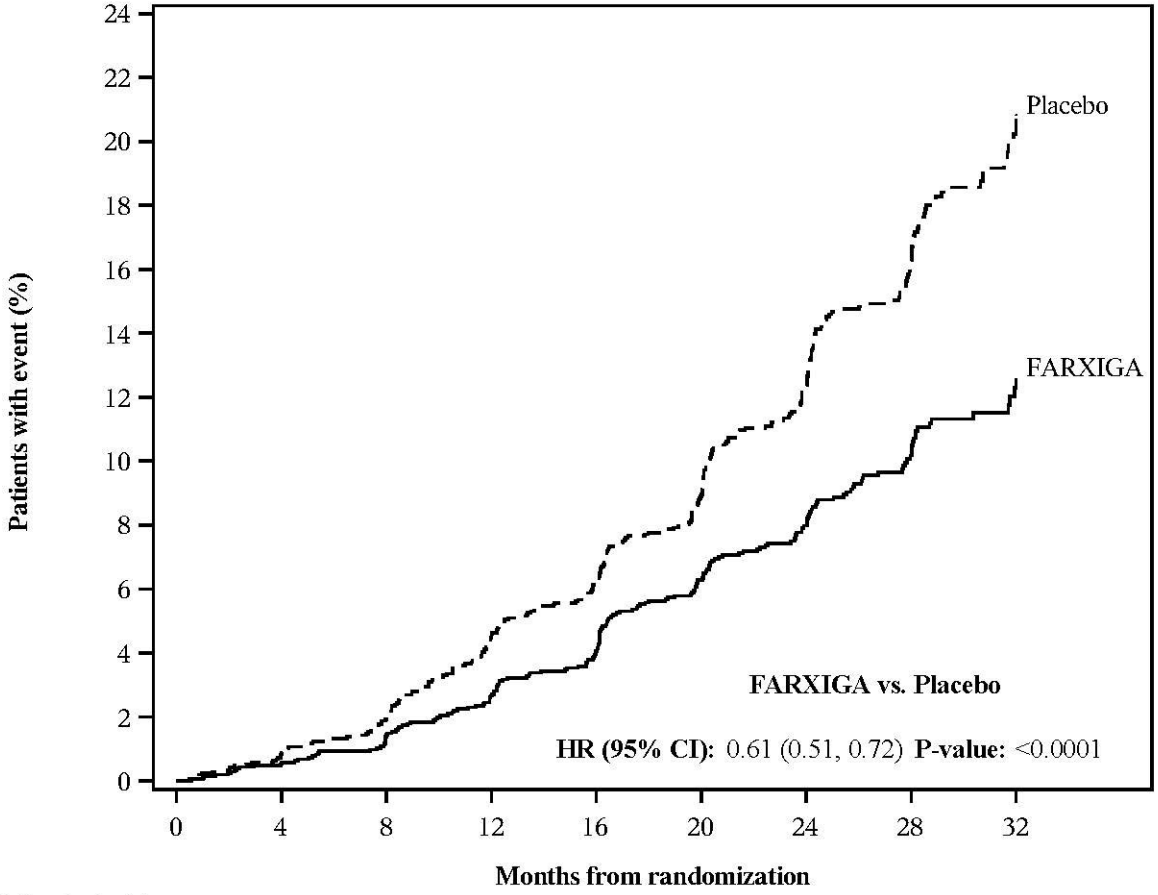
N=Number of patients, CI=Confidence interval, CV=Cardiovascular, ESKD=End stage kidney disease.

* ESKD is defined as sustained eGFR<15 mL/min/1.73 m^2, initiation of chronic dialysis treatment, or transplant.

NOTE: Time to first event was analyzed in a Cox proportional hazards model. Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

There were too few events of renal death to compute a reliable hazard ratio.

Figure 6: Time to First Occurrence of the Primary Composite Endpoint, ≥50% Sustained Decline in eGFR, ESKD, CV or Renal Death (DAPA-CKD Study)



Patients at risk

FARXIGA:	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo:	2152	1993	1936	1858	1791	1664	1232	774	270

Patients 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.
HR=hazard ratio; CI=confidence interval; eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; CV=cardiovascular; *vs*=versus.

The results of the primary composite endpoint were consistent across the subgroups examined, including CKD patients with and without type 2 diabetes mellitus, causes of CKD, age, biological sex, race, UACR, and eGFR.

DAPA-CKD enrolled a population with relatively advanced CKD at high risk of progression. Exploratory analyses of a randomized, double-blind, placebo-controlled trial conducted to determine the effect of FARXIGA on CV outcomes (the DECLARE trial) support the conclusion that FARXIGA is also likely to be effective in patients with less advanced CKD.

14.4 Heart Failure

The efficacy and safety of FARXIGA 10 mg were assessed independently in two Phase 3 studies in patients with heart failure.

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.

Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure (DELIVER, NCT03619213) was an international, multicenter, randomized, double-blind, placebo-controlled study in patients aged ≥40 years with heart failure (NYHA class II-IV) with LVEF >40% and evidence of structural heart disease to determine whether FARXIGA reduces the risk of cardiovascular death, hospitalization for heart failure or urgent heart failure visits. Of 6263 patients, 3131 were randomized to FARXIGA 10 mg and 3132 to placebo and were followed for a median of 28 months. The study included 654 (10%) heart failure patients who were randomized during hospitalization for heart failure or within 30 days of discharge.

In DAPA-HF, 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.

In DELIVER, at baseline, 77% of patients were treated with ACEi, ARB or ARNI, 83% with beta-blocker, 43% with MRA, 98% with diuretic.

In both studies, FARXIGA reduced the incidence of the primary composite endpoint of CV death, hospitalization for heart failure or urgent heart failure visit (see Table 17).

Table 17: Treatment Effect for the Primary Composite Endpoint*, its Components* in the DAPA-HF and DELIVER Studies

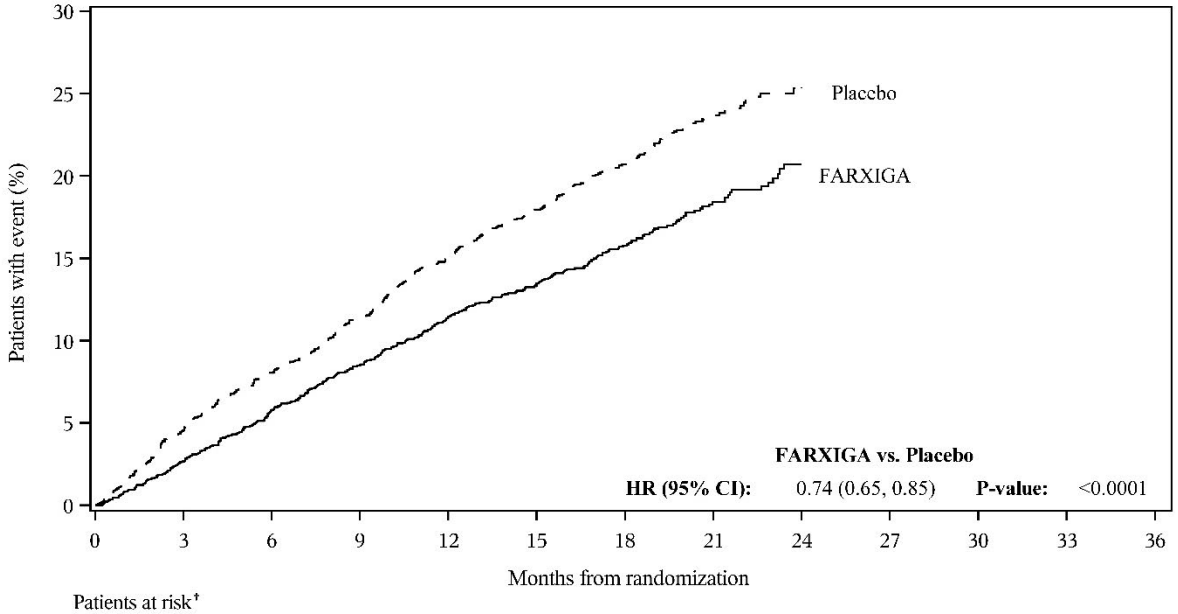
	DAPA-HF Study				DELIVER Study			
	Patients with events (event rate)		Hazard ratio (95% CI)	p-value†	Patients with events (event rate)		Hazard ratio (95% CI)	p-value†
Efficacy Variable (Time to first occurrence)	**FARXIGA 10 mg N=2373**	**Placebo N=2371**			**FARXIGA 10 mg N=3131**	**Placebo N=3132**		
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	512 (7.8)	610 (9.6)	0.82 (0.73, 0.92)	0.0008
Components of the composite endpoints								
CV Death‡	227 (6.5)	273 (7.9)	0.82 (0.69, 0.98)		231 (3.3)	261 (3.8)	0.88 (0.74, 1.05)	
Hospitalization for Heart Failure or Urgent Heart Failure Visit	237 (7.1)	326 (10.1)	0.70 (0.59, 0.83)		368 (5.6)	455 (7.2)	0.79 (0.69, 0.91)	
Hospitalization for Heart Failure	231 (6.9)	318 (9.8)	0.70 (0.59, 0.83)		329 (5.0)	418 (6.5)	0.77 (0.67, 0.89)	
Urgent Heart Failure Visit	10 (0.3)	23 (0.7)	0.43 (0.20, 0.90)		60 (0.9)	78 (1.1)	0.76 (0.55, 1.07)	

N=Number of patients, CI=Confidence interval, CV=Cardiovascular.
* Full analysis set.
† Two-sided p-values.
‡ In DAPA-HF, the CV death component of the primary endpoint included death of undetermined cause. In DELIVER, the CV death component of the primary endpoint excluded death of undetermined cause.
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.

In both studies, all three components of the primary composite endpoint individually contributed to the treatment effect. In both studies, the FARXIGA and placebo event curves separated early and continued to diverge over the study period (see Figures 7 and 9).

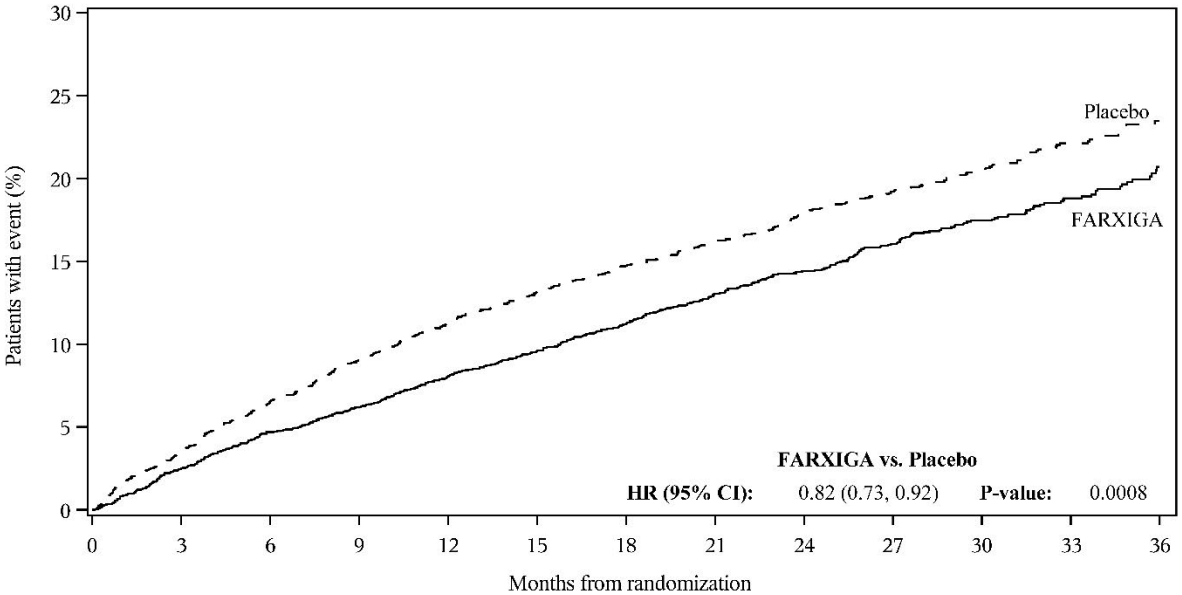
Figure 7: Time to the First Occurrence of the Composite of Cardiovascular Death*, Hospitalization for Heart Failure or Urgent Heart Failure Visit

A) DAPA-HF Study



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

B) DELIVER Study



Patients at risk†													
FARXIGA:	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389
Placebo:	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383

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).

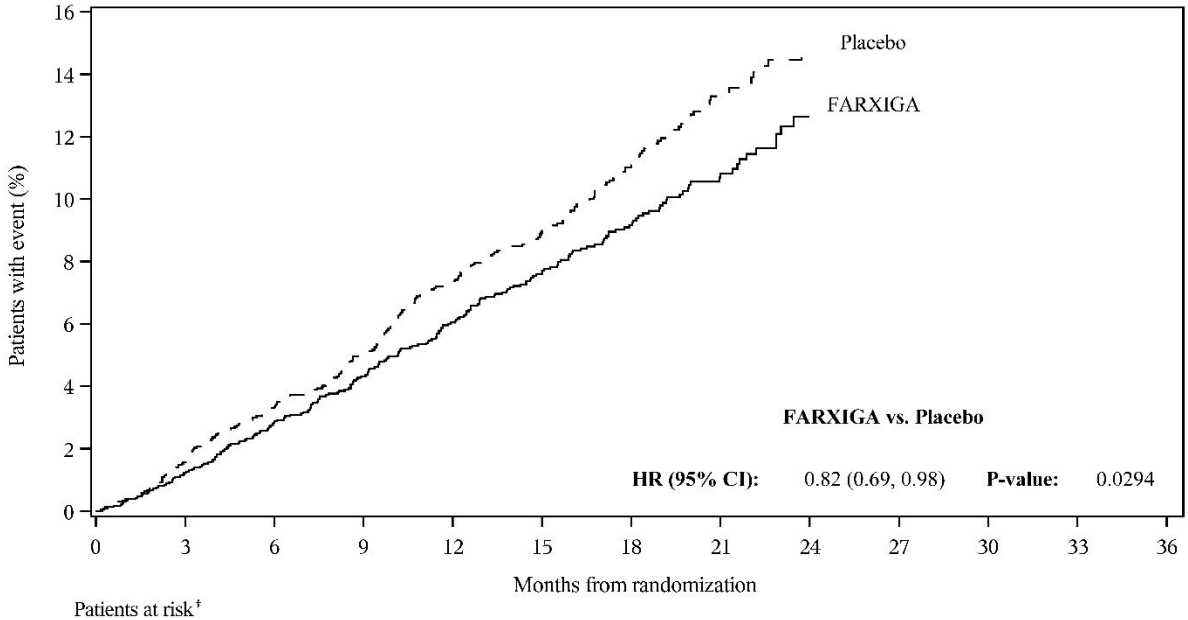
* In DAPA-HF, the CV death component of the primary endpoint included death of undetermined cause. In DELIVER, the CV death component of the primary endpoint excluded death of undetermined cause.

† Patients at risk is the number of patients at risk at the beginning of the period.

HR=Hazard ratio, CI=Confidence interval, CV=Cardiovascular.

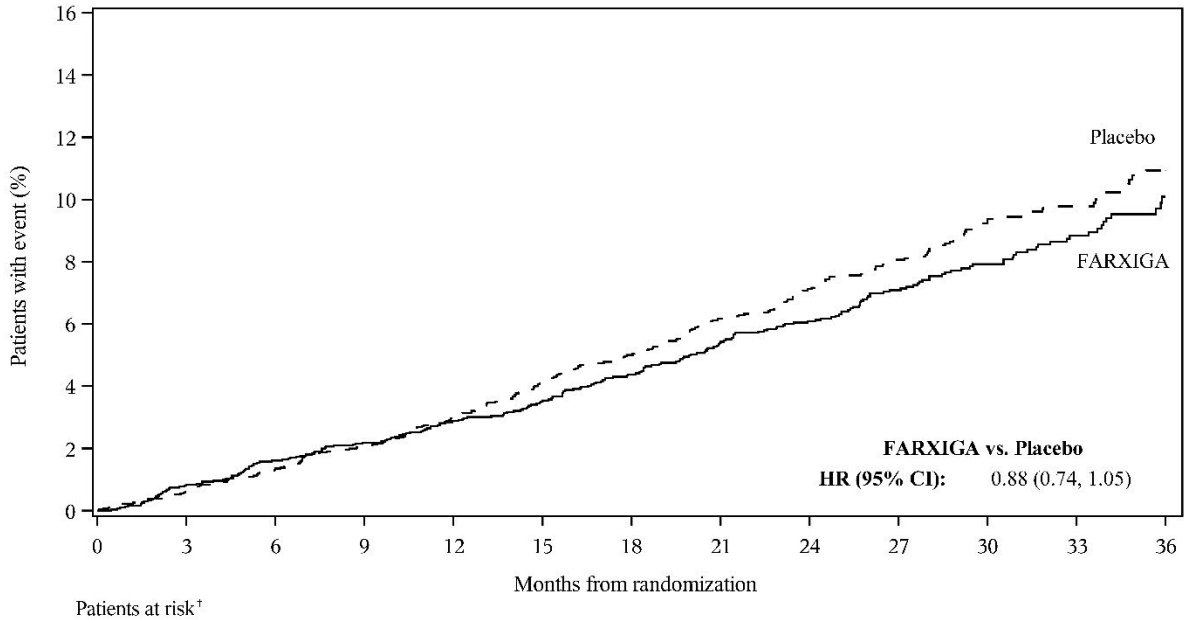
Figure 8: Time to Cardiovascular Death*

A) DAPA-HF Study



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

B) DELIVER Study



Patients at risk†													
FARXIGA:	3131	3091	3046	3006	2960	2892	2584	2339	2171	1775	1312	903	441
Placebo:	3132	3096	3054	3008	2957	2872	2570	2314	2157	1759	1306	910	451

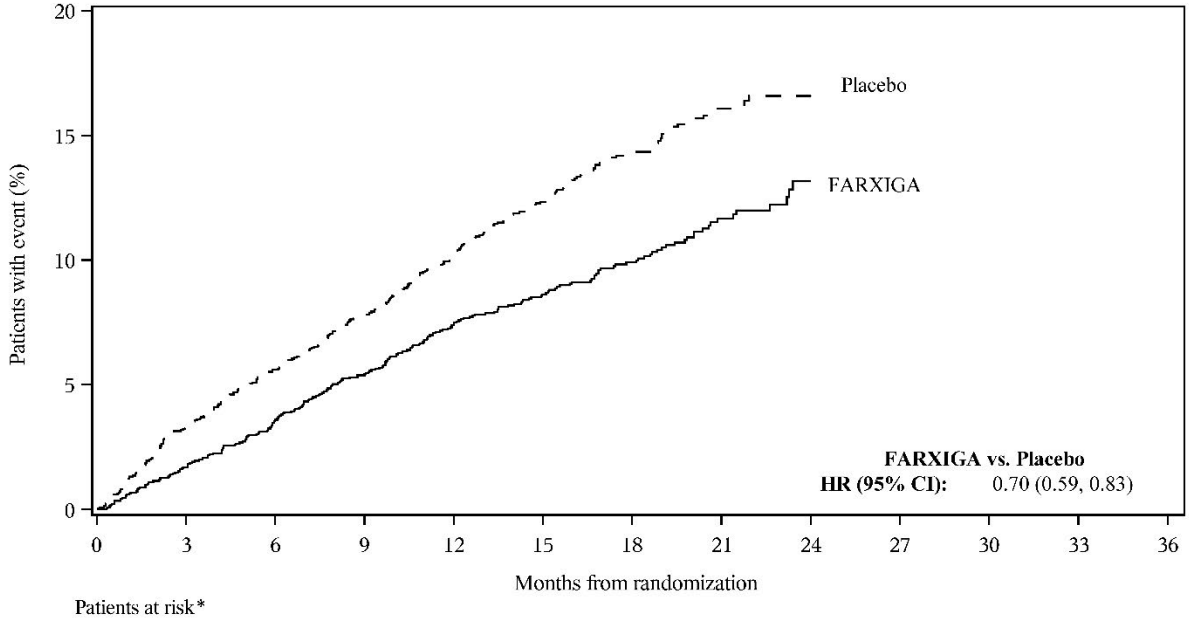
* In DAPA-HF, the CV death component of the primary endpoint included death of undetermined cause. In DELIVER, the CV death component of the primary endpoint excluded death of undetermined cause.

† Patients at risk is the number of patients at risk at the beginning of the period.

HR=Hazard ratio, CI=Confidence interval, CV=Cardiovascular.

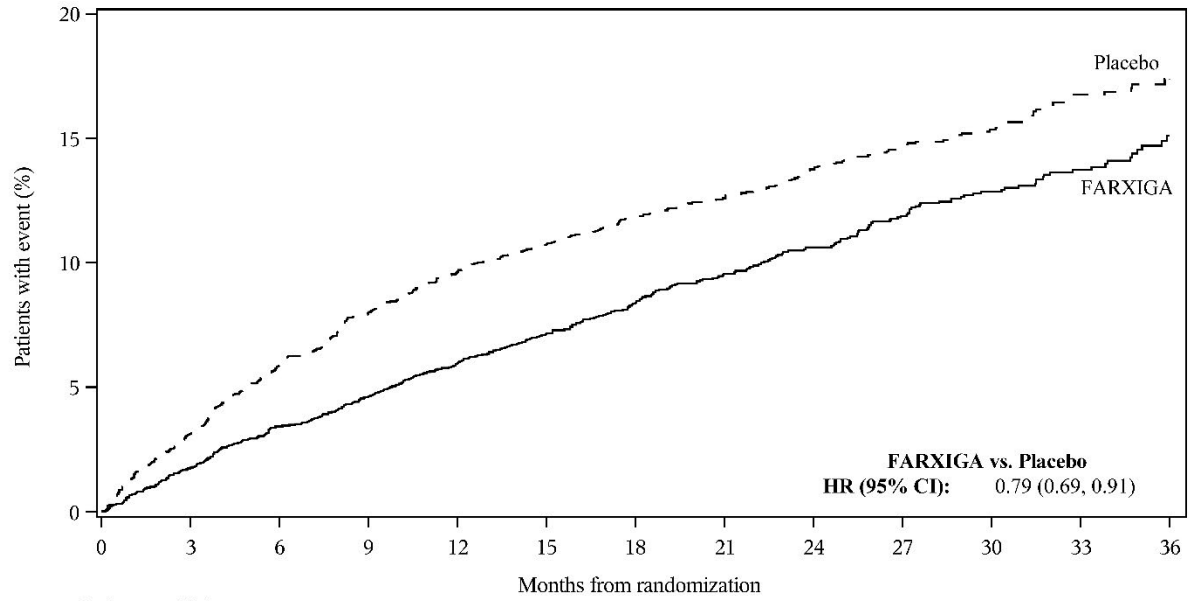
Figure 9: Time to the First Occurrence of Hospitalization for Heart Failure or Urgent Heart Failure Visit

A) DAPA-HF Study



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

B) DELIVER Study



Patients at risk*													
FARXIGA:	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389
Placebo:	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383

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

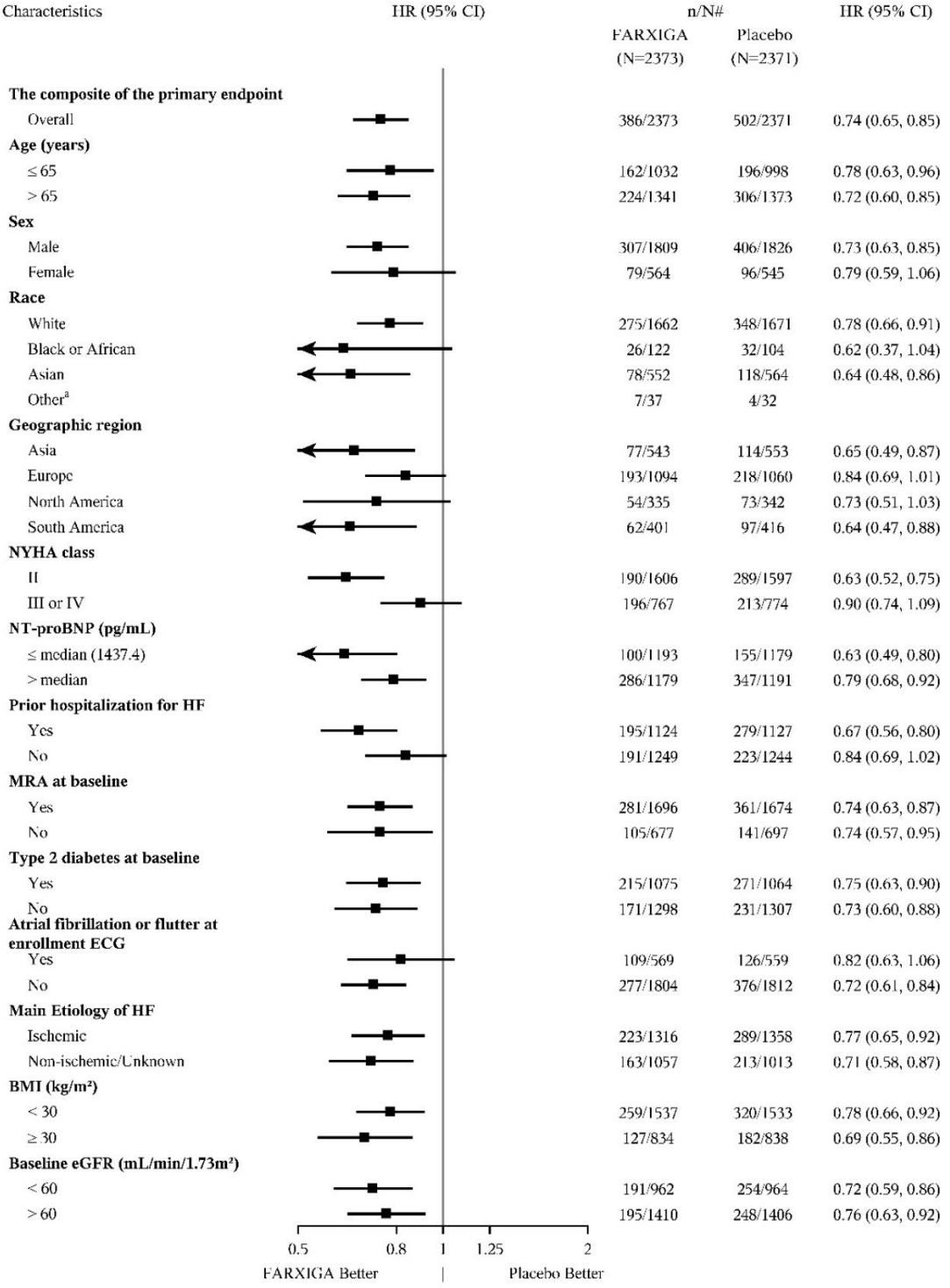
In DAPA-HF, FARXIGA reduced the total number of hospitalizations for heart failure (first and recurrent) events and CV death, with 567 and 742 total events in the FARXIGA-treated vs placebo group (Rate Ratio 0.75 [95% CI 0.65, 0.88]; p=0.0002).

In DELIVER, FARXIGA reduced the total number of heart failure events (first and recurrent hospitalization for heart failure or urgent heart failure visit) and CV death, with 815 and 1057 total events in the FARXIGA treated vs placebo group (Rate Ratio 0.77 [95% CI 0.67, 0.89]; p=0.0003).

In both studies, the results of the primary composite endpoint were consistent across the subgroups examined (see Figure 10).

Figure 10: Treatment Effects for Primary Composite Endpoint (Cardiovascular Death and Heart Failure Events) Subgroup Analysis

A) DAPA-HF Study



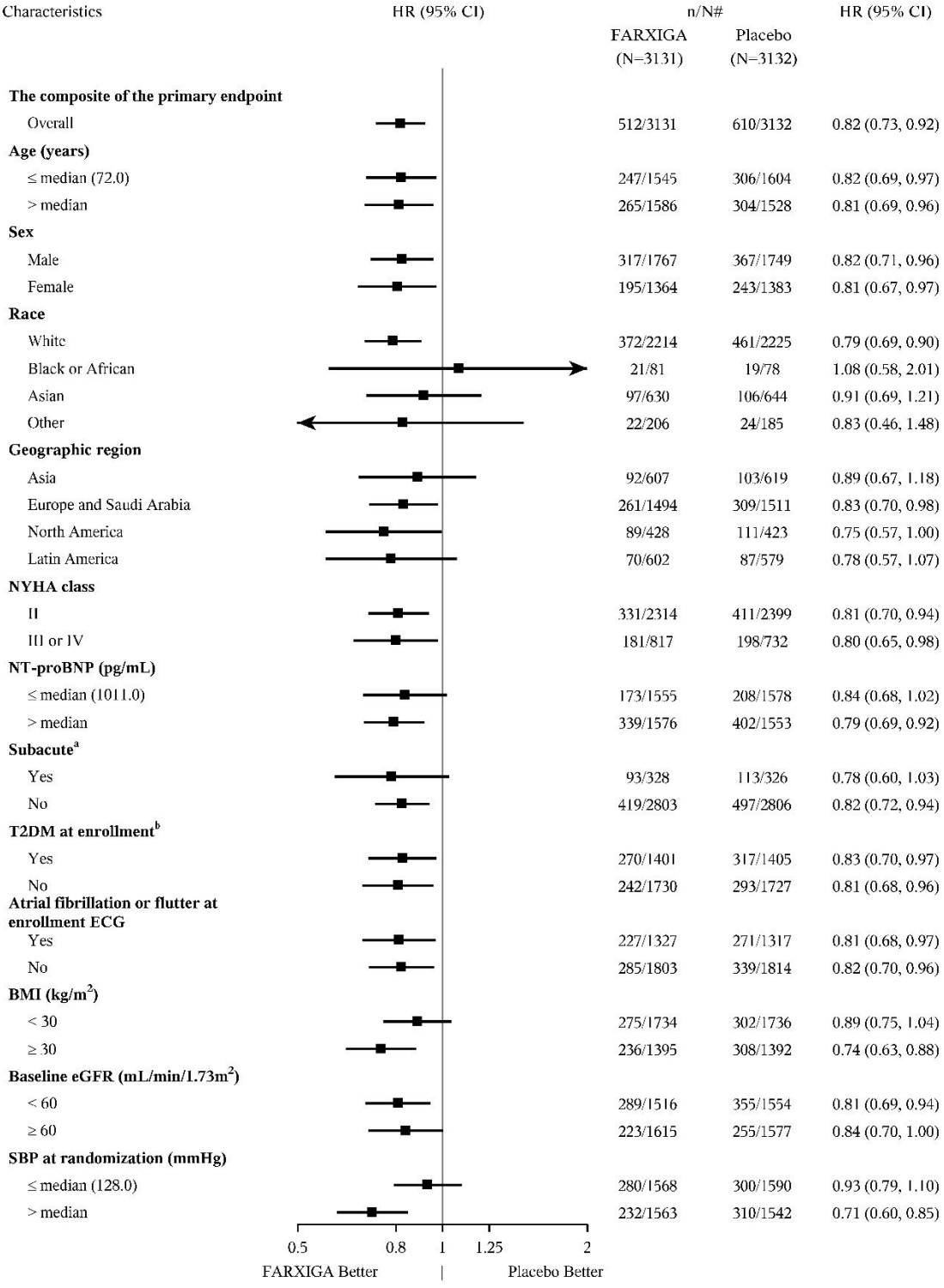
[a] Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

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.

B) DELIVER Study

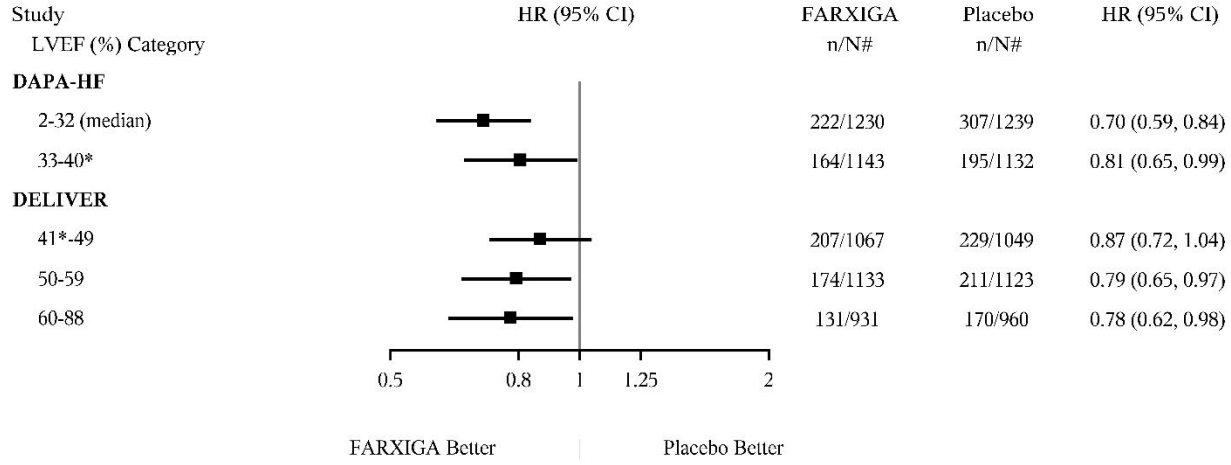


[a] Subacute patient defined as randomized during hospitalization for heart failure or within 30 days of discharge.

[b] Defined as history of type 2 diabetes mellitus. This analysis does not include type 2 diabetes mellitus as a stratification factor.
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, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, BMI = body mass index, SBP = systolic blood pressure, T2DM = type 2 diabetes mellitus.
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.

The treatment effect of FARXIGA on the composite endpoint of cardiovascular death, hospitalization for heart failure or urgent heart failure was consistent across the LVEF range as evaluated in DAPA-HF and DELIVER studies (Figure 11).

Figure 11: Treatment Effects for Primary Composite Endpoint (Cardiovascular Death and Heart Failure Events) by LVEF (DAPA-HF and DELIVER Studies)



* 1 patient in DAPA-HF study had LVEF >40. 4 patients in DELIVER study had LVEF≤40.
In DAPA-HF study, the 5% and 95% percentiles of LVEF were 20 and 40 respectively. In DELIVER study, the 5% and 95% percentiles of LVEF were 42 and 70, respectively.

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 18.

Table 18: 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

Table 18: FARXIGA Tablet Presentations

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
10 mg	yellow, biconvex, diamond-shaped	"10" engraved on one side and "1428" engraved on the other side	Bottles of 30	0310-6210-30
			Hospital Unit Dose Blister Pack: Carton containing 30 tablets (3 blister cards x 10 tablets per card)	0310-6210-39

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).

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 (5.1)]*.

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 (5.2)]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

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

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

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

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

FARXIGA can cause serious side effects, including:

- **Dehydration.** FARXIGA can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). 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 healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis. 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.
- **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:
  - to reduce the risk of further worsening of your kidney disease, end-stage kidney disease (ESKD), death due to cardiovascular disease, and hospitalization for heart failure in adults with chronic kidney disease
  - to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit in adults with heart failure, when the heart cannot pump enough blood to the rest of your body
  - to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes who also have known cardiovascular disease or multiple cardiovascular risk factors
  - along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes.
- FARXIGA is not for people with type 1 diabetes. FARXIGA may increase the risk of diabetic ketoacidosis (increased ketones in your blood or urine) in people with type 1 diabetes.
- FARXIGA is not for use to improve blood sugar (glucose) control in adults with type 2 diabetes who have moderate to severe kidney problems, because it may not work.
- FARXIGA is not for people with certain genetic forms of polycystic kidney disease, or who are taking or have recently received immunosuppressive therapy to treat kidney disease. FARXIGA is not expected to work if you have these conditions.
- 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.

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 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.

FARXIGA may affect the way other medicines work, and other medicines may affect how FARXIGA works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

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**.**

- **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 right away 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 05/2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s026

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	Efficacy Supplement
Application number(s)	202293 S26
Priority or standard	Standard
Submit date(s)	7/8/2022
Received date(s)	7/8/2022
PDUFA goal date	5/3/2023
Division/office	Division of Cardiovascular and Renal Products (DCaRP)
Review completion date	4/6/2023
Established name	Dapagliflozin
(Proposed) trade name	FARXIGA®
Pharmacologic class	Sodium-glucose cotransporter 2 (SGLT2) inhibitor
Code name	Click or tap here to enter name.
Applicant	AstraZeneca
Dose form/formulation(s)	Oral Tablets
Dosing regimen	10 mg once daily
Applicant proposed indication(s)/population(s)	To reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visits in adults with heart failure
Proposed SNOMED indication	Heart failure
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	To reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visits in adults with heart failure
Approved SNOMED indication	Heart Failure

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I. Executive Summary

1. Summary of Regulatory Action

Recommended Regulatory Action

Pursuant to §21 CFR 314.126, it can fairly and responsibly be concluded that the Applicant provided substantial evidence to support approval of dapagliflozin for the indication to reduce the risk of cardiovascular death, hospitalization for heart failure (HF), and urgent heart failure visits in adult with HF.

Background

Dapagliflozin is a potent, selective, and reversible inhibitor of sodium glucose co-transporter 2 (SGLT2). SGLT2 is expressed almost exclusively in the proximal renal tubule and is responsible for the reabsorption of most of the glucose filtered at the glomerulus. The mechanism of action is inhibition of renal SGLT2 leading to a reduction in the reabsorption of filtered glucose and sodium, thereby increasing urinary glucose excretion, osmotic diuresis, and increase in the delivery of sodium to the distal tubule.

Dapagliflozin is currently approved in the United States for the following indications:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (*based on trials evaluating monotherapy and with concomitant anti-diabetic agents*)
- To reduce the risk of hospitalization for heart failure in adults with T2DM and either established cardiovascular disease or multiple cardiovascular risk factors (*based on the DECLARE-TIMI 58 trial*)
- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression (*based on the DAPA-CKD trial*)
- To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure New York Heart Association (NYHA class II-IV) with reduced ejection fraction (*based on the DAPA-HF trial*)

Pivotal Trial Description

Evidence supporting the proposed indication was based on the DELIVER trial (*Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure*), comparing dapagliflozin 10 mg administered once daily (QD) to placebo. DELIVER was a phase III randomized, multicenter, double-blind, placebo controlled, parallel-group, event driven study in patients with HF and left ventricular ejection fraction (LVEF) >40%.

The primary efficacy endpoint was the composite of cardiovascular (CV) death or an HF event (i.e., hospitalization for worsening HF or an urgent HF visit leading to an unplanned assessment and escalated treatment).

Secondary efficacy endpoints, listed in pre-specified hierarchical order, included: 1) total number of HF events (first and recurrent) and CV death; 2) change from baseline in the TSS of the

KCCQ at 8 months; 3) time to the occurrence of CV death; and 4) time to the occurrence of death from any cause.

Key inclusion criteria were stable male or female patients ≥40 years old with NYHA class II - IV symptomatic HF with a LVEF >40% and NT-pro BNP ≥300 pg/mL (>600 pg/mL with ongoing atrial fibrillation / atrial flutter-AFF) at baseline. Eligibility included ambulatory or hospitalized patients not on intravenous HF medications for at least 24 hours prior to randomization. Patient candidates were excluded if they sustained an acute coronary syndrome, stroke, transient ischemic attack, or ablation for AFF 12 weeks prior to enrollment. Patients with pulmonary disease (pulmonary hypertension, chronic obstructive pulmonary disease requiring oxygen or steroids, chronic pulmonary embolism), infiltrative cardiomyopathy, obstructive hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, uncorrected vascular disease, acute/chronic liver disease, cancer (except non-melanomatous skin cancer) or a life expectancy of less than two years, were also excluded.

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints was used to control for the overall Type 1 error in addition to the planned interim analysis.

The full analysis set (FAS) included all patients randomized to study drug irrespective of their protocol adherence and continued participation in the study and was used for all efficacy analysis of the primary, secondary, and exploratory endpoints. A preplanned subgroup analysis was performed in subjects with baseline LVEF <60%. The safety analysis set (SAS) included all randomized patients who received at least one dose of randomized treatment.

DELIVER was designed to target 1117 patients with a primary endpoint event. Originally, 844 primary endpoint events were targeted to provide at least 90% power, under equal randomization, two-sided alpha of 5% to detect a hazard ratio of 0.8 or less between dapagliflozin and placebo. To allow testing for the LVEF <60% subgroup as per the final version of the protocol, the target number of patients with the primary endpoint was increased to 1117 to ensure at least 70% of the events will be available for the LVEF <60% subpopulation.

Pivotal Trial Results

Efficacy

A total of 10,418 subjects were enrolled, and 6263 subjects were randomized at 353 study sites across 20 countries (3131 subjects randomized to dapagliflozin and 3132 randomized to placebo). The first subject was randomized on August 27, 2008, and the last subject visit was on March 27, 2022. Of the 4155 subjects enrolled who were not randomized, 3955 (95%) failed to meet the eligibility criteria. The most common failed eligibility criterion (n = 3373) was NT-pro BNP ≥300 pg/mL (≥600pg/mL, for patients with ongoing AFF).

A total of 886 (14.1%) subjects discontinued study treatment; 14.2% in the dapagliflozin treatment group and 14.1% in the placebo group; 99.2 % of the randomized subjects had complete follow-up of the primary endpoint.

The duration of exposure to the investigational drug ranged from 0 to 42.2 months. Median duration of exposure was similar between treatment groups: 26.9 months in the dapagliflozin group and 27.0 months in the placebo group. There were 6426 patient years of exposure to dapagliflozin in the study. During this period, 6253 subjects (99.8% of randomized cohort) received at least one dose of study drug (dapagliflozin or placebo).

In the FAS population, a total of 512 subjects in dapagliflozin arm (incidence rate (IR) of 7.7 per 100 patient-years (PY)) and 610 subjects in placebo arm (IR of 9.5 per 100 PY) experienced a primary composite endpoint, with an adjusted hazard ratio of 0.82 (95% CI: 0.73, 0.92; two-sided p<0.001). The estimated difference in IR of the primary composite endpoint comparing dapagliflozin to placebo was -1.7 per 100 PY (95% CI: -2.7, -0.7 per 100 PY) favoring dapagliflozin. The results were driven by the HF event component of the composite endpoint, specifically hospitalization for HF (Hazard Ratio 0.77, 95% CI: 0.67, 0.89; nominal p-value <0.001). There were no differences between dapagliflozin and placebo for urgent HF visits or CV death. The results for the primary efficacy endpoint were consistent between the FAS population and pre-specified subgroups (age, gender, race, ethnicity, geographic region, NYHA class, LVEF (<50%, 50% - 60%, ≥60%), NT-proBNP, T2DM, eGFR (<60 or >60 mL/min/1.73m^2), and baseline AFF).

In the pre-specified subgroup of subjects with LVEF <60% (n = 2200 in the dapagliflozin arm; n = 2172 in the placebo arm), the hazard ratio for the primary efficacy endpoint was similar to that of the FAS population: HR 0.83 (95% CI: 0.73, 0.95; two-sided p = 0.009). The primary endpoint for the LVEF ≥60% population was also consistent with the findings from the FAS population.

Regarding secondary efficacy endpoints in the FAS population, there was a statistically significant reduction in the risk of recurrent HF events and CV death for dapagliflozin compared to placebo (rate ratio (RR): 0.77; 95% CI: 0.67, 0.89; p<0.001). Results for the CV death and recurrent HF event endpoint in the LVEF < 60% subpopulation were similar to the FAS population.

As reported by the Applicant, the results for KCCQ-TSS at 8 months was limited to the subgroup of subjects who had the 8-month assessment (Visit 5) planned or performed prior to 11 March 2020 and was statistically significant. Only 1316 subjects on dapagliflozin and 1311 subjects on placebo had available data for the change from baseline in KCCQ-TSS analysis. The mean change in KCCQ-TSS from baseline at 8 months was 8.3 and 5.2 in the dapagliflozin group and in the placebo group, respectively. The estimated win ratio was 1.11 (95% CI: 1.03, 1.21; p-value from the ranked ANCOVA test = 0.009. The magnitude of this KCCQ-TSS treatment effect is small and of unknown clinical meaningfulness.

Safety

The number of any adverse event (severe, moderate, mild), as well as serious adverse events, and adverse events leading to permanent discontinuation or dose interruption, were similar between the two treatment arms.

Adverse events of specific interest (AESI): volume depletion, urinary tract infections, genital infections, Fournier's gangrene, renal events, diabetic ketoacidosis, major hypoglycemia, amputations, adverse events leading to amputations, risk factors for amputation (i.e., diabetic foot related cellulitis and skin ulcer), vascular adverse events (i.e., PAD), myocardial infarction, unstable angina, and stroke, were rare and balanced between the two treatment arms.

Sensitivity analyses conducted by the review team using reviewer's additional queries for AESIs provided similar results as Applicant defined AESIs.

All AEs experienced by subjects in DELIVER were already adequately described in the label.

Summary

The single phase 3 trial DELIVER was an adequate and well-controlled trial, and satisfied the statutory requirement for substantial evidence of effectiveness for the proposed indication to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in adult with HF.

No safety risk was identified from the DELIVER trial; all AEs experienced by subjects in DELIVER were already adequately described in the label.

The benefit of dapagliflozin in patients with symptomatic NYHA class II - IV symptomatic HF with LVEF >40% outweighed the risk of dapagliflozin, thereby yielding a recommendation for approval.

2. Glossary

ANCOVA	analysis of covariance
ASCVD	atherosclerotic cardiovascular disease
BP	blood pressure
CEA	clinical events adjudication
CEC	clinical events classification
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
COVID-19	Coronavirus disease 2019
CV	cardiovascular
DAE	diabetic adverse event
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DAPA-HF	Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction
DKA	diabetic ketoacidosis
DMC	data monitoring committee
eGFR	Estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
IMP	investigational medical product
IND	investigational new drug
IP	investigational product
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PACD	primary analysis censoring date
PREA	Pediatric Research Equity Act
PY	patient-years
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SGLT2	sodium glucose co-transporter 2
SMC	Standard MedDRA Query
T2DM	Type 2 diabetes mellitus

TEAE	treatment-emergent adverse event
TSS	total symptom score
US	United States
UTI	urinary tract infection
WHO	World Health Organization

3. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	*Heart Failure (HF) is a clinical syndrome characterized by signs (jugular venous distension, pulmonary rales, and S3 gallop) and symptoms (dyspnea, fatigue) of cardiac dysfunction resulting from impairments in the structure and function of the heart which ultimately result in reduced cardiac output under normal filling pressures or alternatively elevated filling pressures to main normal cardiac output.*[1] *HF is a growing public health and economic burden due to the significant health-care resource utilization, morbidity and mortality associated with the high rates of hospitalizations in patients with HF.*[2] *The prevalence of HF ranges between 1% to 3% in adults using data from epidemiology studies from industrialized countries and the number is expected to increase in large part due to aging of the population and improved diagnostic modalities.*[3] *Among patients with the clinical syndrome of heart failure, assessment of systolic function with left ventricular ejection fraction (LVEF) has been used as a clinically important phenotypic marker for classification of patients into homogenous groups for diagnosis, prognosis, clinical trial design and to assess response to treatments. Historically, HF with reduced ejection fraction (HFrEF) has been defined as LVEF ≤40% while the definition of HF with preserved EF (HFpEF) has varied. More recent guidelines use a threshold of LVEF ≥50%, however historical*	Heart Failure is a substantial global public health burden associated with significant health-care resource utilization, poor quality of life, and premature mortality.

[1] Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032.
[2] Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14(10):591-602
[3] Yancy, C. W. 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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	studies have classified HFpEF with LVEF >40 % or 45%.[4] [5] *Approximately 50% of patients with HF are currently classified as HFpEF. The hallmark feature of HFpEF is evidence of impaired left ventricle relaxation resulting in elevated filling pressures, congestion, and dyspnea at rest or with exercise.*	
Current Treatment Options	*The current paradigm in the treatment of patients with LVEF ≤40% involves four medication classes, renin-angiotensin aldosterone system inhibition with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) or angiotensin receptor- neprilysin inhibitor (ARNi), beta- adrenergic receptor blockers, mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i).*[6] [7] *In HF patients with evidence of congestion, diuretics are recommended to relieve congestion and improve symptoms. Therapies approved for use in special populations include Hydralazine and Isosorbide Dinitrate (African Americans who remain symptomatic on ACEi or ARB, beta blockers, and MRA), digoxin in patients with symptoms despite optimal medical therapy, ivabradine for symptomatic patients with heart rate ≥70 bpm in sinus rhythm (SR) receiving optimal therapies including a beta blocker at maximum tolerated dose, and oral soluble guanylate cyclase stimulator (vericiguat) in adult patients with recent worsening of chronic HF (LVEF <45%) on optimal medical therapies.* *In patients with HF and LVEF >40%, the indication for sacubitril/valsartan (Entresto) was expanded to treat HF in patients with mildly reduced LVEF after demonstrating a numerical reduction in the*	Current guideline recommendations for the management of patients with HF and LVEF >50% involve Class I recommendations for treatment of risk factors for HF (hypertension, Diabetes mellitus, O*besity, Atrial fibrillation), diuretics to treat congestion and improve symptoms, MRAs, ARBs, and ARNIs in selected patients.* Empagliflozin (SGLT2i) was the first SGLT2 approved based on the results of the EMPEROR-Preserved Trial in patients with heart failure with LVEF >40%, when used on top of standard of care. While recent treatment options have been approved for the treatment of patients with mildly reduced or normal ejection fraction, there continues to be a need for more options to address the impact of HF on quality of life, HF hospitalizations, and premature mortality.

[4] Borlaug, B. A. & Redfield, M. M. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation 123, 2006–2013 (2011).
[5] McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-3726
[6] Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032.
[7] Del Buono MG, Iannaccone G, Scacciavillani R, et al. Heart failure with preserved ejection fraction diagnosis and treatment: An updated review of the evidence. Prog Cardiovasc Dis. 2020;63(5):570-584.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	rate of the composite endpoint of total (first and recurrent) HF hospitalizations and CV death. Other therapies approved include SGLT2 inhibitors and vericiguat (LVEF <45%). *Drug development in HFpEF has been limited by the highly heterogenous nature of the disease without a unifying pathophysiological adaptation underling HFpEF.* *Until recently, recommendations for management of patients with HF and normal LVEF (>50%) were limited to treatment of risk factors for HF (hypertension, diabetes mellitus, obesity, atrial fibrillation), use of diuretics to reduce congestion and improve symptoms, MRAs, and ARBs in selected patients. Sacubitril/valsartan (Entresto) was the first to demonstrate benefit in patients with LVEF 45% to 57% driven by a reduction in HF hospitalizations.[8] Empagliflozin (SGLT2i) was recently approved based on the results of the EMPEROR-Preserved Trial which demonstrated reduction in hospitalization for HF and CV death in patients with heart failure with LVEF >40%, when used on top of standard of care.[9]*	
Benefit	*DELIVER was a phase III international, multi-center, event-driven, randomized trial in adult patients with HF and LVEF >40% designed to evaluate the efficacy and safety of once daily dapagliflozin 10 mg tablets compared to placebo. The primary endpoint in DELIVER was a composite of cardiovascular (CV) death or an HF event (i.e., hospitalization for worsening HF or an urgent HF visit leading to an unplanned assessment and escalated treatment). DELIVER randomized 6263 subjects in a 1:1 ratio to dapagliflozin or placebo. Treatment with dapagliflozin was superior to placebo in reducing the incidence of the primary composite endpoint of CV death or an HF event. (HR 0.82 [95% CI 0.73, 0.92], p = 0.0008).*	DELIVER provided substantial evidence of efficacy for Dapagliflozin compared to placebo in reducing the incidence of CV death, hospitalization for HF, or an urgent HF visit in patients with HF and LVEF >40% when used in addition to the standard of care regardless of Type 2 DM status.

[8] Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381(17):1609-1620

[9] Packer M, Butler J, Zannad F, et al. Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial. Circulation. 2021;144(16):1284-1294.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	*Dapagliflozin is currently approved as 1) an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM); 2) to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors (based on the DECLARE-TIMI 58 trial); 3) to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease or at risk of progression (DAPA-CKD); and 4) 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 (DAPA-HF). The label for Dapagliflozin tablets describes the following adverse events/reactions:* *Warnings and Precautions: ketoacidosis in patients with Diabetes Mellitus, volume depletion, urosepsis, pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's Gangrene) and genital mycotic infections* *Most common adverse reactions (5% or greater incidence) were female genital mycotic infections, nasopharyngitis, and urinary tract infections. The label describes increases in serum creatinine, hematocrit, LDL and decreases in eGFR and serum bicarbonate* *Safety assessment of dapagliflozin in DELIVER focused on SAEs and predefined AEs of special interest (AESIs) based on the potential risks in the same class.* *The three most commonly reported SAEs of volume depletion by PT, were syncope, hypotension, and dehydration in both treatment groups. There were 3 cases of volume depletion with a fatal outcome: 2 in the dapagliflozin group and 1 in the placebo group.* *An independent, blinded adjudication committee reviewed and adjudicated all potential events of diabetes ketoacidosis (DKA). There were 17 potential DKA events in 15 patients (0.5%) in the dapagliflozin group and 20 events in 20 patients (0.6%) in the placebo group*	No new dapagliflozin-associated risks were *identified in the DELIVER 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. There are no new safety concerns identified through additional post-marketing experience than what is already described in the current dapagliflozin labeling

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	There were no important imbalances in the incidence of deaths, serious TEAEs, and TEAEs leading to discontinuation between treatment groups Commonly reported AESIs (>5%) in either treatment group were renal events, urinary tract infection (UTI), and potential risk factor AEs for amputations affecting lower limbs (preceding events) in DELIVER. Volume depletion (4.6% and 3.9% in dapagliflozin and placebo groups, respectively), UTI (5.2% and 4.9%, respectively), and genital infection (0.9% and 0.4%, respectively) occurred at a slightly higher frequency in patients treated with dapagliflozin in DELIVER.	

Conclusions Regarding Benefit-Risk

The single phase 3 trial DELIVER was an adequate and well-controlled trial, and satisfied the statutory requirement for substantial evidence of effectiveness for the proposed indication to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in adult with HF.

No safety risk was identified from the DELIVER trial; all AEs experienced by subjects in DELIVER were already adequately described in the label.

The benefit of dapagliflozin in patients with symptomatic NYHA class II - IV symptomatic HF with LVEF >40% outweighed the risk of dapagliflozin, thereby yielding a recommendation for approval.

II. Interdisciplinary Assessment

4. Introduction

The Applicant submitted a single, phase 3 trial (DELIVER) in support of the supplemental new drug application (sNDA) for FARXIGA® (dapagliflozin) for the following expanded indication:

FARXIGA® is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit in adults with heart failure.

Dapagliflozin is currently approved in the United States for the following indications:

(1) As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)

(2) To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors (DECLARE-TIMI 58)

(3) To reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression [redacted] (b) (4)

(4) To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure New York Heart Association (NYHA class II - IV) with reduced ejection fraction (DAPA-HF)

Dapagliflozin is a potent, selective, and reversible inhibitor of sodium glucose co-transporter 2 (SGLT2). SGLT2 are expressed almost exclusively in the proximal renal tubule and is responsible for the reabsorption of most of the glucose filtered at the glomerulus. The mechanism of action of dapagliflozin is inhibition of renal SGLT2 leading to a reduction in the reabsorption of filtered glucose and sodium, thereby increasing urinary glucose excretion, osmotic diuresis, and increase in the delivery of sodium to the distal tubule.[10] The degree of glucosuria is proportional to plasma glucose level and explains the hypoglycemic effect of dapagliflozin. While the mechanism of cardiorenal benefit observed in cardiovascular outcome trials with dapagliflozin have not been fully elucidated, dapagliflozin has been shown to influence several physiological functions including an acute natriuresis with an associated reduction in plasma volume, systolic and diastolic blood pressure, and body weight. Other effects associated with its use include increases in hematocrit levels, attenuation of inflammatory responses which leads to beneficial effects on cardiac remodeling, diastolic function, and decreased intraglomerular pressure, which is believed to be mediated by increased tubuloglomerular feedback.

[10] Cowie, M.R., Fisher, M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycemic control. Nat Rev Cardiol 17, 761–772 (2020)

Dapagliflozin is currently indicated for the treatment of heart failure (HF) in patients with left ventricular ejection fraction LVEF ≤40% based on the findings from the DAPA-HF trial. DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) was a randomized, placebo-controlled and event driven trial that evaluated the effect of 10 mg of dapagliflozin administered once daily (QD) on top of standard of care in adult patients with NYHA functional class II - IV heart failure symptoms with reduced ejection fraction (LVEF ≤40%). Dapagliflozin reduced the primary composite endpoint of cardiovascular (CV) death and HF hospitalization (including urgent HF visits) compared to placebo by 26% (hazard ratio (HR): 0.74; 95% confidence interval (CI): 0.65, 0.85).[11] The findings were robust for all components, and the reduction in risk was consistently seen in almost all prespecified subgroups, including patients with and without diabetes.

Dapagliflozin also demonstrated superiority in improving glycemic control and noninferiority in the reduction of major adverse cardiovascular events (MACE) versus placebo in patients with DM2 and with or at risk for atherosclerotic cardiovascular disease (ASCVD) based on the results of DECLARE-TIMI 58 - a multicenter, randomized, double blind, placebo-controlled trial of dapagliflozin in patients with T2DM and established ASCVD or with multiple risk factors for ASCVD. The primary efficacy outcomes were MACE and composite of cardiovascular death or hospitalization for heart failure. Dapagliflozin met the prespecified criterion for noninferiority with respect to MACE (upper boundary of the 95% CI, <1.3; p<0.001 for noninferiority) and resulted in a lower rate of cardiovascular death or hospitalization for heart failure than placebo (4.9% vs. 5.8%; HR: 0.83; 95% CI: 0.73, 0.95; p = 0.005). There was also reduction in blood pressure (BP), HF hospitalizations, and a beneficial effect on renal outcomes. These findings were noted irrespective of baseline BP. Among patients with heart failure with reduced ejection fraction (HFrEF), dapagliflozin reduced HF hospitalizations, CV death, and all-cause mortality; however, this cohort comprised only about four percent of the trial population.[12]

Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial assessed the long-term efficacy and safety of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes. The randomized, placebo-controlled trial evaluated the effects of dapagliflozin 10 mg daily compared to placebo in patients with chronic kidney disease, with or without type 2 diabetes, on the time to first occurrence of any event in the composite of ≥50% sustained decline in eGFR from baseline, reaching end stage renal disease (ESRD), or death from renal or CV causes. The primary composite outcome occurred in 9.2% of subjects in the dapagliflozin group and 14.5% in the placebo group (hazard ratio, 0.61; 95% [CI], 0.51 to 0.72; P<0.001). The effect of dapagliflozin on the primary outcome was generally consistent across prespecified subgroups.[13]

Besides dapagliflozin, there are currently 4 other SGLT2 inhibitors approved for use in the Unites States. Brenzavvy® (bexagliflozin), Invokana® (canagliflozin), Jardiance®

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[11] McMurray JJV, DeMets DL, Inzucchi SE, et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). Eur J Heart Fail. 2019;21(5):665-675

[12] Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-357

[13] Heerspink HJL, Stefansson BV, Chertow GM, et al. Rationale and protocol of the Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. Nephrol Dial Transplant. 2020;35(2):274-282

(empagliflozin), and Steglatro® (ertugliflozin) are approved for glycemic control, and some have demonstrated efficacy in the reduction of CV and renal events in at risk populations. While the mechanism cardiorenal effects for the therapeutic class has not been fully characterized it is believed to be independent of blood glucose lowering.

HF is a clinical syndrome associated with poor quality of life, substantial health-care resource utilization, and a significant cause of premature mortality worldwide.[14] Heart failure (HF) affects over 6.2 million American adults, with an incidence approaching 21 per 1,000 population after the age of 65 years.[15] HF is the leading cause of hospital admissions in patients over the age of 65-years in the US where there has been an increase in this trend over the last 2 decades.[16] HF affects more than 64 million people worldwide and attempts to decrease its social and economic burden have become a major global public health priority.[17]

HF is characterized by signs (jugular venous distension, pulmonary rales, and S3 gallop) and symptoms (dyspnea, fatigue) of cardiac dysfunction resulting from impairments in the structure and function of the heart which ultimately result in reduced cardiac output under normal filling pressures or alternatively elevated filling pressures to maintain normal cardiac output. HF is a growing public health and economic burden due to the significant health-care resource utilization, morbidity and mortality associated with the high rates of recurrent hospitalizations in these patients.[18]

Historically, heart failure with reduced ejection fraction (HFrEF) has been defined as LVEF < 40% while the definition of HF with preserved EF heart failure with preserved ejection fraction (HFpEF) has varied. Recent guidelines use a threshold of LVEF > 50%, however historical studies have classified HFpEF with LVEF > 40 % or 45%. Approximately 50% of patients with HF are currently classified as HFpEF. The hallmark feature of HFpEF is evidence of impaired left ventricle relaxation resulting in elevated filling pressures, congestion, and dyspnea at rest or with exercise.

Assessment of systolic function using ejection fraction has emerged as a clinically important phenotypic marker for classification of HF patients into homogenous groups for diagnosis, prognosis, clinical trial design, and to assess response to therapies. LVEF can be assessed using multiple noninvasive imaging modalities, including echocardiography, cardiac magnetic resonance (CMR) imaging, or gated single-photon emission computed tomography (SPECT). The choice of modality often depends on patient-specific factors, availability of technology or expertise, and need for serial assessments. Echocardiography is the most commonly used imaging modality due to the accessibility, portability, and negligible risk. The American Society of Echocardiography recommends biplane method of disks as the preferred method for assessing LVEF in patients with good image quality. Normal values for 2D echo derived mean LVEF ±

[14] Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14(10):591-602
[15] Truby L, Rogers J, et al. Advanced Heart Failure. J Am Coll Cardiol HF. 2020 Jul, 8 (7) 523–536
[16] Agarwal MA, Fonarow GC, Ziaeian B. National trends in heart failure hospitalizations and readmissions from 2010 to 2017. JAMA Cardiol.2021;6:952–956.
[17] Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;118(17):3272-3287
[18] Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032.

SD (2-SD range) according to gender is defined as 62 ± 5% (52 to 72) in males and 64 ± 5 % (54 to 74) in females. However, echocardiography can have up to 5-10 % inter and intra-observer and temporal variability in assessment of LVEF depending on the technique(s) used.[19,20]

The various thresholds for LVEF used in previous HFpEF trials, multiple pathophysiological mechanisms which underlie the heterogeneous phenotypes of HFpEF evident clinically, and the lack of a single diagnostic test with predictive characteristics for the diagnosis of HFpEF, underscores the heterogenous nature of HFpEF – a systemic condition associated with impaired QoL, high risk of hospitalization and mortality. There is a significant unmet need in this patient population.

The Division considers patients with LVEF of 41 to 51% in males and 41 to 53% in females to have mildly abnormal LVEF, i.e., mild left ventricular systolic dysfunction. Patients with mildly abnormal LVEF are considered similar to patients with HFrEF, defined as HF with LVEF ≤40%, based on their therapeutic response to candesartan, spironolactone and sacubitril/valsartan. Patients with HF with LVEF >51% and 53% in males and females, respectively have normal LVEF and are considered distinct from those with HFrEF or HF with mildly reduced LVEF. Hence, the intended population for this sNDA is heterogenous and includes patients with mildly abnormal and normal LVEF.

Sacubitril/valsartan (Entresto) became the first to obtain a modified indication after demonstrating benefit in patients with LVEF 45 to 57% driven by a reduction in HF hospitalizations with updated labeling to treat patients with mildly abnormal LVEF. Empagliflozin (SGLT2i) also demonstrated a reduction in hospitalization for HF and CV death in patients with heart failure with LVEF >40%, when used on top of standard of care in the EMPEROR-preserved Trial leading to an expanded indication to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure independent of left ventricular ejection fraction. The benefits are clearly evident in adults with reduced, mid-range, or preserved ejection fraction.

The 2022 ACC/AHA recommendations for the management of heart failure address the recent developments in the management of patients with HFpEF with the following:

- Class I recommendation for treatment of hypertension
- Class I recommendation for use of diuretics to reduce congestion and improve symptoms
- Class IIa recommendation for the use of SGLT2 inhibitors to reduce HF hospitalizations and cardiovascular mortality based on the results of the EMPEROR-Preserved Trial
- Class IIa recommendation for guideline management of AF can be useful to improve symptoms
- Class IIb recommendation to consider MRAs to decrease HF hospitalizations in appropriately selected patients with symptomatic HFpEF (LVEF ≥45%, elevated BNP levels or HF admission within 1 year, estimated eGFR >30 mL/min/1.73 m2, creatinine <2.5 mg/dL, and potassium <5.0 Eq/L), based on post hoc analyses of the Treatment of

[19] Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popović ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013 Jan 8;61(1):77-84

[20] Pellikka PA, She L, Holly TA, et al. Variability in Ejection Fraction Measured by Echocardiography, Gated Single-Photon Emission Computed Tomography, and Cardiac Magnetic Resonance in Patients With Coronary Artery Disease and Left Ventricular Dysfunction. JAMA Netw Open. 2018;1(4):e181456

Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial

- Class IIb recommendation to consider ARNI in patients with HFpEF to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum LVEF (45-57%)
- Class IIb recommendation to use angiotensin receptor blockers (ARBs) to decrease HF hospitalizations for patients with HFpEF (greater benefit in patients with LVEF close to 50%)

The Applicant's evaluation of patients with chronic HF includes the previously conducted Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial in patients with HFrEF, and Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure (DELIVER) trial. The latter trial serves as the basis of this submission. The dapagliflozin clinical development program has also evaluated renal benefits in patients with HF.

This submission also includes a pooled analysis of patient-level data from DELIVER and DAPA-HF to assess the treatment effect of dapagliflozin across the spectrum of LVEF.

4.1. Approach to the Review

This was a joint clinical and statistical review. Rosalyn Adigun and William Koh focused on the data supporting efficacy, and Tejas Patel focused on the data supporting safety. There were no relevant nonclinical or clinical pharmacology data for review.

This review focused on the single pivotal Phase III study DELIVER (D169CC00001), designed to expand the HF indication of dapagliflozin to include patients with HF and LVEF >40%. The established safety profile of dapagliflozin is based on multiple studies in patients with T2DM and several large CV outcome studies including patients with and without T2DM, with more than 53000 patients, of which 30489 patients were exposed to dapagliflozin. The safety profile is further supported by an extensive post-marketing experience for Dapagliflozin.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Dapagliflozin

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
D1699CC00001	Male or Female adults (≥40 years) with documented diagnosis of symptomatic HF (NYHA class II-IV) with LVEF >40%, evidence of structural heart disease at enrollment, and a medical history of typical symptoms/signs of HF≥6 weeks before enrollment with at least intermittent need for diuretic treatment, elevated NT-proBNP, eGFR ≥25 mL/min/1.73 m^2 and receiving local standard of care for HFpEF	Control Type: Placebo + Standard of care Randomization: 1:1 parallel group Blinding: Double-blind	Drug: Dapagliflozin Dose: 10 mg Number treated: 3126 (Drug) 3127 (Placebo) Duration: 26.9 mo	Primary: Composite endpoint of CV death, hospitalization for HF or urgent HF visit Secondary: 1. Composite of CV death and recurrent HF events 2. Change from Baseline at 8 months in the KCCQ-TSS 3. Time to the occurrence of CV death 4. Time to the occurrence of death from any cause	6263	353 and 20

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
D1699C00001*	Male or Female adults (≥18 years) with an established diagnosis of HFrEF (NYHA class II - IV for ≥2 months), LVEF ≤40% within the last 12 months, elevated NT-proBNP, eGFR ≥30 mL/min/1.73 m^2 at enrollment and receiving local standard of care for HFrEF	Control Type: Placebo + Standard of care Randomization: 1:1 parallel group Blinding: Double-blind	Drug: Dapagliflozin Dose: 10 mg Choose unit. Number treated: 2368 (Drug) 2368 (Placebo) Duration: 17.8 mo	Primary: Composite of CV death, hospitalization for HF or urgent HF visit Secondary: 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

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: BID, twice daily; DB, double-blind; LTE, long-term extension study; MC, multi-center; N, number of subjects; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized
*Safety assessment only

5. Patient Experience Data

DELIVER Trial evaluated the impact of treatment with dapagliflozin compared to placebo in addition to regional standards of care on the patients' perspective of their symptoms mapped to symptom burden and symptom frequency (subset of the Kansas City Cardiomyopathy Questionnaire (KCCQ)) at randomization, and at targeted visits 4- and 8-months following randomization, at premature treatment discontinuation visit (PTDV) and SCV.

A key secondary efficacy variable was the change from baseline at 8 months in the KCCQ total symptom score (TSS). The KCCQ is a 23-item questionnaire that measures symptoms, physical and social limitations, self-efficacy, and quality of life in patients with HF. The self-administered questionnaire represents the patient's perspective of their symptoms mapped to 7 domains (symptom burden, symptom frequency, symptom stability, physical limitations, social limitations, quality of life, and self-efficacy) in patients with heart failure. The patient-reported instrument has a recall period of two weeks to account for the day-to-day variability in heart failure symptoms experienced by patients.

Details are discussed in Section 7.4.1.

6. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

No new information regarding clinical pharmacology is included in this application. For relevant clinical pharmacology **information, consult the current product label and Module** 2.7.2 Summary of Clinical Pharmacology Studies and Associated Analytical Methods from the original dapagliflozin application.

6.1. Nonclinical Assessment of Potential Effectiveness

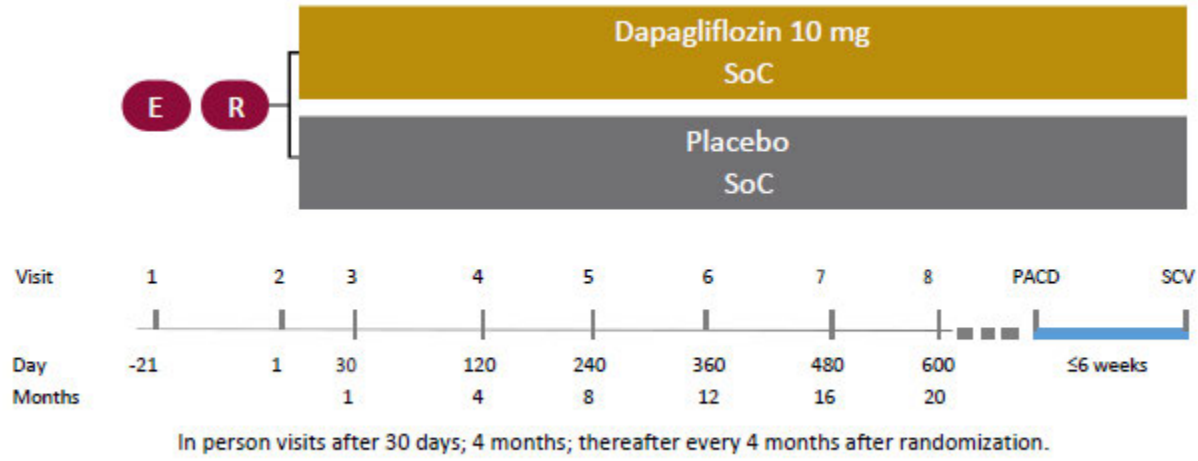
N/A

7. Evidence of Benefit (Assessment of Efficacy)

In support of the proposed indication, the Applicant conducted a single phase 3 pivotal Trial (DELIVER). DELIVER was a phase III international, multi-center, parallel-group, event-driven, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of once daily (QD) dapagliflozin 10 mg tablets compared to placebo in reducing the composite of CV death or an HF event in patients with HF and LVEF >40%. DELIVER is described below according to Protocol Version 4.0. Relevant protocol amendments are described in the Appendices.

The primary objective of DELIVER was to determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalization for HF or urgent HF visit) in patients with HF and LVEF >40%. Trial design is depicted below (Figure 1) and details summarizing the endpoints of DELIVER are shown in Table 4**Error! Reference source not found.**.

Figure 1. Study Design, DELIVER



E=Enrolment; R=Randomization; SoC= Standard of Care; PACD=Primary Analysis Censoring Date; SCV=Study Closure Visit; FU=Follow Up

Source: Figure 1 from Protocol Version 4.0

Table 4 Endpoints for DELIVER Trial

Primary Endpoint
Time to the first occurrence of any of the components of the composite of CV death, hospitalization for HF or urgent HF visit
Secondary Endpoint(s)
Total number of HF events (first and recurrent) and CV death
Change from baseline in the TSS of the KCCQ at 8 months
Time to the occurrence of CV death
Time to the occurrence of death from any cause
Exploratory Endpoint(s)
Time to the first occurrence of hospitalization from any cause
Proportion of patients with worsened NYHA class from baseline to 8 months
Health status assessed by EQ-5D-5L
Change in systolic BP from baseline
Change in body weight from baseline
Change in eGFR from baseline
Change in clinical summary score, TSS subscores, overall summary score, QoL score

Source: Clinical Reviewer
Abbreviations: CV, cardiovascular, HF, heart failure; TSS, total symptom score; KCCQ, Kansas City cardiomyopathy questionnaire; NYHA, New York Heart Association; EQ-5D-5L, EuroQol 5-dimensional 5-level questionnaire; BP, blood pressure; eGFR, estimated glomerular filtration rate; QoL, quality of life

7.1. Assessment of Dose and Potential Effectiveness

No formal dose-ranging study was performed with dapagliflozin in patients with HF as there are currently no established biomarkers. Pharmacokinetic and pharmacodynamic data have previously demonstrated that 10 mg dose of dapagliflozin results in near maximal inhibition of SGLT2. In the Type 2 Diabetes Mellitus development program, Dapagliflozin 10-mg dose demonstrated **a favorable benefit-risk balance, with superior efficacy and comparable safety to the 5 mg dose.**

7.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

7.2.1. Trial Design

To support the proposed indication, the Applicant conducted a single phase 3 Trial (D169CC00001) titled "Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure (DELIVER)." The first global clinical study protocol version 1.0, dated April 24, 2018, was amended three times. The description provided is based on the final version 4.0, dated November 12, 2020.

Trial D169CC00001, referred to as DELIVER, was an international, multicenter, parallel-group, event-driven, randomized, double-blind study conducted in patients with HFpEF. The primary objective of DELIVER was to determine the effect of 10-mg dapagliflozin, compared to placebo, administered once daily (QD) in additional to background regional standard of care therapy in patients with HF and preserved systolic function in reducing the composite of cardiovascular (CV) death and heart failure events (hospitalizations for HF or urgent HF visits). In version 4.0 of the protocol, the primary objective also included evaluation in the subpopulation with LVEF <60%.

DELIVER was an event driven trial with a target of 1117 subjects with a primary endpoint event. Originally, 844 primary endpoint events were targeted to provide at least 90% power, under equal randomization, two-sided alpha of 5% to detect a hazard ratio of 0.8 or less between dapagliflozin and placebo. To allow testing for the dual primary analyses in the LVEF <60% subpopulation, per the final version of the protocol, the target number of subjects with the primary endpoint was increased to 1117 to ensure at least 70% of the events will be available for the LVEF <60% subpopulation.

Primary Objectives

To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalization for HF or urgent HF visit) in patients with HF and preserved systolic function in (1) full study population, and (2) the subpopulation of patients with baseline LVEF <60%.

Secondary Objectives

- To determine whether dapagliflozin is superior to placebo in improving patient-reported outcomes (PROs) measured by KCCQ
- To determine whether dapagliflozin is superior to placebo in reducing CV death
- To determine whether dapagliflozin is superior to placebo in reducing all-cause mortality

Safety Objectives

- To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients with HFpEF

Exploratory Objectives

- To determine whether dapagliflozin is superior to placebo in reducing all-cause hospitalization
- To determine whether dapagliflozin is superior to placebo in reducing the proportion of patients with worsened NYHA class

- To describe health status assessed by EuroQol 5-dimensional 5-level questionnaire (EQ-5D-5L) to support health economic analysis and health technology assessment
- To determine whether dapagliflozin compared with placebo will have an effect on systolic BP
- To determine whether dapagliflozin compared with placebo will have an effect on body weight
- To determine whether dapagliflozin compared with placebo will have an effect on eGFR
- To explore whether dapagliflozin compared to placebo improves KCCQ summary scores, subscores of TSS (symptom frequency and symptom burden) and domains
- To collect and store blood samples for future exploratory genetic research

Primary efficacy endpoint:

Time to the first occurrence of any of the components of this composite:

(1) CV death
(2) Hospitalization for HF
(3) Urgent HF visit (e.g., emergency department or outpatient visit)

Key secondary efficacy endpoints (included for multiplicity):

(1) Total number of HF events (first and recurrent) and CV death
(2) Change from baseline in the TSS of the KCCQ at 8 months
(3) Time to the occurrence of CV death
(4) Time to the occurrence of death from any cause

Exploratory endpoints

(1) Time to the first occurrence of hospitalization from any cause
(2) Proportion of patients with worsened NYHA class from baseline to 8 months
(3) Change in systolic BP from baseline
(4) Change in body weight from baseline
(5) Change in eGFR from baseline
(6) Change in clinical summary score, TSS subscores, overall summary score, QoL score

Study Committees

Data monitoring committee

The data monitoring committee (DMC) was responsible for safeguarding the interests of the patients in the study by assessing the safety of the investigational product (IP) during the study and for reviewing the overall conduct of the study. The DMC under an established charter ensured maintenance of the blinding and integrity of accumulating study data and interactions with the EC. The DMC had access to the individual treatment codes and was able to merge these with the collected study data while the study was ongoing.

Executive Committee

The Executive Committee (EC) was responsible for the overall study design, development of the study protocol and eCRF, supervision of the study conduct and progress, development of protocol amendments, liaison with the Clinical events adjudication (CEA) Committee and DMC as needed, development of the statistical analysis plan (SAP), interpretation of the final data and reporting of the study.

The EC was comprised of designated international academic leaders and non-voting members of AstraZeneca, and operating under an EC charter.

Clinical Event Adjudication (CEA) Committee

The CEA committee independently reviewed, interpreted, and adjudicated all potential endpoints experienced by the patients as outlined in the charter. The CEA Committee members did not have access to individual treatment codes for any patient or efficacy and safety events.

National Lead Investigator (NLI) Committee

The National Lead Investigator Committee was comprised of National Lead Investigators from each country where the study was conducted and was supervised by the EC. Members of the

committee were responsible for providing clinical guidance on study implementation, recruitment, and study conduct in their respective country.

7.2.2. Eligibility Criteria

Inclusion Criteria

For inclusion in the study, patients had to fulfil the following criteria:

1. Sign the informed consent document prior to any study specific procedures.
2. Male or female patients aged ≥40 years.
3. Documented diagnosis of symptomatic HF (NYHA class II to IV) at enrollment, medical history of typical signs and symptoms of HF ≥6 weeks before enrolment with at least an intermittent need for diuretic therapy.
4. LVEF >40% and evidence of structural heart disease (i.e., left ventricular hypertrophy or left atrial enlargement) documented by the most recent echocardiogram, and/or cardiac magnetic resonance within the last 12 months prior to enrolment. For patients with prior acute cardiac events or procedures that may reduce LVEF, e.g., as defined in exclusion criterion 6, qualifying cardiac imaging assessment at least 12 weeks following the procedure/event is required.
5. NT-pro BNP ≥300 pg/mL at Visit 1 for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at Visit 1, NT-pro BNP must be ≥600 pg/mL.
6. Patients may be ambulatory, or hospitalized; patients must be off intravenous HF therapy (including diuretics) for at least 12 hours prior to enrolment and 24 hours prior to randomization.

Exclusion Criteria

Any of the following were regarded as a criterion for exclusion from the study:

1. Receiving therapy with an SGLT2 inhibitor within 4 weeks prior to randomization or previous intolerance to an SGLT2 inhibitor
2. Type 1 Diabetes Mellitus
3. eGFR <25 mL/min/1.73 m2 (CKD-EPI formula) at Visit 1
4. Systolic BP <95 mmHg on 2 consecutive measurements at 5-minute intervals, at Visit 1 or at Visit 2
5. Systolic BP ≥160 mmHg if not on treatment with ≥3 BP lowering medications or ≥180 mmHg irrespective of treatments, on 2 consecutive measurements at 5-minute intervals, at Visit 1 or at Visit 2
6. MI, unstable angina, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), ablation of atrial flutter/fibrillation, valve repair/replacement within 12 weeks prior to enrolment. Before enrolment, these patients must have their qualifying echocardiography and/or cardiac Magnetic Resonance Imaging examination at least 12 weeks after the event
7. Planned coronary revascularization, ablation of atrial flutter/fibrillation and valve repair/replacement
8. Stroke or transient ischemic attack within 12 weeks prior to enrollment
9. Probable alternative or concomitant diagnoses which in the opinion of the Investigator could account for the patient's HF symptoms and signs (e.g., anemia, hypothyroidism)
10. Body mass index >50 kg/m^2

11. Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including chronic obstructive pulmonary disease (COPD) (i.e., requiring home oxygen, chronic nebulizer therapy or chronic
    oral steroid therapy, or hospitalization for exacerbation of chronic obstructive pulmonary disease (COPD) requiring ventilatory
    assist within 12 months prior to enrollment)
12. Previous cardiac transplantation, or complex congenital heart disease. Planned cardiac resynchronization therapy
13. HF due to any of the following: known infiltrative cardiomyopathy (e.g., amyloid, sarcoid, lymphoma, endomyocardial fibrosis), active myocarditis, constrictive pericarditis, cardiac tamponade, known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, or uncorrected primary valvular disease
14. A life expectancy of less than 2 years due to any non-cardiovascular condition, based on Investigator's clinical judgement
15. Inability of the patient, in the opinion of the Investigator, to understand and/or comply with study medications, procedures and/or follow-up, OR any conditions that, in the opinion of the Investigator, may render the patient unable to complete the study
16. Active malignancy requiring treatment (with the exception of basal cell or squamous cell carcinomas of the skin)
17. Acute or chronic liver disease with severe impairment of liver function (e.g., ascites, esophageal varices, coagulopathy)
18. Women of child-bearing potential (i.e., those who are not chemically or surgically sterilized or post-menopausal) not willing to use a medically accepted method of contraception considered reliable in the judgement of the Investigator, OR who have a positive pregnancy test at randomization, OR who are breast-feeding
19. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca personnel and/or personnel at the study site)
20. Previous randomization in the present study
21. Participation in another clinical study with an IP or device during the last month prior to enrollment

7.2.3. Statistical Analysis Plan

The SAP was drafted on August 27, 2018 and amended four times. In version 2.0 (dated November 06, 2020), the primary objective was expanded to incorporate the LVEF <60% subpopulation. The interim analysis for efficacy was planned to be conducted on May 25, 2021, and used SAP version 4.0 (dated May 20, 2021). The DMC meeting for the interim analysis was held on June 25, 2021. Per the recommendation of the DMC, the study continued as planned. The SAP (version 5.0) was finalized on December 08, 2021. There were minor changes to the SAP between version 4.0 and 5.0 (finalized SAP). Revisions to the SAP version 4.0 were generally limited to formatting, clarification of the statistical procedure for confirmatory testing in the subpopulation, and sensitivity analyses for events censored at the onset date associated with Coronavirus disease 2019 (COVID-19) infections. The primary analysis censoring date (PACD) is determined to be February 13, 2022. Based on the information submitted, the statistical reviewer considered revisions made to the SAP post interim analysis to be appropriate.

Key details of the statistical analysis plan (SAP) are included below.

Interim Analysis

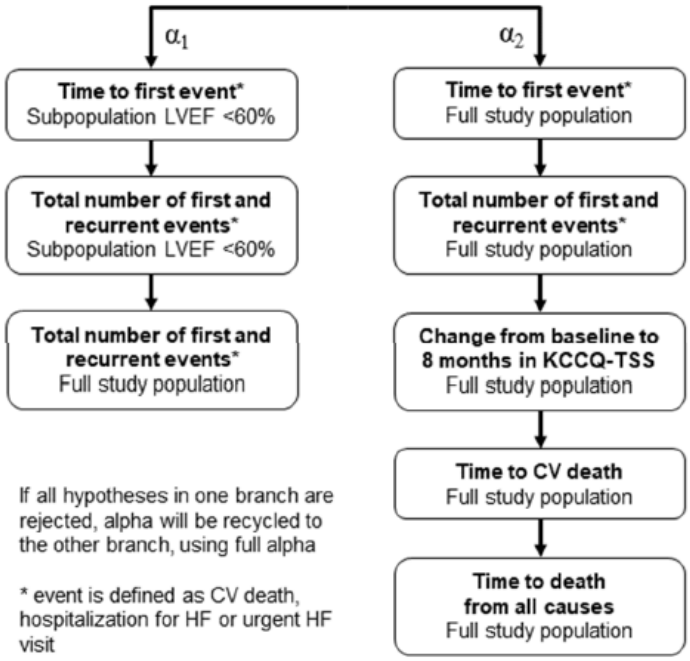
An interim analysis is planned to be performed when approximately 67% of the target number of patients have an adjudicated primary endpoint event, using a Haybittle-Peto rule. The interim analysis will assess for superiority of dapagliflozin to placebo based on a nominal two-sided alpha level of 0.002. The primary composite endpoint will be evaluated in the full study population first based on the specified alpha level. If superiority is achieved for the primary, then superiority for the CV death endpoint will be evaluated comparing dapagliflozin with placebo using the same two-sided level alpha of 0.002. If CV death was significant in the full study population, 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 also has the flexibility to conduct additional interim analysis if deemed necessary. The significance level for the final analysis will be based on the actual number of interim analyses, using the East Software, based on the Haybittle-Peto function.

Multiplicity

A closed testing procedure including a pre-specified hierarchical ordering of the primary and secondary endpoints was used to control for the overall Type 1 error in addition to the planned interim analysis.

If the study continues to the end, i.e., did not stopped at the interim analysis for efficacy, the following multiplicity testing procedure as shown in Figure 2 will be applied to evaluate the full study population and the subpopulation per the study objectives. The total significance level, alpha, will be split for the two primary analyses of the primary endpoint, allocating α_1 to test the subpopulation and α_2 to test the full population Figure 2. Additional mathematical details of obtaining the values of alpha1 are described in III.17.

Figure 2. Testing Procedure for Primary and Key Secondary Endpoints at the Final Analysis, DELIVER



Source: Figure 2 from SAP version 5.0
If the study is stopped for efficacy at the interim analysis, testing of the secondary endpoints will be evaluated in the full study population using the two-sided alpha of 0.2% according to the right branch of the above figure.
Abbreviations: CV, cardiovascular; HF, heart failure; KCCQ, Kansas City cardiomyopathy questionnaire; LVEF, left ventricular ejection fraction; TSS, total symptom score

If the study was stopped for efficacy at the interim analysis, a two-sided alpha of 0.002 will be used to evaluate the key secondary endpoints in the full study population. There will not be any evaluation of endpoints in the subpopulation of patients with baseline LVEF <60%, i.e., the left branch of Figure 2.

Analysis Sets

The full analysis set (FAS) included all patients randomized to the study drug irrespective of their protocol adherence and continued participation in the study. The FAS will be used for all efficacy analysis of the primary, secondary, and exploratory endpoints.

A subset of the FAS consisting of patients with baseline LVEF <60% is used for the planned analysis for the LVEF <60% subpopulation.

The safety analysis set (SAS) included all randomized subjects who received at least one dose of randomized treatment. Subjects were analyzed according to the treatment they actually received. Subjects who got both incorrect and correct treatment will be analyzed according to their randomized treatment. Subjects who got only the incorrect treatment will be analyzed according to that treatment.

Censoring Dates

The last clinical event assessment is defined as the last date when the event assessment question for a potential heart failure event was completed on the eCRF event assessment page.

Complete follow up of the primary endpoint will be defined when the patient had a primary endpoint event, died from non-CV death or had complete event assessment on or after the PACD (i.e., the patient was not censored due to incomplete follow-up of endpoints).

For CV death endpoint, patients who did not die from CV death, will be censored at the earliest of death due to other cause, withdrawal of consent, PACD, or for any patients who are lost-to-follow-up (LTFU), at last date known to be alive.

For all-cause mortality endpoint, patients who are alive will be censored at PACD, or for any patients who are lost-to-follow-up (LTFU), at last date known to be alive.

Statistical Analysis

The primary composite endpoint was analyzed using a Cox proportional hazards model adjusting for treatment group, stratified by Type 2 Diabetes (T2D) status (Yes or No) at randomization. Efron's method will be used to break ties. The estimated hazard ratio from the Cox model comparing dapagliflozin with placebo, respective 95% CI, and Wald-based p-value used for confirmatory testing are reported.

Subjects who did not have an adjudicated primary endpoint event on or prior to PACD will be censored at the earliest of date of withdrawal of consent or non-CV death when applicable, and otherwise at the date of the last clinical event assessment or the PACD, whichever occurs first.

The contribution of each component of the primary composite endpoint to the overall treatment effect will be evaluated based on analysis of the first event of the given type regardless of any non-fatal composite event of the other type. The analysis method will be similar to the primary composite endpoint using similar variables for adjustment.

The statistical reviewer also included analysis of the primary endpoint and the individual components for the LVEF ≥60% population.

Subgroup analysis will be conducted for the list of characteristics below

- Age (≤median, >median)
- Sex (Male, female)
- Race (White, Black or African American, Asian, Other)
- Geographic region
- New York Heart Association (NYHA) class at enrolment (II vs III/IV)
- Left ventricular ejection fraction (LVEF) at enrolment (%) (≤49, 50 - 59, ≥60)
- N-terminal pro B-Type natriuretic peptide (NT-proBNP) at enrollment (pg/mL) (≤median, >median)
- Randomized during hospitalization for HF or within 30 days of discharge (Yes, No)
- Estimated glomerular filtration rate (eGFR) at enrolment (ml/min/1.73m^2) (<60, ≥60)
- Body mass index (BMI) at enrolment (kg/m^2) (<30, ≥30)
- Type 2 diabetes at enrolment (Yes, No)
- Systolic blood pressure at randomization (≤median, >median)
- Atrial fibrillation or flutter at enrolment electrocardiogram (ECG) (Yes, No)

The statistical reviewer included ethnicity (Hispanic or Latino vs not Hispanic or Latino) as additional subgroup analysis.

For all time to event endpoints, i.e., time to CV death and time to all-cause mortality, the same Cox regression model used for the primary composite endpoint will be used. In addition, for all time-to

first event endpoints, the incidence rate, risk differences (difference in incidence rates) between arms and 95% CI for risk differences are reported. The incidence rate (IR) is the number of subjects with a first event divided by the total duration of follow-up across all subjects in the given group. The 95% CI for risk differences comparing dapagliflozin and placebo are estimated based on normal approximation to differences in Poisson rates.

The composite outcome of total number of HF events (first and recurrent) and CV death with onset on or prior to PACD, adjudicated and confirmed by the CEA committee, was analyzed using the semi-parametric proportional rates model (Lin et al 2000;[21] abbreviated as the LWYY) to test the treatment effect and to quantify the treatment difference in terms of the rate ratio with 95% confidence interval and p-value. If a HF event and CV death occurred at the same day, then only CV death will be counted. The two components of the composite endpoint were also analyzed separately using the Lin Wei Yang Ying (LWYY) approach, with CV death considered as semi-competing risk. For CV death component, result was reported based on the time to first event analysis.

Change from baseline at 8 months in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) was analyzed using the rank analysis of covariance (ANCOVA) adjusting for baseline KCCQ-TSS and stratified by T2D status at randomization. The p-value will be calculated from the Cochran-Mantel-Haenszel test stratified by T2D status at randomization and used for the confirmatory testing multiplicity procedure described earlier. To estimate the treatment effect, the win ratio and respective 95% CI based on Wang and Pocock 2016[22] will be used. Due to COVID-19 pandemic, on-site assessments of KCCQ were not conducted in a number of sites, with some sites done remotely and some others cancelled. As such, the main analysis of this endpoint includes the population with patients who had a planned or performed 8-month assessment (Visit 5) prior to the major COVID-19 outbreak, defined as March 11, 2020 (the date when WHO declared COVID-19 a pandemic) thus unaffected by the pandemic's possible impact on health-related quality of life.

The Applicant included sensitivity analyses for the primary efficacy endpoint in the full population as well as in the LVEF <60% population. As a sensitivity analysis, the Applicant included undetermined deaths as CV deaths in the primary endpoint. We reported the results of the sensitivity analyses in the full population. In addition, we requested further sensitivity analyses based on (1) including investigator reported CV death and HF events in the primary composite endpoint and (2) including investigator reported HF events in the primary composite endpoint.

To address issues related to missing follow-up of the primary endpoint, the Applicant considered a tipping point analysis. For simplicity, we included a worst-case analysis where subjects on dapagliflozin arm who did not have complete follow-up of the primary endpoint (due to lost-to-follow-up, or incomplete event assessment) were considered to have the primary endpoint at the time of censoring while patients on placebo who did not have complete follow-up of the primary endpoint were considered not to have the primary endpoint at the time of censoring.

[21] Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. Journal of the Royal Statistical Society: Series B (Statistical Methodology) 2000;62(4):711–730.

[22] Wang D, Pocock S. A win ratio approach to comparing continuous non-normal outcomes in clinical trials. Pharmaceut. Statist. 2016;15:238–245.

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

A total of 10418 were enrolled and 6263 subjects were randomized at 353 study sites across 20 countries. The first subject was randomized on August 27, 2008, and the last subject visit was on March 27, 2022. 3131 subjects were randomized to dapagliflozin treatment group and 3132 to the placebo group. Of the 4155 subjects enrolled who were not randomized, 3955 (95%) failed to meet the eligibility criteria. The most common failed eligibility criterion was NT-pro BNP ≥300 pg/mL (≥600 pg/mL, for patients with ongoing atrial fibrillation/flutter). This criterion was not met by 3373 subjects.

A total of 886 (14.1%) subjects discontinued study treatment; 14.2% in the dapagliflozin treatment group and 14.1% in the placebo group. Vital status was known for all except 1 of the 18 subjects who withdrew consent. A total of 99.2 % of the randomized subjects had complete follow-up of the primary endpoint.

Reviewer's comments: *Baseline demographics, subject characteristics, and heart failure therapies were well balanced between the dapagliflozin and placebo arms (Table 5, Table 6, Table 7).*

Table 5. Baseline Demographic and Clinical Characteristics, FAS, DELIVER

Demographic Information	Dapa 10 mg N=3131	Placebo N=3132
Age		
Mean (SD)	72 (9.6)	72 (9.5)
Median	73	72
Min, Max	40, 99	40, 99
Age Category, n (%)		
≤50	85 (3)	74 (2)
>50 - 65	658 (21)	687 (22)
>65 - 75	1184 (38)	1228 (39)
>75	1204 (38)	1143 (36)
Analysis Sex, n (%)		
Female	1364 (44)	1383 (44)
Male	1767 (56)	1749 (56)
Race, n (%)		
White	2214 (71)	2225 (71)
Black/African American	81 (3)	78 (2)
Asian	630 (20)	644 (21)
American Indian/Alaska Native	93 (3)	96 (3)
Other	113 (4)	89 (3)
Ethnicity, n (%)		
Hispanic or Latino	632 (20)	598 (19)
Not (Hispanic or Latino)	2499 (80)	2534 (81)
Geographic Region 1, n (%)		
North America	428 (14)	423 (14)
Europe and Saudi Arabia	1494 (48)	1511 (48)
Latin America	602 (19)	579 (18)
Asia	607 (19)	619 (20)
US Only, n (%)		
US	276 (9)	276 (9)
Outside of US	2855 (91)	2856 (91)

Source: Statistical Reviewer
Abbreviations: FAS, full analysis set; N, number of randomized subjects; n, number of subjects with available data; LVEF, left ventricular ejection fraction, SD, standard deviation; US, United States; Dapa=dapagliflozin

Table 6. Baseline Disease Characteristics, FAS, DELIVER

Baseline Disease Characteristics	Dapa 10 mg N=3131	Placebo N=3132
Time from Last HF Hosp to Rand V2, n (%)		
No Prior HF Hospitalization	1861 (59)	1864 (60)
Randomized in Hospital - 3 Months	505 (16)	497 (16)
>3 Months	765 (24)	771 (25)
Randomized during hosp for HF or within 30 days of discharge, n (%)		
Yes	328 (10)	326 (10)
No	2803 (90)	2806 (90)
Prior HF Hospitalization, n (%)		
Yes	1270 (41)	1269 (41)
No	1861 (59)	1863 (59)
NYHA Class at Baseline, n (%)		
I or II	2314 (74)	2400 (77)
III or IV	817 (26)	732 (23)
Baseline LVEF (%)		
Mean (SD)	54 (8.6)	54 (8.9)
Median	54	54
Min, Max	35, 85	35, 88
LVEF Group 1, n (%)		
<50	1067 (34)	1049 (33)
50 - 59	1133 (36)	1123 (36)
≥60	931 (30)	960 (31)
Baseline NT-proBNP (ng/L)		
Mean (SD)	1584 (1954.9)	1549 (1999.4)
Median	1021	1005
Min, Max	300, 26590	237, 31290
NT-proBNP Group 1, n (%)		
≤Median	1555 (50)	1578 (50)
>Median	1576 (50)	1553 (50)
Missing	0 (0)	1 (0)
Baseline eGFR (mL/min/1.73m2)		
Mean (SD)	61 (19.0)	61 (19.3)
Median	60	60
Min, Max	23, 147	22, 121
eGFR (mL/min/1.73m2), n (%)		
<60	1516 (48)	1554 (50)
≥60	1615 (52)	1577 (50)
Missing	0 (0)	1 (0)

Source: Statistical Reviewer
Abbreviations: FAS, full analysis set; N, number of randomized subjects; n, number of subjects with available data; SD, standard deviation; LVEF, left ventricular ejection fraction; HF, heart failure, NYHA, New York Heart Association; NT-proBNP, N-terminal pro b-type natriuretic peptide; eGFR, estimated glomerular filtration rate; Dapa=dapagliflozin

Table 7. Baseline Concomitant Medications, FAS, DELIVER

Medications, n (%)	Dapa 10 mg N=3131	Placebo N=3132
ACEi	1144 (37)	1151 (37)
ARB	1133 (36)	1139 (36)
ARNI	165 (5)	136 (4)
Beta Blocker	2592 (83)	2585 (83)
Calcium Channel Block	939 (30)	976 (31)
Diuretics	3061 (98)	3062 (98)
MRA	1340 (43)	1327 (42)
Loop Diuretics	2403 (77)	2408 (77)
Other Diuretics	654 (21)	689 (22)
Digitalis Glycosides	150 (5)	146 (5)
Vasodilators	271 (9)	286 (9)
Lipid Lowering Drugs	2061 (66)	2096 (67)
Statins	2004 (64)	2035 (65)
Acetylsalicylic Acid	1077 (34)	1102 (35)
Vitamin K Antagonists	606 (19)	608 (19)
Heparin Group	14 (<1)	13 (<1)
Direct Oral Anticoagulant	1074 (34)	1078 (34)
Other Antithrombotic Agent	1 (<1)	-
Other Antiplatelets	473 (15)	488 (16)
ACEi or ARB	2262 (72)	2281 (73)
ACEi or ARB or ARNI	2420 (77)	2412 (77)
(ACEi or ARB or ARNI) and beta blocker	2036 (65)	2023 (65)
(ACEi or ARB or ARNI) and beta blocker and MRA	933 (30)	898 (29)

Source: Statistical Reviewer
Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inh bitor; MRA, mineralocorticoid receptor antagonist; FAS, full analysis set; N, number of randomized subjects; n, number of subjects with available data; Dapa=dapagliflozin

Extent of Exposure

The duration of exposure to the investigational drug ranged from 0 to 42.2 months. Median duration of exposure was similar between treatment groups were similar: 26.9 months in the dapagliflozin group and 27.0 months in the placebo group. There were 6426 patient years of exposure to dapagliflozin in the study. During this period, 6253 subjects (99.8% of randomized cohort) received at least one dose of the IP.

Treatment compliance

Treatment compliance was high (>95% of patients had >80% compliance) and balanced between treatment groups.

Conclusion on study subjects

Of the 6263 randomized subjects, 99.2% 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

On June 25, 2021, the pre-specified interim analysis was carried out after the accrual of 70.9% (792 events) of the final target number of 1117 primary events. Per the recommendation of the DMC, the study continued as planned. Key details of the interim results are reported in Table 8. The study did not meet the pre-specified criterion for CV death endpoint and thus continued per the recommendation of the DMC.

Table 8. Interim Analysis Results Based on June 25, 2021, Closed Session Reports, DELIVER

	Adjusted Hazard ratio[c]		*Two-sided p-value*	
Endpoint[a]	*(95% CI)*	*Events*[d]	*Stopping boundary*[e]	*Observed result*
Primary composite[b]	0.76 (0.66, 0.87)	792	0.002	0.00013
CV death	0.89 (0.71, 1.12)	287	0.002	0.33

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.
d. Number of patients with at least one CEA-confirmed event.
e. Haybittle-Peto boundary.
Data received: CRF: 25MAY21
Presentation manually compiled. (page 1 of 1)
Source: DMC Closed Session Reports June 25, 2021.

The study disposition is shown in Table 9. In summary, less than 1% of the subjects withdrew consent to follow-up.

Table 9. Disposition of Subjects, DELIVER

Disposition	**Dapa 10 mg N=3131**	**Placebo N=3132**
Subjects randomized, n (%)	3131 (100%)	3132(100%)
FAS, n (%)	3131 (100%)	3132(100%)
LVEF <60%, n (%)	2200 (70%)	2172 (69%)
SAS, n (%)	3126 (>99%)	3127(>99%)
Did not withdraw consent from the study, n (%)	3123 (>99%)	3122 (>99%)
Alive	2613 (83%)	2592 (83%)
Dead	508 (16%)	529 (17%)
Vital status unknown	2 (<1%)	1 (<1%)
Withdrawal of consent from the study, n (%)	8 (<1%)	10 (<1%)
Alive	6 (<1%)	5 (<1%)
Dead	2 (<1%)	4 (<1%)
Vital status unknown	-	1 (<1%)

Source: Statistical Reviewer
Abbreviations: FAS, full analysis set; N, number of randomized subjects; n, number of subjects with available data; LVEF, left ventricular ejection fraction, SAS, safety analysis set, Dapa=dapagliflozin

Primary Endpoint

The primary efficacy endpoint was the composite of time to CV death or HF event planned to be evaluated in the FAS population and the subpopulation of subjects with LVEF <60%.

In the full population, a total of 512 (incidence rate of 7.7 per 100 patient-years (PY)) subjects in dapagliflozin arm and 610 (IR of 9.5 per 100 PY) subjects in placebo experience a primary

composite endpoint, with an adjusted hazard ratio of 0.82 (95% CI: 0.73, 0.92; two-sided p<0.001) (Table 10). The estimated difference in IR of the primary composite endpoints comparing dapagliflozin with placebo was -1.7 per 100 PY (95% CI: -2.7, -0.7 per 100 PY) favoring dapagliflozin.

Table 10. Primary Efficacy Endpoint and the Individual Components, FAS, DELIVER

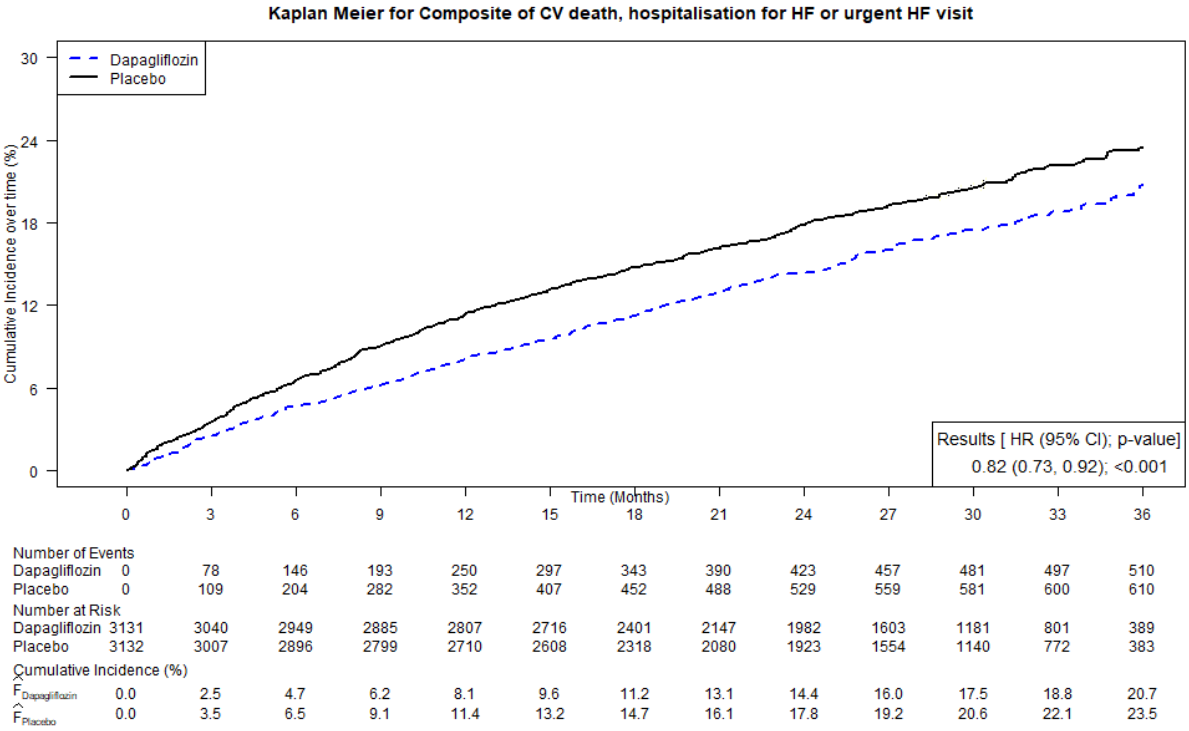
Trial Endpoint	Dapa 10 Mg N=3131 n (IR)	Placebo N=3132 n (IR)	HR (95% CI) [1]	Nominal p-Value	Risk Difference (95% CI) [2]
Primary Endpoint	512 (7.7)	610 (9.5)	0.82 (0.73, 0.92)	<0.001	-1.7 (-2.7, -0.7)
CV death	231 (3.3)	261 (3.7)	0.88 (0.74, 1.05)	0.2	-0.4 (-1.1, 0.2)
HF event [3]	368 (5.6)	455 (7.1)	0.79 (0.69, 0.91)	<0.001	-1.5 (-2.4, -0.6)
Hospitalization for HF	329 (4.9)	418 (6.4)	0.77 (0.67, 0.89)	<0.001	-1.5 (-2.3, -0.7)
Urgent HF visit	60 (0.9)	78 (1.1)	0.76 (0.55, 1.07)	0.1	-0.3 (-0.6, 0.1)

Source: Statistical Reviewer
n: The number of events for the individual components are the number of first events for each component and their sum exceeds the number of events for the composite endpoint.
IR: Incidence rates are presented as the number of subjects with first event per 100 patient-years of follow-up.
[1] Hazard ratio for Dapa 10mg vs placebo, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model stratified by T2DM status at randomization, with factors for treatment group.
[2] Risk difference is computed based on the difference in incidence rates comparing dapagliflozin with placebo. The 95% CI is estimated based on normal approximation to Poisson rates.
[3] An HF event includes hospitalizations for HF and urgent HF visits.
Abbreviations: 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

The treatment effect in the full population is mainly driven by hospitalization for HF (Table 10). The incidence of hospitalization for HF was nominally significantly lower on the dapagliflozin arm compared to placebo arm. The incidence of CV death, and urgent HF visits both trended lower in dapagliflozin arm compared to placebo.

The observed cumulative incidence of the primary composite endpoint for the dapagliflozin arm was lower than that for the placebo arm over the follow-up period (Figure 3), consistent with the above results of the Cox proportional hazards regression.

Figure 3. Kaplan-Meier Curve for the Primary Composite Endpoint, FAS, DELIVER



Source: Statistical Reviewer
Abbreviations: CI, confidence interval; HR, hazard ratio; F, cumulative incidence; FAS, full analysis set; CV, cardiovascular; HF, heart failure

The Applicant conducted the following sensitivity analysis for the primary endpoint in the full population

- Deaths adjudicated as undetermined were included in the primary endpoint (HR: 0.83; 95% CI: (0.74, 0.93); p = 0.001; Risk Difference: -1.7 per 100 PY; 95% CI (per 100 PY): -2.8, -0.7))
- Investigator reported CV death and HF events included in the primary composite endpoint. (HR:0.80, 95% CI: 0.72, 0.89))

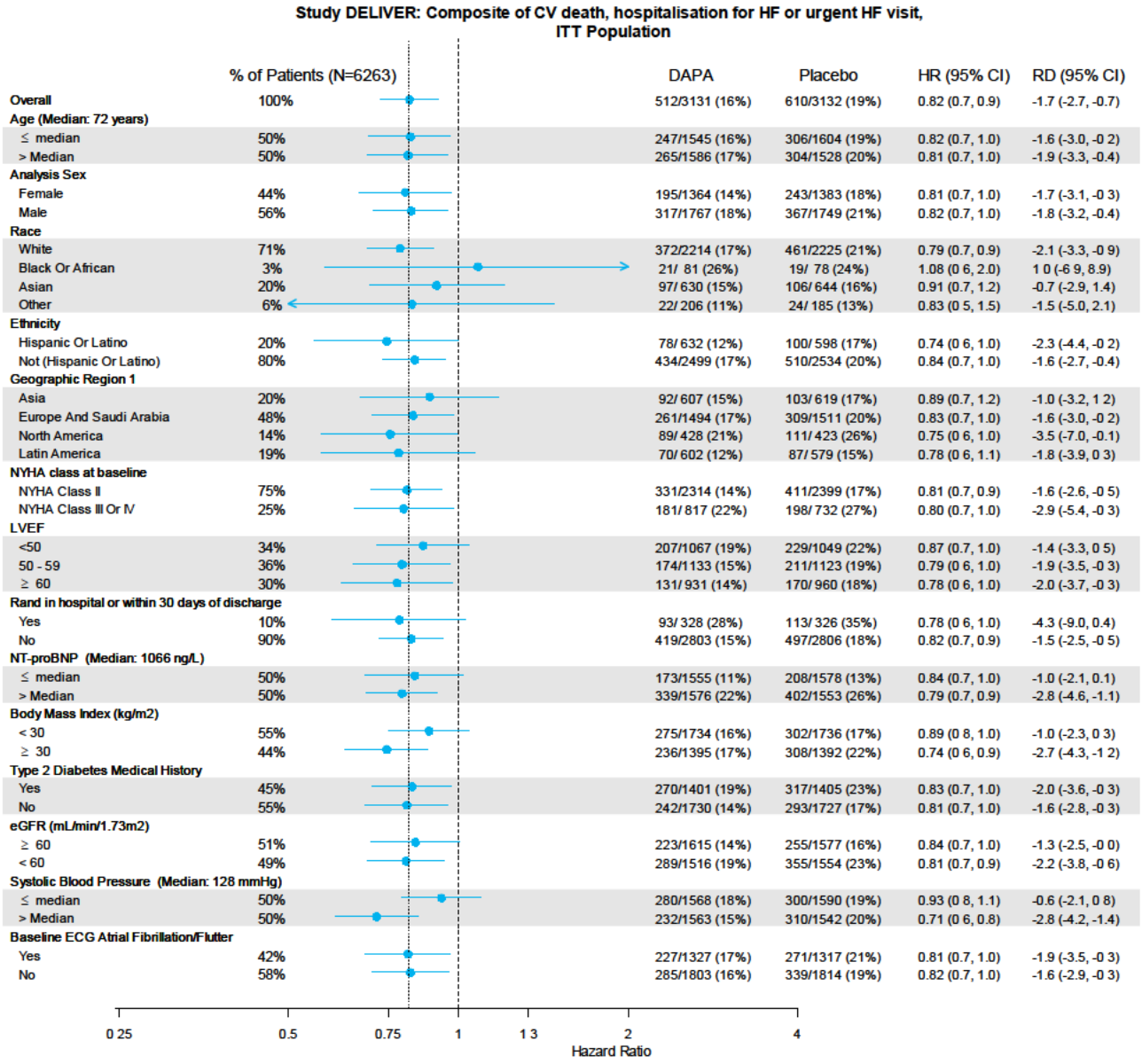
We included the additional sensitivity analysis for the primary endpoint in the full population

- Investigator reported HF events included in the primary composite endpoint. (HR:0.80, 95% CI: 0.72, 0.88))
- Worst-case: 0.85 (95% CI: 0.77, 0.96)

Subgroup analysis

Subgroup analyses were performed for the primary efficacy endpoint for age, sex, race, geographic regions, and prespecified variables of interest and were generally consistent with results in the FAS (Figure 4).

Figure 4. Subgroup Analysis for the Primary Composite Endpoint, FAS, DELIVER



Source: Statistical Reviewer
Ethnicity was included by the Statistical Reviewer
In the Applicant's clinical study report, patients who were randomized in hospital or within 30 days of discharge were labelled as subacute hospitalization for the subgroup analysis.
Abbreviations: FAS, full analysis set; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; NT-proBNP, N-terminal pro–B-type natriuretic peptide, eGFR, estimated glomerular filtration rate; ECG, electrocardiography; DAPA, dapagliflozin, HR, hazard ratio; CI, confidence intervals; RD, risk difference

The Applicant conducted pre-specified analysis in the LVEF <60% population (Table 11). In the LVEF <60% population, the adjusted hazard ratio comparing dapagliflozin with place was 0.83 (95% CI: 0.73, 0.95; two-sided p = 0.009) (Table 11) with findings similar to the full population. Analogous results for the LVEF ≥60% population are presented in Table 12. The primary endpoint for the LVEF ≥60% population was also consistent with the findings in the full population.

Table 11. Primary Efficacy Endpoint and the Individual Components, LVEF <60%, DELIVER

Outcomes	Dapa 10 mg N=2200 n (IR)	Placebo N=2172 n (IR)	HR (95% CI) [1]	Nominal p-Value [1]	Risk Difference (95% CI) [2]
Primary Endpoint	381 (8.2)	440 (9.9)	0.83 (0.73, 0.95)	0.009	-1.7 (-2.9, -0.4)
CV death	186 (3.8)	194 (4.0)	0.95 (0.78, 1.16)	0.6	-0.2 (-1.0, 0.6)
HF event [3]	261 (5.6)	325 (7.3)	0.77 (0.66, 0.91)	0.002	-1.7 (-2.7, -0.6)
Hospitalization for HF	233 (5.0)	299 (6.6)	0.75 (0.63, 0.89)	0.001	-1.7 (-2.6, -0.7)
Urgent HF visit	45 (0.9)	59 (1.2)	0.75 (0.51, 1.10)	0.1	-0.3 (-0.7, 0.1)

Source: Statistical Reviewer
n: The number of events for the individual components are the number of first events for each component and their sum exceeds the number of events for the composite endpoint.
IR: Incidence rates are presented as the number of subjects with first event per 100 patient-years of follow-up.
[1] Hazard ratio for Dapa 10mg vs placebo, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model stratified by T2DM status at randomization, with factors for treatment group.
[2] Risk difference is computed based on the difference in incidence rates comparing dapagliflozin with placebo. The 95% CI is estimated based on normal approximation to Poisson rates.
[3] An HF event includes hospitalizations for HF and urgent HF visits.
Abbreviations: 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

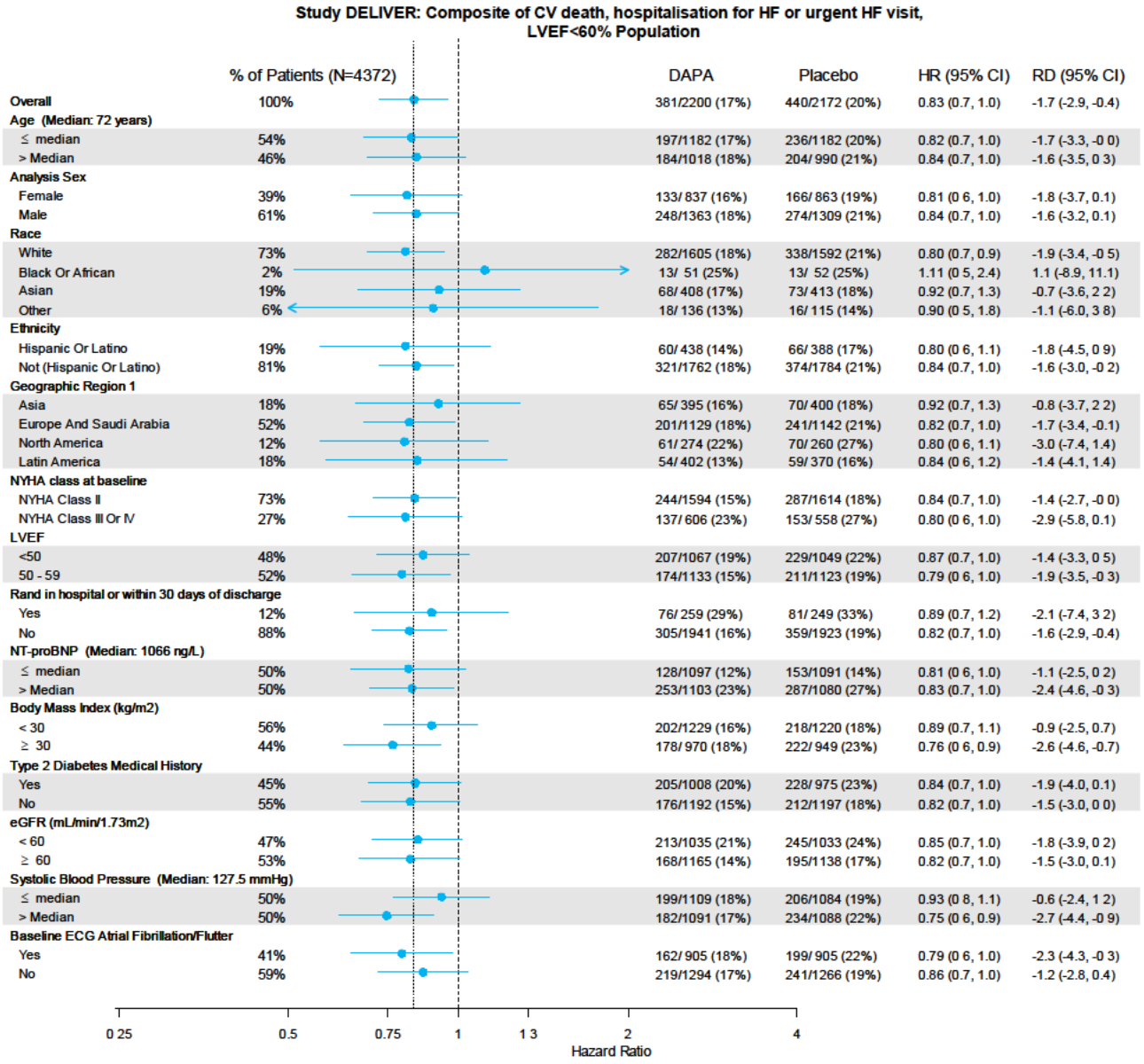
Table 12. Primary Efficacy Endpoint and the Individual Components, LVEF ≥60%, DELIVER

Outcomes	Dapa 10 mg N=931 n (IR)	Placebo N=960 n (IR)	HR (95% CI) [1]	Nominal p-Value [1]	Risk Difference (95% CI) [2]
Primary Endpoint	131 (6.6)	170 (8.5)	0.78 (0.62, 0.98)	0.03	-2.0 (-3.7, -0.3)
CV death	45 (2.1)	67 (3.1)	0.68 (0.47, 1.00)	0.05	-1.0 (-2.0, -0.0)
HF event [3]	107 (5.4)	130 (6.5)	0.83 (0.64, 1.07)	0.2	-1.2 (-2.7, 0.4)
Hospitalization for HF	96 (4.8)	119 (5.9)	0.82 (0.62, 1.07)	0.1	-1.1 (-2.6, 0.3)
Urgent HF visit	15 (0.7)	19 (0.9)	0.80 (0.41, 1.57)	0.5	-0.2 (-0.7, 0.4)

Source: Statistical Reviewer
n: The number of events for the individual components are the number of first events for each component and their sum exceeds the number of events for the composite endpoint.
IR: Incidence rates are presented as the number of subjects with first event per 100 patient-years of follow-up.
[1] Hazard ratio for Dapa 10mg vs placebo, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model stratified by T2DM status at randomization, with factors for treatment group.
[2] Risk difference is computed based on the difference in incidence rates comparing dapagliflozin with placebo. The 95% CI is estimated based on normal approximation to Poisson rates.
[3] An HF event includes hospitalizations for HF and urgent HF visits.
Abbreviations: 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

Subgroup analysis results for the LVEF <60% is shown in Figure 5 **Error! Not a valid bookmark self-reference.**and consistent with the primary findings in the LVEF <60% population. Results for the LVEF ≥60% population are generally consistent with the findings in the LVEF ≥60% population (Figure 8).

Figure 5. Subgroup Analysis for the Primary Composite Endpoint, LVEF <60%, DELIVER



Source: Statistical Reviewer
Ethnicity was included by the Statistical Reviewer
In the Applicant's clinical study report, patients who were randomized in hospital or within 30 days of discharge were labelled as subacute hospitalization for the subgroup analysis.
Abbreviations: FAS, full analysis set; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; NT-proBNP, N-terminal pro–B-type natriuretic peptide, eGFR, estimated glomerular filtration rate; ECG, electrocardiography; DAPA, dapagliflozin, HR, hazard ratio; CI, confidence intervals; RD, risk difference

Secondary Endpoints

Recurrent HF events and CV death

For the FAS population, treatment with dapagliflozin compared to placebo significantly reduced the risk of recurrent HF events and CV death (rate ratio (RR): 0.77; 95% CI: 0.67, 0.89; p<0.001) (Table 13). Results for the CV death and recurrent HF event endpoint in the LVEF <60% subpopulation was similar to the full population (Table 14).

Table 13. Analysis Results for the CV Death and Recurrent HF Event Endpoint, FAS, DELIVER

Outcomes	Dapa 10 Mg N=3131	Placebo N=3132	RR[1]/HR[2] (95% CI)	P-Value
Composite of CV Death and recurrent HF events[1]	815 (11.8)	1057 (15.3)	0.77 (0.67, 0.89) [1]	<0.001
Recurrent HF events[1]	584 (8.4)	796 (11.5)	0.73 (0.62, 0.87) [1]	<0.001
CV Death [2]	231 (3.3)	261 (3.8)	0.88 (0.74, 1.05) [2]	0.17

Source: Statistical Reviewer
Event rates are presented as the number of events per 100 patient-years of follow-up.
[1] Rate ratio for Dapa 10 mg vs placebo, CI, and 2-sided p-value are calculated from the LWYY proportional rates model stratified by T2DM status at randomization, with a factor for treatment group as a covariate. If HF event and CV death occurred on the same day, then only CV death is counted in this table.
[2] Hazard ratio and respective 95% CI are presented based on Cox proportional hazards model stratified by T2DM status at randomization, with a factor for treatment group as a covariate.
Abbreviations: CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure; LWYY, Lin Wei Yang Ying; N, number of subjects in treatment group; T2DM, type 2 diabetes mellitus.

Table 14 Analysis Results for the CV Death and Recurrent HF Event Endpoint, LVEF <60%, DELIVER

Outcomes	Dapa 10 Mg N=2200	Placebo N=2172	RR[1]/HR[2] (95% CI)	P-Value
Composite of CV Death and recurrent HF events[1]	605 (12.5)	782 (16.3)	0.77 (0.65, 0.90) [1]	<0.01
Recurrent HF events[1]	419 (8.7)	588 (12.3)	0.71 (0.58, 0.86) [1]	<0.001
CV Death [2]	186 (3.9)	194 (4.1)	0.95 (0.78, 1.16) [2]	0.61

Source: Statistical Reviewer
Event rates are presented as the number of events per 100 patient-years of follow-up.
1 Rate ratio for Dapa 10 mg vs placebo, CI, and 2-sided p-value are calculated from the LWYY proportional rates model stratified by T2DM status at randomization, with a factor for treatment group as a covariate. If HF event and CV death occurred on the same day, then only CV death is counted in this table.
Hazard ratio and respective 95% CI are presented based on Cox proportional hazards model stratified by T2DM status at randomization, with a factor for treatment group as a covariate
Abbreviations: CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure; LWYY, Lin Wei Yang Ying; N, number of subjects in treatment group; T2DM, type 2 diabetes mellitus

A by-arm summary of the number of patients with recurrent HF events or CV death and recurrent HF events only was reported in Table 15 for the full population (See Table 27 for tabulation in the LVEF <60% population).

Table 15. Number of Events Per Patient for the CV Death and Recurrent HF Events or HF Events Only, FAS, DELIVER

	CV Death and Recurrent HF events		HF Events	
Outcomes	**Dapa 10 Mg N=3131**	**Placebo N=3132**	**Dapa 10 Mg N=3131**	**Placebo N=3132**
With 0 Events	2619	2522	2763	2678
With 1 Events	342	378	250	281
With 2 Events	96	133	63	95
With 3 Events	45	53	39	39
With 4 Events	18	19	7	19
With 5 Events	3	12	1	9
With >5 Events	8	15	8	11

Source: Statistical Reviewer
Abbreviations: Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure; CV, cardiovascular

As reported by the Applicant, the results for KCCQ-TSS at 8 months was limited to the subgroup of subjects who had the 8-month assessment (Visit 5) planned or performed prior to March 11, 2020, was statistically significant. Only 1316 subjects on dapagliflozin and 1311 subjects on placebo had available data for the change from baseline in KCCQ-TSS analysis. The mean change in KCCQ-TSS from baseline at 8 months was 8.3 and 5.2 in the dapagliflozin group and in the placebo group, respectively. The estimated win ratio was 1.11 (95% CI: 1.03, 1.21; p-value from the ranked ANCOVA test = 0.009; Source, Applicant's CSR, Table 20).

CV death endpoint was reported previously in the primary efficacy endpoint section. In summary, there was no difference in CV death between arms despite numerical trends towards dapagliflozin arm (HR: 0.88; 95% CI: 0.74, 1.05; p = 0.17).

There was no difference in all-cause mortality between arms (HR: 0.94; 95% CI: 0.83, 1.07; p = 0.3). A summary of the causes of adjudicated deaths are reported in Table 16. There was numerically more all-cause death in the placebo arm compared to dapagliflozin arm. Among subjects with CV deaths, there were numerically more subjects on placebo compared to dapagliflozin. Of these deaths, more subjects on placebo had CV death recorded as sudden cardiac deaths compared to patients on dapagliflozin.

Table 16. Summary of the Causes of Death, FAS, DELIVER

Cause of Death	Dapa 10 Mg N=3131	Placebo N=3132
Total deaths[1]	495 (16%)	522 (17%)
Total CV Deaths	231 (7.4%)	261 (8.3%)
Sudden Cardiac Death	109 (3.5%)	126 (4%)
Death Due to Heart Failure	79 (2.5%)	85 (2.7%)
Death Due to Stroke	27 (<1%)	25 (<1%)
Death Due to Acute Myocardial Infarction (Mi)	12 (<1%)	15 (<1%)
Death Due to Other Cardiovascular Causes	3 (<1%)	8 (<1%)
Death Due to Cardiovascular Procedures	1 (<1%)	1 (<1%)
Death Due to Cardiovascular Hemorrhage	0 (<1%)	1 (<1%)
Total Non-CV Deaths	197 (6.3%)	188 (6%)
Infection (Includes Sepsis)	123 (3.9%)	112 (3.6%)
Malignancy	41 (1.3%)	47 (1.5%)
Trauma	5 (<1%)	6 (<1%)
Hemorrhage Neither CV Bleeding nor Stroke	6 (<1%)	3 (<1%)
Gastrointestinal Causes	3 (<1%)	4 (<1%)
Neurological (Non-Cardiovascular)	4 (<1%)	3 (<1%)
Other	5 (<1%)	1 (<1%)
Hepatobiliary	3 (<1%)	2 (<1%)
Non-CV Procedure or Surgery	2 (<1%)	3 (<1%)
Renal Failure	1 (<1%)	3 (<1%)
Pancreatic	0 (<1%)	2 (<1%)
Pulmonary Failure	1 (<1%)	1 (<1%)
Suicide	1 (<1%)	1 (<1%)
Inflammatory/Immune	1 (<1%)	0 (<1%)
Prescription Drug Reaction or Overdose	1 (<1%)	0 (<1%)
Undetermined Cause of Death	67 (2.1%)	73 (2.3%)

Source: Statistical Reviewer
[1] Total Deaths is the sum of total CV death, total non-CV deaths, and undetermined cause of death
Abbreviations: FAS, full analysis set; N, number of randomized subjects; n, number of subjects with available data; LVEF, left ventricular ejection fraction, SAS, safety analysis set, Dapa=dapagliflozin

7.4. Review Issues Relevant to the Evaluation of Benefit

7.4.1. Important Review Issue #1 Relevant to Benefit

In DELIVER, a key secondary efficacy variable was the change from baseline at 8 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) TSS. The observed between-group difference in change in KCCQ-TSS from baseline at 8 months of 3.1 points falls below the range deemed clinically meaningful, and while this difference was statistically significant the significance of this change is unknown.

The KCCQ is a 23-item questionnaire that measures symptoms, physical and social limitations, self-efficacy, and quality of life in patients with HF. The self-administered questionnaire represents the patient's perspective of their symptoms mapped to 7 domains (symptom burden, symptom frequency, symptom stability, physical limitations, social limitations, quality of life, and self-efficacy) in patients with heart failure. The patient-reported instrument has a recall period of two weeks to account for the day-to-day variability in heart failure symptoms experienced by patients. The symptom frequency and symptom burden domains constitute the TSS. Scores obtained on the KCCQ-TSS questionnaire are transformed on a 0-to-100-point scale, where lower

scores represent more symptoms and/or limitations and higher scores reflect minimal to no symptoms or limitations, and better function.[23]

Baseline KCCQ-TSS score in DELIVER was defined as the value at the time of randomization (visit 2) and the change from baseline at each post-baseline analysis time point was calculated as the value at the corresponding post-baseline analysis time point minus the baseline value. KCCQ was assessed by the patient at randomization, at the visits targeted 1-, 4- and 8-months following randomization and at premature treatment discontinuation visit (PTDV) and SCV. By the ITT principle, the analysis included all data irrespective of whether the patient has discontinued study drug.

Due to the potential impact of the COVID-19 pandemic on the trial, the Applicant amended the study protocol to analyze this endpoint in subjects who had the 8-month assessment (Visit 5) planned or performed prior to the date when the COVID-19 outbreak was declared a pandemic by the World Health Organization (WHO): March 11, 2020. The rationale for this amendment was that these subjects were the least likely to be affected by the pandemic.

To account for subjects who died prior to the 8-month assessment and to accommodate non-normal distribution of KCCQ scores, a composite rank-based endpoint was used. The values of change from baseline to 8 months in TSS of patients who survived to 8 months was converted to ranks (across both treatment groups combined) with lower ranks attributed to worse outcomes (i.e., lower ranks corresponding to negative or smaller values of change from baseline). Subjects who died prior to the 8-month assessment were assigned the worst rank, i.e., worse than any patient surviving to 8 months. All subjects deceased prior to the 8-month assessment will be assigned the same worst rank regardless of the relative timing of their death reduce the impact of treatment differences in time to CV death on the assessment of this KCCQ secondary endpoint.

To determine what constituted a clinically meaningful within-patient change (CMWPC) from baseline at 8 months in KCCQ-TSS, the Applicant used an anchor-based approach based on patient-reported outcome (PRO) of patient global impression of severity (PGIS) in HF symptoms at baseline and at 8 months performed on the blinded study data. The anchor-based analysis of change from baseline KCCQ-TSS at 8 months in different categories of change from baseline patient global impression of severity (PGIS) at 8 months revealed the following for patients with HF and LVEF >40%:

- An improvement of ≥13 points corresponded to a small or moderate improvement
- An improvement of ≥17 points corresponded to a large improvement
- A deterioration of ≥5 points corresponded to a moderate deterioration
- A deterioration of ≥14 points corresponded to a large deterioration

See appendices for additional details on the Applicant's approach to anchor-based and KCCQ-TSS analyses in DELIVER.

DELIVER evaluated the secondary efficacy endpoint of change in KCCQ -TSS from baseline to 8 months as a measure of symptom improvement in a subpopulation of patients whose planned visit was performed prior to March 11, 2020, prior to COVID-19 being declared a pandemic by WHO.

[23] Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;76(20):2379-2390

In this subpopulation, the mean change in KCCQ-TSS from baseline at 8 months in DELIVER was 8.3 in the dapagliflozin group (n = 1273) and 5.2 in the placebo group (n = 1276). Based on the prespecified rank based ANCOVA analysis, this endpoint was statistically significant (p = 0.0086), with the estimated win ratio of 1.11 (95% CI: 1.03, 1.21) comparing dapagliflozin group with placebo.

This minimally clinically important difference (MCID) in KCCQ scores in HFpEF and the magnitude to which it differs from HFrEF remains unclear. A MCID of 5 points in the KCCQ-OSS has been identified and validated in the literature as representative of clinically meaningful in HFrEF. More recently, a threshold of >9 and ≥7 was identified as meaningful thresholds for or meaningful within-patient change in KCCQ-TSS in patients with HFrEF and HFpEF respectively based on anchor bases analyses and potentially suggests differences in the MCID in KCCQ scores across the spectrum of LVEF.[24]

7.4.2. Important Review Issue #2 Relevant to Benefit

In the summary of clinical efficacy, the Applicant presented pooled efficacy analyses for DAPA-HF and DELIVER for the primary efficacy and CV death endpoints. The rationale provided for the analyses was to assess whether the treatment effect of dapagliflozin in patients with HF is modified by LVEF, and to provide a more precise estimate of the overall treatment effect of CV death. (b) (4)

(b) (4)

[redacted]

[24] Butler J, Shahzeb Khan M, Lindenfeld J, et al. Minimally Clinically Important Difference in Health Status Scores in Patients With HFrEF vs HFpEF. JACC Heart Fail. 2022;10(9):651-661

Table 17. Summary of Baseline Characteristics, DAPA-HF and DELIVER

Baseline Characteristics	DAPA-HF (LVEF <40%) (N=4744)	DELIVER (LVEF ≥40%) (N=6263)
Female (%)	23.4	43.9
Age, Median	67	72
Range (Min, Max)	(22, 94)	(40, 99)
18 to <65	43%	24%
>75	21%	38%
NYHA Class II	3203 (68%)	4713 (75%)
NYHA Class III	1498 (32%)	1531 (24%)
NYHA Class IV	43 (<1%)	18 (<1%)
Medications at Baseline		
ACEi, ARB or ARNI	4442 (94%)	4832 (77%)
Beta blockers	4558 (96%)	5177 (83%)
MRA	71%	2667 (43%)
Diuretics	93%	6123 (98%)
LVEF, Median	32%	54%
Range (Min, Max)	(2%, 45%)	(35%, 88%)

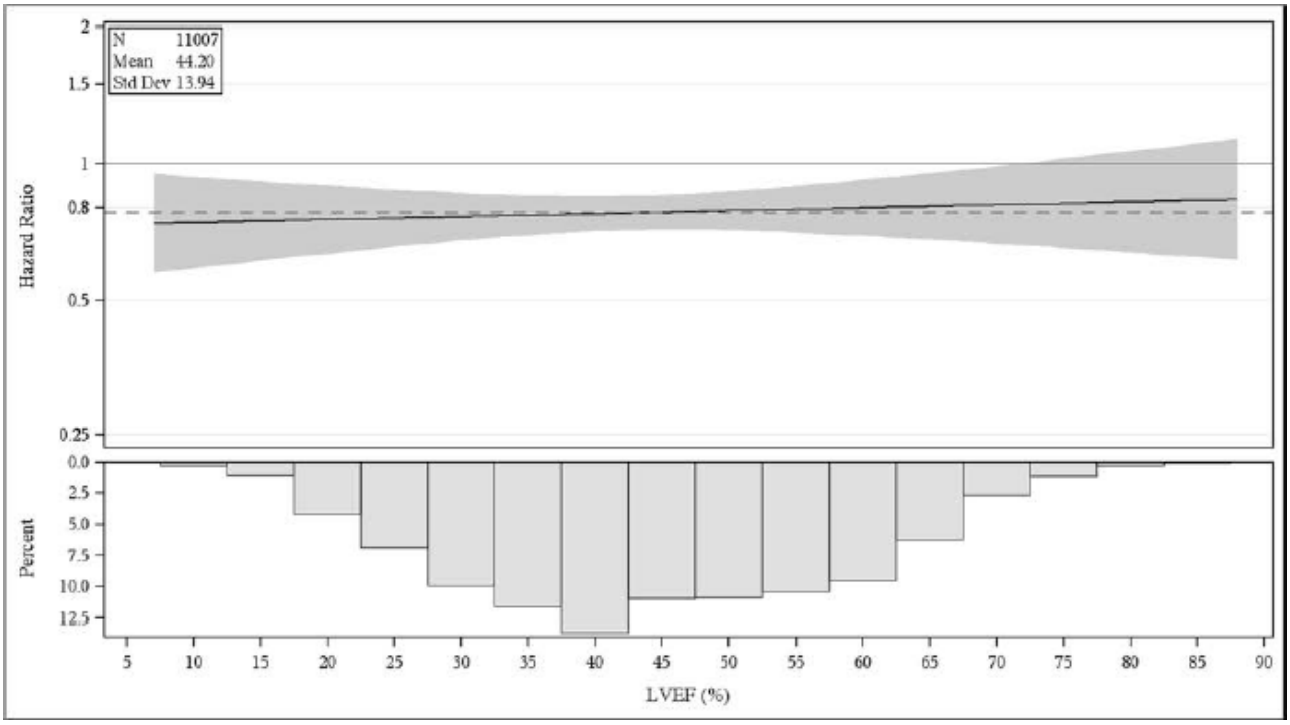
Source: Statistical Reviewer
[1] Total Deaths is the sum of total CV death, total non-CV deaths, and undetermined cause of death
Abbreviations: FAS, full analysis set; N, number of randomized subjects; n, number of subjects with available data; LVEF, left ventricular ejection fraction; SAS, safety analysis set; Dapa=dapagliflozin

(b) (4)

7.4.3. Important Review Issue #3 Relevant to Benefit

The Applicant presented the following linear plot analysis of the primary composite endpoint by baseline LVEF pooling patients from DAPA-HF and DELIVER (Figure 6) in Module 2.7.3 of the Summary of Clinical Efficacy with the objective of providing additional summary of results using pooled analysis for DAPA-HF and DELIVER.

Figure 6. Linear Plot of Hazard Ratio of the Primary Composite Endpoint by Baseline LVEF (%), DAPA-HF, DELIVER



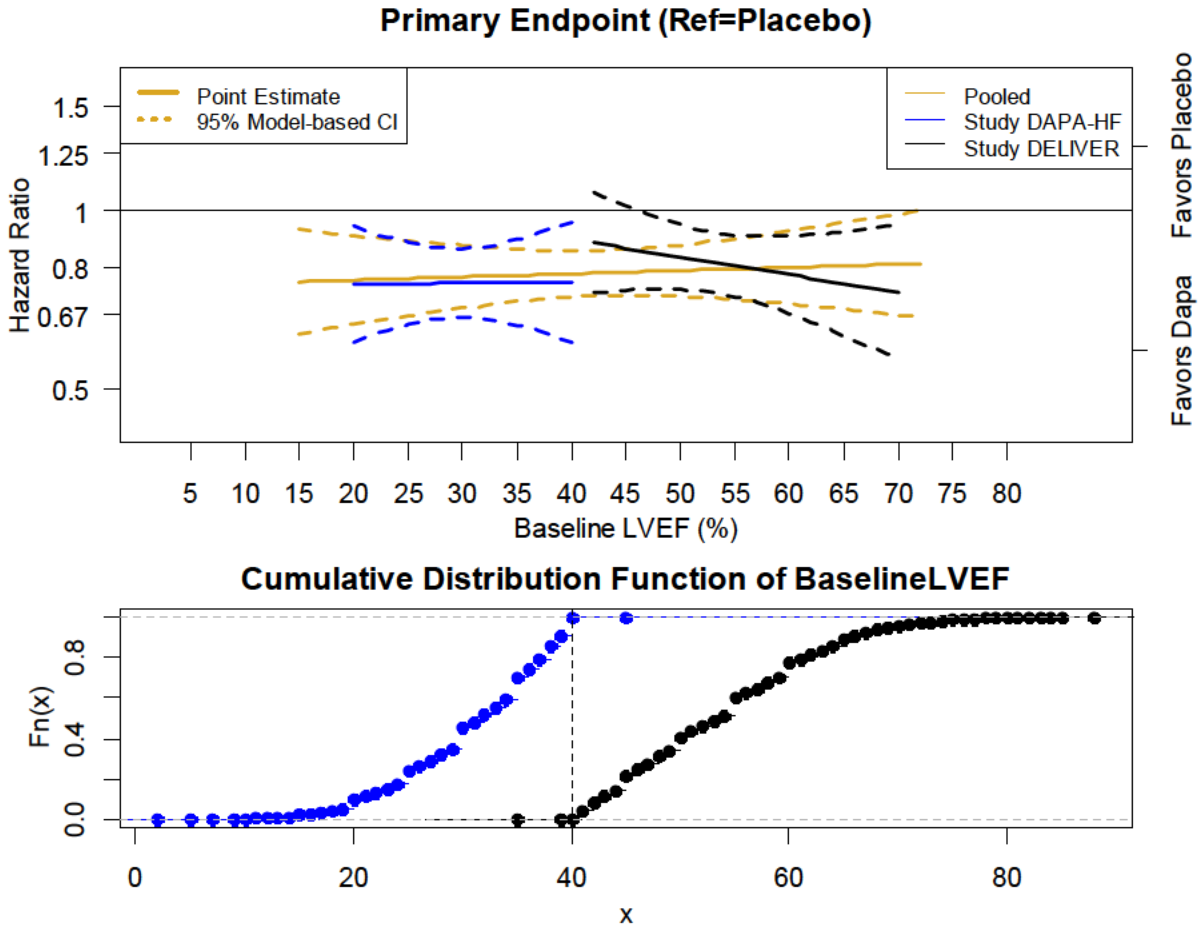
Source: Module 2.7.3, Summary of Clinical Efficacy; Figure 2.7.3.11
Definitions of the primary composite endpoints from each study are used. In DAPA-HF the primary composite endpoint included death with undetermined cause of death. The dotted line represents the overall HR. Hazard ratios for Dapa 10 mg vs placebo and confidence intervals are calculated from Cox proportional hazards model stratified by study and T2DM status at randomization, including in the model the continuous variable LVEF, the treatment group, and the interaction between treatment group and the continuous variable LVEF. Note that history of hospitalization for HF was not found in the submitted pooled dataset.
Abbreviations: Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N, number of subjects; T2DM, type 2 diabetes mellitus.

As noted in Section 7.4.2, the subject population in DAPA-HF had baseline LVEF <40% while subjects randomized in DELIVER had baseline LVEF >40%. There were few patients whose baseline LVEF overlap across the two studies. Specifically, in DELIVER, there were four patients with baseline LVEF ≤40% while in DAPA-HF, there was one patient with LVEF >50%.

Therefore, there were concerns that pooling of patients to model the relationship between the primary endpoint and baseline LVEF could be misleading. Without a substantial overlap of the patient population with baseline LVEF in the 35% to 45% range, the relationship with the primary outcome would be informed by the individual study alone, without accounting for differences in other patient demographics, disease characteristics, or concomitant medications. In addition, the presentation of the above information as modelled by a relatively linear continuous relationship can be misleading.

The statistical reviewer included analogous Cox PH model for each study as shown in Figure 7. Although the relationship between the primary composite endpoint by baseline LVEF has a linear monotonic trend, in DELIVER, the linear trend appeared to differ from the overall pooled trend. There are additional limitations with such an analysis. From the figure, it is unclear whether the distribution of the events across LVEF is considered equal. An alternative and reasonable presentation, though not best, would be to present the forest plots for the primary endpoint by the LVEF cutoff specified in the SAP for each study.

Figure 7. (Top) Linear Plot of Hazard Ratio of the Primary Composite Endpoint by Baseline LVEF (%) for Each Study DAPA-HF, DELIVER, and Pooled. (Bottom) Cumulative Distribution Function of the Baseline LVEF for Each Study.



Source: Statistical Reviewer
A Cox proportional hazards model stratified T2DM status at randomization, including in the model the continuous variable LVEF, the treatment group, and the interaction between treatment group and the continuous variable LVEF was used for each study. In the pooled analysis, the model was further stratified by study.
The top figure shows the relationship between the primary composite endpoint by baseline LVEF modelled and presented for the range of values in each study. Specifically, predicted values of the outcomes based on the Cox model were presented for the range of LVEF between 5th percentile to 95th percentile within each study (blue for DAPA-HF and black for DELIVER). Of note, there is minimal overlap in baseline LVEF at 40% within +/- range.

In summary, the review team recommends that the presentation of the primary composite endpoint by baseline LVEF (%) be presented separately for DELIVER and DAPA-HF based on the issues described above.

8. Risk and Risk Management

8.1. 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.

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

Known safety concerns and laboratory changes based on drug class of SGLT2 inhibitors include the following:

- Ketoacidosis
- Volume depletion
- Urosepsis and pyelonephritis
- Hypoglycemia with concomitant insulin and insulin secretagogues
- Necrotizing fasciitis of the perineum (Fournier's gangrene)
- Genital mycotic infections.
- Transient increase in serum creatinine and decrease in eGFR
- Increase in low density lipoprotein cholesterol (LDL-C)
- Increase in hematocrit

Known safety concerns and laboratory changes for specific SGLT2 inhibitors include the following:

- Lower limb amputation (canagliflozin and ertugliflozin)
- Hypersensitivity reactions (canagliflozin and empagliflozin)
- Bone fracture (canagliflozin)
- Decrease in bone mineral density (canagliflozin)

8.3. Potential Safety Concerns Identified Through Postmarket Experience

There are no new safety concerns identified through additional post-marketing experience than what is already described in the current dapagliflozin labeling.

8.4. FDA Approach to the Safety Review

There are no concerns regarding submission quality, conduct of the studies with respect to assessment of safety, or the Applicant's characterization of adverse events.

The clinical safety review was based on the data collected from the phase 3 Trial, DELIVER (D169CC00001) (Table 3). The safety review was presented for the safety population (defined as randomized population who received at least 1 dose or part of a dose of the investigational medical product [IMP] and analyzed according to the treatment received). The on-treatment period was used for primary analysis of all safety variables, except for adverse events (AEs) with outcome of death, amputations, and preceding events, for which the on- and off-treatment period was considered the primary approach. On-treatment period included events with an onset date and laboratory values taken on or after the date of first IMP dose until 30 days after the last IMP dose. On- and off-treatment period included all events with onset on or after first IMP dose regardless of whether patients were on or off IMP at the time of the event. AEs were presented as the number and percentage of patients with the adverse event and as the absolute risk difference (RD), which was calculated as the difference in the percentage of patients with adverse events between dapagliflozin and placebo groups: negative RD values favor dapagliflozin and positive RD favor placebo.

AEs were primarily analyzed by Medical Dictionary for Regulatory Activities (MedDRA, version 24.1) preferred terms (same as the Applicant's analyses) and by pooling similar AEs using FDA Medical Query [FMQ], Standard MedDRA Query [SMQ, version 24.1], and customized MedDRA Query [CMQ]. Adverse events of special interest (AESIs) were based on the approved product labels of SGLT2 inhibitors and the mechanism of action of dapagliflozin. In addition to performing additional queries (described in Table 18), the safety reviewer evaluated all Applicant defined AESIs.

Table 18. AESI Approach for Dapagliflozin

AESI	Applicant's Approach	Reviewer's Additional Queries
Volume depletion	Pre-defined PT list	Broad FMQ "Volume depletion"
Renal events	Pre-defined list of PTs identified based on narrow SMQ of "Acute renal failure"	Broad FMQ "Acute kidney injury"; broad SMQ "Acute renal failure"
Fournier's gangrene	Pre-defined PT list	–
Genital infection	Pre-defined PT list	Customized PT list
Urinary tract infection	Pre-defined PT list	Customized PT list
Diabetic ketoacidosis	Investigator's opinion as collected on the dedicated eCRF and adjudication by an independent, blinded adjudication committee	Narrow FMQ "Diabetic ketoacidosis"
Major hypoglycemia	Investigator's opinion as collected on the dedicated eCRF	Narrow FMQ "Hypoglycemia"
Amputations	Investigator's opinion as collected on the dedicated eCRF	–
AEs leading to amputations	Investigator's opinion as collected on the dedicated eCRF	–
Potential risk factor AEs for amputations affecting lower limbs (Preceding events)	Pre-defined list of PTs identified by EMA Pharmacovigilance Risk Assessment Committee	–
Myocardial infarction	Investigator's opinion as collected on the dedicated eCRF	–
Unstable angina	Investigator's opinion as collected on the dedicated eCRF	–
Stroke	Investigator's opinion as collected on the dedicated eCRF	–

Source: Reviewer's table
Abbreviations: AE, adverse event; eCRF, electronic case report form; EMA, European Medicines Agency; FMQ, FDA medical query; PT, preferred term; SMQ, standard MedDRA query
The statistical software R was used for safety analyses.

8.5. Adequacy of the Clinical Safety Database

Dapagliflozin was administered to a total of 3126 subjects and placebo was administered to a total of 3127 subjects (Table 19). Exposure was balanced between the dapagliflozin and the placebo groups in DELIVER. There were over 2500 subjects who had exposure to dapagliflozin longer than 52 weeks.

Table 19. Duration of Exposure, Safety Population, DELIVER

Exposure	Dapa 10mg N=3126 n (%)	Placebo N=3127 n (%)
Duration of treatment, days		
Mean (SD)	740.0 (317.4)	741.4 (313.2)
Median (min, max)	807.5 (1.0, 1266.0)	810.0 (1.0, 1259.0)
Patients treated, by duration, n (%)		
≥12 weeks	2987 (95.6%)	3005 (96.1%)
≥36 weeks	2782 (89.0%)	2810 (89.9%)
≥52 weeks	2675 (85.6%)	2694 (86.2%)
≥78 weeks	2283 (73.0%)	2277 (72.8%)
≥104 weeks	1859 (59.5%)	1865 (59.6%)
≥156 weeks	363 (11.6%)	363 (11.6%)

Source: Reviewer's analysis [adsl, adex]; Software: R
Abbreviations: dapa, dapagliflozin; N, number of patients in treatment group; n, number of patients with given treatment duration; SD, standard deviation
Applicant's reference CSR table: 14.3.1.1

Reviewer's Comment: *The safety exposure to dapagliflozin was adequate both in terms of the number of patients exposed to study drug and the duration of exposure to support the safety evaluation.*

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

The safety evaluation of dapagliflozin in DELIVER was adequate and acceptable for the proposed indication.

8.6.1. Overall Adverse Event Summary

There were no important imbalances in the incidence of deaths, serious treatment-emergent adverse events (TEAEs), and TEAEs leading to discontinuation between treatment groups in DELIVER (Table 20).

Table 20. Overview of Adverse Events, Safety Population, DELIVER, On-Treatment[1]

Event	Dapa 10mg N=3126 n (%)	Placebo N=3127 n (%)	Absolute Risk Difference (95.0% CI)[2]
Any AE	2026 (64.8%)	2152 (68.8%)	-4.0 (-6.3, -1.7)
Severe	814 (26.0%)	870 (27.8%)	-1.8 (-4.0, 0.4)
Moderate	1074 (34.4%)	1142 (36.5%)	-2.2 (-4.5, 0.2)
Mild	1165 (37.3%)	1247 (39.9%)	-2.6 (-5.0, -0.2)
SAE	1361 (43.5%)	1423 (45.5%)	-2.0 (-4.4, 0.5)
Death	401 (12.8%)	421 (13.5%)	-0.6 (-2.3, 1.0)
Life-threatening	317 (10.1%)	334 (10.7%)	-0.5 (-2.1, 1.0)
Persistent or significant disability/incapacity	114 (3.6%)	125 (4.0%)	-0.4 (-1.3, 0.6)
Requires or prolongs hospitalization	1147 (36.7%)	1198 (38.3%)	-1.6 (-4.0, 0.8)
Congenital anomaly or birth defect	2 (0.1%)	3 (0.1%)	-0.0 (-0.2, 0.1)
Other	641 (20.5%)	640 (20.5%)	0.0 (-2.0, 2.0)
AE leading to permanent discontinuation	182 (5.8%)	181 (5.8%)	0.0 (-1.1, 1.2)
AE leading to interruption of study drug	436 (13.9%)	494 (15.8%)	-1.9 (-3.6, -0.1)

Source: Reviewer's analysis [adsl, adae]; Software: R
Abbreviations: AE, adverse event; dapa, dapagliflozin; IMP, investigational medical product; CI, confidence interval; N, number of patients in treatment group; n, number of patients with an event; SAE, serious adverse event
[1]On-treatment period includes AEs with an onset after the first IMP dose until 30 days after the last IMP dose.
[2]Difference is shown between dapagliflozin 10mg and placebo.
Applicant's reference CSR table: 14.3.2.1

8.6.2. Deaths

There was no imbalance in the incidence of deaths between treatment groups in DELIVER (Table 21). In both groups, common TEAEs that resulted in death were cardiac failure and COVID-19 pneumonia.

Table 21. AEs Leading to Deaths with PTs >0.2% in Any Treatment Group, Safety Population, DELIVER, On- and Off-Treatment[1]

Preferred Term[2]	Dapa 10 mg N=3126 n (%)	Placebo N=3127 n (%)	Absolute Risk Difference (95.0% CI)[3]
AEs leading to death	507 (16.2%)	529 (16.9%)	-0.7 (-2.5, 1.1)
Cardiac failure	61 (2.0%)	61 (2.0%)	0.0 (-0.7, 0.7)
Death	54 (1.7%)	52 (1.7%)	0.1 (-0.6, 0.7)
COVID-19 pneumonia	42 (1.3%)	36 (1.2%)	0.2 (-0.4, 0.7)
Sudden cardiac death	26 (0.8%)	37 (1.2%)	-0.4 (-0.8, 0.1)
Sudden death	24 (0.8%)	26 (0.8%)	-0.1 (-0.5, 0.4)
COVID-19	23 (0.7%)	16 (0.5%)	0.2 (-0.2, 0.6)
Pneumonia	20 (0.6%)	17 (0.5%)	0.1 (-0.3, 0.5)
Cardiac arrest	17 (0.5%)	15 (0.5%)	0.1 (-0.3, 0.4)
Ischemic stroke	17 (0.5%)	15 (0.5%)	0.1 (-0.3, 0.4)
Septic shock	13 (0.4%)	12 (0.4%)	0.0 (-0.3, 0.3)
Acute respiratory failure	9 (0.3%)	6 (0.2%)	0.1 (-0.1, 0.3)
Acute myocardial infarction	8 (0.3%)	8 (0.3%)	0.0 (-0.3, 0.3)
Myocardial infarction	8 (0.3%)	12 (0.4%)	-0.1 (-0.4, 0.2)
Sepsis	8 (0.3%)	12 (0.4%)	-0.1 (-0.4, 0.2)
Cardiac failure acute	7 (0.2%)	4 (0.1%)	0.1 (-0.1, 0.3)
Suspected COVID-19	7 (0.2%)	5 (0.2%)	0.1 (-0.2, 0.3)
Cardiogenic shock	6 (0.2%)	8 (0.3%)	-0.1 (-0.3, 0.2)
Cardiac failure congestive	5 (0.2%)	18 (0.6%)	-0.4 (-0.7, -0.1)
Respiratory failure	2 (0.1%)	9 (0.3%)	-0.2 (-0.4, -0.0)

Source: Reviewer's analysis [adsl, adae]; Software: R
Abbreviations: AE, adverse event; dapa, dapagliflozin; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an AE leading to death
[1]On-and off-treatment period includes AEs with an onset on or after first IMP dose regardless of whether patients were on or off IMP at the time of the event.
[2]MedDRA version: 24.1
[3]Difference is shown between dapagliflozin 10mg and placebo.
Applicant's reference CSR table: 14.3.3.4

8.6.3. Serious Adverse Events

There were no important imbalances in serious adverse events (SAEs) between treatment groups in DELIVER (Table 22). There were no SAEs reported with a RD >0.5% except COVID-19.

There were no unexpected SAEs grouped by FMQs or SMQs (narrow and broad) reported in DELIVER (data not shown).

Table 22. Serious Adverse Events With Risk Difference >0.2%, Safety Population, DELIVER, On-Treatment[1]

Primary System Organ Class	Dapa 10 mg N=3126	Placebo N=3127	Absolute Risk Difference
Preferred Term[2]	n (%)	n (%)	(95.0% CI)[3]
Cardiac disorders	577 (18.5%)	664 (21.2%)	-2.8 (-4.8, -0.8)
Atrial fibrillation	57 (1.8%)	47 (1.5%)	0.3 (-0.3, 1.0)
Atrial flutter	10 (0.3%)	2 (0.1%)	0.3 (0.0, 0.5)
Infections and infestations	512 (16.4%)	506 (16.2%)	0.2 (-1.6, 2.0)
COVID-19	165 (5.3%)	131 (4.2%)	1.1 (0.0, 2.1)
Cellulitis	31 (1.0%)	18 (0.6%)	0.4 (-0.0, 0.9)
Injury, poisoning and procedural complications	83 (2.7%)	86 (2.8%)	-0.1 (-0.9, 0.7)
Spinal compression fracture	10 (0.3%)	2 (0.1%)	0.3 (0.0, 0.5)
Vascular disorders	81 (2.6%)	64 (2.0%)	0.5 (-0.2, 1.3)
Peripheral arterial occlusive disease	22 (0.7%)	14 (0.4%)	0.3 (-0.1, 0.6)
Metabolism and nutrition disorders	62 (2.0%)	72 (2.3%)	-0.3 (-1.0, 0.4)
Hypokalaemia	9 (0.3%)	2 (0.1%)	0.2 (0.0, 0.4)

Source: Reviewer's analysis [adsl, adae]; Software: R
Abbreviations: AE, adverse event; CI, confidence interval; dapa, dapagliflozin; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event
[1]On-treatment period includes AEs with an onset after the first IMP dose until 30 days after the last IMP dose.
[2]MedDRA version: 24.1
[3]Difference is shown between dapagliflozin 10mg and placebo.
Applicant's reference CSR table: 14.3.4.3

8.6.4. Dropouts and/or Discontinuations Due to Adverse Events

In DELIVER, less than 6% of subjects had TEAEs that led to study drug discontinuation (Table 20). None of the TEAEs leading to study drug discontinuation in dapagliflozin had RD >0.2% (Table 23).

Table 23. Adverse Events Leading to Discontinuation With Risk Difference >0.1%, Safety Population, DELIVER, On-Treatment[1]

Primary System Organ Class	Dapa 10mg N=3126	Placebo N=3127	Absolute Risk Difference
Preferred Term[2]	n (%)	n (%)	(95.0% CI)[3]
Infections and infestations	35 (1.1%)	28 (0.9%)	0.2 (-0.3, 0.7)
Urinary tract infection	11 (0.4%)	6 (0.2%)	0.2 (-0.1, 0.4)
Vascular disorders	7 (0.2%)	5 (0.2%)	0.1 (-0.2, 0.3)
Hypotension	6 (0.2%)	1 (<0.1%)	0.2 (-0.0, 0.3)

Source: Reviewer's analysis [adsl, adae]; Software: R
Abbreviations: AE, adverse event; CI, confidence interval; dapa, dapagliflozin; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event
[1]On-treatment period includes AEs with an onset after the first IMP dose until 30 days after the last IMP dose.
[2]MedDRA version: 24.1
[3]Difference is shown between dapagliflozin 10mg and placebo.
Applicant's reference CSR table: 14.3.5.2

8.6.5. Adverse Events of Special Interest

Table 24 and Table 25 summarize Applicant-defined AESIs and Reviewer's additional queries in DELIVER. Commonly reported AESIs (>5%) in either treatment group were renal events, urinary tract infection (UTI), and potential risk factor AEs for amputations affecting lower limbs (preceding events) in DELIVER. Volume depletion (4.6% and 3.9% in dapagliflozin and placebo groups, respectively), UTI (5.2% and 4.9%, respectively), and genital infection (0.9% and 0.4%, respectively) occurred at a slightly higher frequency in subjects treated with dapagliflozin in DELIVER. These AEs are consistent with the known clinical profile of dapagliflozin and other selective SGLT2 inhibitors. There were no imbalances in the other AESIs between treatment groups.

Sensitivity analyses using Reviewer's additional queries for AESIs provided similar results as Applicant defined AESIs (Table 24 and Table 25), and hence, AESIs are presented based on Applicant's definition in the section below.

Table 24. Adverse Events of Special Interest, Safety Population, DELIVER, On-Treatment[1]

	SAE		DAE	
AESI	Dapa 10 mg N=3126 n (%)	Placebo N=3127 n (%)	Dapa 10 mg N=3126 n (%)	Placebo N=3127 n (%)
Volume depletion				
Applicant defined	35 (1.1%)	31 (1.0%)	9 (0.3%)	3 (0.1%)
FMQ, broad	14 (0.4%)	9 (0.3%)	4 (0.1%)	3 (0.1%)
Urinary tract infections				
Applicant defined	41 (1.3%)	37 (1.2%)	13 (0.4%)	9 (0.3%)
CMQ	46 (1.5%)	47 (1.5%)	16 (0.5%)	11 (0.4%)
Genital infections				
Applicant defined	1 (<0.1%)	1 (<0.1%)	3 (0.1%)	0 (0.0%)
CMQ	3 (0.1%)	6 (0.2%)	5 (0.2%)	1 (<0.1%)
Fournier's gangrene				
Applicant defined	1 (<0.1%)	3 (0.1%)	0 (0.0%)	1 (<0.1%)
Renal events				
Applicant defined	57 (1.8%)	68 (2.2%)	23 (0.7%)	18 (0.6%)
FMQ, broad	59 (1.9%)	69 (2.2%)	23 (0.7%)	23 (0.7%)

Source: Reviewer's analysis [adsl, adae]; Software: R
Abbreviations: AE, adverse event; CMQ, customized MedDRA query; dapa, dapagliflozin; FMQ, FDA medical query; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event; SMQ, standard MedDRA query
[1]On-treatment period includes AEs with an onset after the first IMP dose until 30 days after the last IMP dose.
Applicant's reference CSR table: 14.3.11.1, 14.3.11.3, 14.3.11.7, 14.3.11.12, and 14.3.11.15

Table 25. Adverse Events of Special Interest, Safety Population, DELIVER

AESI	Dapa 10 mg N=3126 n (%)	Placebo N=3127 n (%)
DKA[1]		
Applicant defined (Definitive DKA)	2 (0.1%)	0 (0.0%)
FMQ, narrow	3 (0.1%)	3 (0.1%)
Major hypoglycemia[1]		
Applicant defined	6 (0.2%)	7 (0.2%)
FMQ, narrow (Hypoglycemia)	32 (1.0%)	30 (1.0%)
Amputations[2] (Applicant-defined)	19 (0.6%)	26 (0.8%)
AEs leading to amputation[2] (Applicant-defined)	19 (0.6%)	26 (0.8%)
Potential risk factor AEs for amputations affecting lower limbs (Preceding events)2, Applicant-defined	206 (6.6%)	218 (7.0%)
Myocardial infarction[1]	68 (2.2%)	71 (2.3%)
Unstable angina[1]	53 (1.7%)	70 (2.3%)
Stroke[1]	106 (3.4%)	101 (3.2%)

Source: Reviewer's analysis [adsl, adae, adce, adtte]; Software: R
Abbreviations: AE, adverse event; CMQ, customized MedDRA query; dapa, dapagliflozin; FMQ, FDA medical query; IMP, investigational medical product; N, number of patients in treatment group; n, number of patients with an event; SMQ, standard MedDRA query
[1]DKA, major hypoglycemia, myocardial infarction, unstable angina, and stroke were analyzed for the on-treatment period. There were no events of probable DKA in any treatment group.
[2]Amputations, AEs leading to amputations, and preceding events were analyzed for the on-and off-treatment period.
Applicant's reference CSR table: 14.3.2.1 and 14.3.2.2

8.6.5.1. Volume Depletion

There were no imbalances in the incidence of SAEs of volume depletion between treatment groups (Table 24). The three most commonly reported SAEs of volume depletion by preferred term (PT),

were syncope, hypotension, and dehydration in both treatment groups. There were three cases of volume depletion with a fatal outcome: two in the dapagliflozin group and one in the placebo group.

Reviewer's Comment: *All 3 patients with a fatal case of volume depletion had multiple severe underlying conditions and were on IMP for at least one year before the fatal event occurred. The cause of death in all 3 fatal cases was likely associated with patients' medical condition and was not related to dapagliflozin.*

The incidence of adverse event leading to discontinuation of IP (DAEs) of volume depletion were uncommon and numerically higher in the dapagliflozin group (Table 24).

8.6.5.2. Urinary Tract Infections

There were no imbalances in the incidence of SAEs and DAEs of UTIs between treatment groups (Table 24). The most common SAE of UTI, by preferred term (PT), was urinary tract infection, occurring in 30 subjects (1.0%) in the dapagliflozin group and 32 subjects (1.0%) in the placebo group.

8.6.5.3. Genital Infections and Fournier's Gangrene

The incidence of SAEs and DAEs of genital infections were rare. Two subjects, one in each treatment group, had an SAE of genital infection. There were three subjects with a DAE of genital infection in the dapagliflozin group and none in the placebo group. There were no fatal events related to genital infection.

The incidence of Fournier's gangrene is shown in Table 24. No events were confirmed as Fournier's gangrene in DELIVER, based on internal blinded clinical review of SAEs and DAEs.

8.6.5.4. Renal Events

The Applicant evaluated renal AEs using the narrow SMQ of "acute renal failure." There were no imbalances in the incidence of renal SAEs and DAEs between treatment groups (Table 24). There were 11 cases of renal events with a fatal outcome: 5 in the dapagliflozin group and 6 in the placebo group.

Reviewer's Comment: *Of 5 patients with fatal outcomes in the dapagliflozin group, 4 patients received dapagliflozin treatment from 16-24 months and 1 patient, admitted to hospital for cardiopulmonary arrest, received dapagliflozin treatment for 1 month. The cause of death in all 5 fatal cases was likely associated with patients' underlying medical condition and was not related to dapagliflozin.*

8.6.5.5. Diabetic Ketoacidosis

An independent, blinded adjudication committee reviewed and adjudicated all potential events of diabetes ketoacidosis (DKA). There were 17 potential DKA events in 15 patients (0.5%) in the dapagliflozin group and 20 events in 20 subjects (0.6%) in the placebo group that were sent for adjudication. The incidence of adjudicated DKA events is shown in Table 25. There were 2 subjects with definite DKA events in the dapagliflozin group compared with none in the placebo group. Both subjects had T2DM and were treated with insulin, and none of the events had a fatal outcome. There were no events of probable DKA in any treatment group. There were no events of probable or definitive DKA during the off-treatment period.

8.6.5.6. Major Hypoglycemia

Major hypoglycemia was identified based on investigator's opinion as an event where all the following criteria were met: (1) symptoms of severe impairment in consciousness or behavior, (2) need of external assistance, (3) intervention to treat hypoglycemia, and (4) prompt recovery of acute symptoms following the intervention.

There were no imbalances in the incidence of major hypoglycemia between treatment groups (Table 25). All major hypoglycemia events were reported in subjects with T2DM.

8.6.5.7. Amputations and AEs leading to Amputations

There were no imbalances in the incidence of surgical or spontaneous/non-surgical amputation or AEs leading to amputation between treatment groups (Table 25). All but one (in placebo group) were surgical amputations; all but one (in dapagliflozin group) were lower limb amputations; and all but 4 subjects in each treatment group had T2DM at baseline. The numbers of subjects with major amputations (below knee and above knee) were the same in both treatment groups (8 patients in each treatment group).

Most common precipitating events leading to amputation were osteomyelitis, peripheral arterial occlusive disease, or peripheral ischemia in DELIVER.

8.6.5.8. Preceding Events

There were no imbalances in the incidence of potential risk factor AEs for amputations affecting lower limbs (preceding events) between treatment groups (Table 25). The most common AEs were diabetic foot related AEs (e.g., cellulitis and skin ulcer) and vascular AEs (e.g., peripheral arterial occlusive disease). Of subjects with preceding events, 18 subjects (0.6%) in the dapagliflozin group and 25 subjects (0.8%) in the placebo group had subsequent amputations.

8.6.6. Laboratory and Vital Signs Findings

Section 6.1 Clinical Studies Experience of the current label describes increases in serum creatinine, hematocrit, low density lipoprotein (LDL) and decreases in eGFR and serum bicarbonate. In DELIVER, there were no new laboratory or vital signs findings than what is previously known about this product.

8.7. Review Issues Relevant to the Evaluation of Risk

There were no review issues identified and all AEs were adequately described in the current product labeling.

9. Therapeutic Individualization

9.1. Intrinsic Factors

Not applicable

9.2. Drug Interactions

Not applicable

9.3. Pediatric Labeling/Plans for Pediatric Drug Development

In accordance with 21 Code of Federal Regulations (CFR)314.55(c)(2)(ii), The Applicant requested a full waiver from the Pediatric Research Equity Act (PREA) requirement to evaluate the effect of dapagliflozin on CV death or worsening heart failure in a HFpEF pediatric population. The rationale for the request for a full waiver was because trials in the pediatric population are going to be impossible or highly impracticable because the number of pediatric patients with HFpEF physiology is too small and the outcome of any such study will not represent meaningful improvement on currently available therapies.

9.4. Pregnancy and Lactation

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

10. Product Quality

Not applicable

10.1. Device or Combination Product Considerations

Not applicable

11. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

DELIVER Trial was performed in accordance with the ethical principles laid out in the Declaration of Helsinki, practices consistent with the International Council for Harmonization (ICH)/Good Clinical Practice (GCP), all applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. The study and all amendments were approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of each investigational center prior to the implementation of the trial at that center.

12. Advisory Committee Summary

Not applicable

III. Appendices

13. Summary of Regulatory History

Applicant-FDA meetings related to the DELIVER are listed below:

November 6, 2017, Written Responses to Applicant's Type B meeting request

The Applicant requested a type B meeting to obtain FDA advice on the appropriateness of the proposed randomized, placebo or dapagliflozin added to standard of care treatment study to support an expanded indicated for HFpEF in the Dapagliflozin label. This study would be in addition to an ongoing study outcome study to investigate the efficacy and safety of dapagliflozin in adult patients with heart failure with reduced ejection fraction (HFrEF), defined as LVEF ≤40%. FDA recommendations provided in the written response are outlined below:

(1) If both studies are well-conducted and successful at a $p < 0.05$, data from your study in patients with HFrEF could be used to support a marketing application for the treatment of patients with heart failure with preserved ejection fraction (HFpEF), defined as LVEF >40%.
(2) The proposed primary endpoint of time to the first component of a composite endpoint of cardiovascular (CV) death or a decompensated HF event (hospitalization for HF or urgent HF visit, e.g., emergency or outpatient visit) was deemed acceptable
Agreement was reached on the proposed definition of HF events to include both HF hospitalizations and unplanned HF visits requiring urgent treatment independently of whether the exacerbation of HF results in hospitalization
FDA agreed with the Applicant's proposed plan for adjudication of HF events under an established clinical events classification (CEC) charter with pre-specified criteria which include discharge summaries, admission note and physical examination, relevant progress or consultation notes/treatment provided, echocardiogram, right heart catheterization report, central laboratory reports, i.e., proBNP, local lab reports (NT-proBNP and ischemic biomarkers troponin/CKMB), chest X-ray or chest imaging report, and other non-invasive cardiac testing reports (e.g., radionuclide measurement of LV ejection fraction, ECG).
(3) FDA advised the Applicant not to include all-cause mortality in the testing chain for secondary endpoints (total number of recurrent HF events and CV death, CV death, CV hospitalization, all-cause mortality, NYHA class and all-cause hospitalization) since an effect on all-cause mortality is likely to be driven by the effect on cardiovascular death.
(4) Agreement was reached on the proposal that safety data will only be collected for serious adverse events (SAEs), adverse event leading to discontinuation of IP (DAEs) (including diabetic ketoacidosis [DKA] and other AEs of interest for dapagliflozin), and events of amputations May 8, 2018, New IND submission for DELIVER Study may proceed letter issued on June 21, 2018, with the following comments The agency recommended sparse PK sample collection in subjects.

May 8, 2018, New IND submission for DELIVER

Study may proceed letter issued on June 21, 2018, with the following comments

(1) The agency recommended sparse PK sample collection in subjects

(2) The agency advised the Applicant to ensure adequate representation of heart failure centers in U.S., Canada, and Western Europe who are likely to provide care similar to U.S. standard of care, collect biomarkers (BNP/NTproBNP) from the time of admission and at randomization to provide a sense of volume status at the time of randomization.
(3) The agency requested justification for age cut-off (>40 years of age) for inclusion criteria
(4) The agency requested clarification on the collection of efficacy events
(5) The agency required disclosure on ICD that another SGLT2 inhibitor is approved to reduce cardiovascular mortality in patients with type 2 diabetes and established cardiovascular disease.
(6) The agency requested the submission of the SAP and clinical events classification (CEC) Charter by the Applicant for review prior to or shortly after study initiation to mitigate any concern that knowledge of study findings influenced your endpoint definitions, analytic plan, or trial results. Clarification on details of interim analyses and statistical implications requested from Applicant.

September 27, 2018, SAP version 1.0 submitted for DELIVER Trial

November 21, 2018, CEC Charter for DELIVER Trial submitted

December 24, 2019, Initial Pediatric Study Plan submitted

(1) Request for full waiver from Pediatric studies submitted by the Applicant, however after PeRC discussions, the Division requested that the Applicant amend plans for full waivers to include a plan for pediatric studies in symptomatic heart failure. The age range included in pediatric studies may not be decided until a later date. After the Applicant submitted an amendment on May 18, 2020, an agreement was reached to grant a full waiver from the Pediatric Research Equity Act (PREA) requirement to evaluate the effect of dapagliflozin on exercise capacity in a HFpEF pediatric population, as necessary studies are impossible or highly impractical because the number of such patients with HFpEF physiology is so small and HFpEF is not a diagnosis that is clearly distinguished in children.

December 22, 2020, SAP amendments version 2.0 and 3.0 submitted to the agency

March 19, 2021, Breakthrough Therapy Designation Request

Request for Breakthrough Therapy designation denied on the basis that the preliminary clinical evidence you submitted did not indicate that the drug demonstrated substantial improvement over existing therapies on one or more clinically significant endpoints.

May 24, 2021, SAP amendment version 4 submitted

September 7, 2021, Pre sNDA Meeting Request submitted

(1) FDA WRO meeting minutes on November 3, 2021, provided response to Applicant requests for adequacy of draft submission to support planned sNDA for DELIVER
(2) FDA disagreed with proposal regarding evaluation of efficacy in DELIVER sNDA. Specifically concerns on the potential inflation of the Type 1 error rate based on the assumptions of the mathematical model used to calculate type I error.
(3) The Agency agreed to waive the 4 Month Safety Update (4-MSU) requirement for the planned FARXIGA® DELIVER sNDA.

May 17, 2022, Top Line Results

The Applicant presented the results of DELIVER Trial, Highlights of the discussion are outlined below:

(1) The Applicant requested priority review based on the proposed indication, however the Division explained that priority review is generally based on an indication and an unmet medical need. The proposed indication is similar to the already approved empagliflozin and while CV death outcomes may appear better when DAPA-HF and DELIVER trial data are pooled, the approach to assigning alpha to the meta-analysis is unclear.
(2) The Division stated the overall effect of CV mortality and the benefit across the LVEF spectrum would be detailed in section 14 of the label. There are ongoing considerations on the best presentation of treatment effect by LVEF. Various approaches have their own limitations.
(3) [redacted] (b) (4)

14. Pharmacology Toxicology Assessments and Additional Information

Not applicable

15. Clinical Pharmacology Assessment: Additional Information

Not applicable

16. Trial Design: Additional Information and Assessment

Full study protocol for DELIVER[25] can be obtained from the supplementary material provided at:

https://www.nejm.org/doi/full/10.1056/NEJMoa2206286

Summary of Protocol Amendments

The original Clinical Study Protocol (CSP) was dated April 24, 2018. There were three amendments to the CSP dated May 9, 2018 (Version 2.0), December 16, 2019 (Version 3.0), and November 12, 2020 (Version 4.0).

[25] Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, Jhund PS, Belohlavek J, Chiang CE, Borleffs CJW, Comin-Colet J, Dobreanu D, Drozdz J, Fang JC, Alcocer-Gamba MA, Al Habeeb W, Han Y, Cabrera Honorio JW, Janssens SP, Katova T, Kitakaze M, Merkely B, O'Meara E, Saraiva JFK, Tereshchenko SN, Thierer J, Vaduganathan M, Vardeny O, Verma S, Pham VN, Wilderäng U, Zaozerska N, Bachus E, Lindholm D, Petersson M, Langkilde AM; DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22;387(12):1089-1098. doi: 10.1056/NEJMoa2206286. Epub 2022 Aug 27. PMID: 36027570.

Changes provided for in the respective amendments are summarized below.

May 9, 2018 (Version 2.0)

Correction of typographical error in Appendix A- Section A3 referencing the International Classification of Diseases (ICD)

A subject who is rescreened is required to sign another International Classification of Functioning, Disability and Health (ICF)

December 16, 2019 (Version 3.0)

- Adjustment of the study sample size and the anticipated recruitment period. The original sample size of 4700 increased to approximately 6100, and the anticipated recruitment period was extended from 18 months to 22 months
- Modification of the subacute subgroup definition: extending the period after the discharge date from hospitalization for HF from 21 days to 30 days

November 12, 2020 (Version 4.0)

- Addition of concomitant medication check to Visit 1 (enrollment visit) to confirm screening eligibility
- Clarification on timing of BP, pulse, weight, and creatinine assessments
- Recording of COVID-19 testing results from Visit 2 onwards was added to safety events assessment
- Addition of phone collection mode of electronic patient-reported outcomes (PROs) as an alternative solution in settings that are affected by the COVID-19 pandemic
- Process of adjudication of potential DKA events by an independent DKA Committee implemented
- Addition of urgent HF visits in addition to hospitalizations for HF as a component of recurrent HF events to be evaluated for the first secondary objective
- Changed from the original single primary analysis (of the full study population) to a dual primary analysis (of the full study population and subpopulation with LVEF < 60%) and accompanying changes were required to maintain statistical power
    - Introduced the new dual primary hypothesis
    - Description of the subpopulation with LVEF <60%
    - Updated the primary variable analysis with the dual primary analysis
    - Updated methods for multiplicity control according to the dual primary hypotheses and changing test procedure
    - Updated that analysis of the composite of CV death and recurrent HF events (first secondary variable analysis) was also done in the subpopulation with LVEF < 60%
    - Added to the full analysis set that a subset of the full analysis set consisting of patients with LVEF <60% was now analyzed separately as part of the confirmatory statistical test procedure
    - Increased the number of primary endpoint events from 844 to 1117
    - Extended the estimated completion date from Q3 2021 to Q4 2021
    - Extended the study duration from 33 months to 39 months
    - Extended the recruitment period from 22 months to 26 months

- Added that the SCV should be performed within 6 weeks of PACD which can be extended if decided by the Global Study Team
- CV death was a component of the primary endpoint and now added as a secondary objective (in the full study population)
- Effect of Dapagliflozin on NYHA functional classification was moved from a secondary objective to exploratory objective
- Effect of Dapagliflozin on Patient global impression of severity (PGIS) questionnaires were removed from exploratory objective
- Clarification of the purpose of the EuroQol analysis
- Added major hypoglycemic events as an adverse event/SAE in specific eCRF
- Clarified that the full study population will be used for the interim analysis
- Removal of futility analysis

Reviewer's comments: *All amendments were made to the sNDA prior to the unblinding of the data and as such these amendments were not expected to impact subject safety or interpretation of efficacy.*

Endpoint Reporting and Adjudication

All potential primary events were adjudicated by an independent clinical events committee blinded to treatment assignment based on prespecified criteria detailed in the CEA charter that was established for this study. The following endpoints were centrally adjudicated using source documents and relevant eCRFs.

-All Death

-Heart failure hospitalization

-Urgent heart failure visit

Although not considered as efficacy variables, potential DKA events were adjudicated as safety events by an independent DKA Committee.

Details of the multiplicity testing procedure

The alpha for final analysis adjusted for the alpha of 0.2% used at the interim analysis will be set to 5% minus 0.2% = 4.8%, rather than 4.98% as determined by the Haybittle-Peto function for 67% of events. As such, the significance level of α2 (for the primary analysis in the full population at the final analysis) will be fixed at 2.4% two-sided.

To calculate α1, the Applicant used the approach described in Spiessen and Debois 2010). The approach relies on estimating the correlation between the full population and the LVEF <60% subpopulation. Per the reference, the test statistics for the primary endpoint in the two population are asymptotically a bivariate normal distribution with correlation equal to the fraction of events in the LVEF <60% subpopulation. The correlation can be estimated based on the square root of the lower bound of a two-sided 95% confidence interval for the proportion of events in the subpopulation with LVEF <60%, based on a normal approximation for proportions.

The threshold α1 will be such that for α2 = 2.4% two-sided; the two-sided probability of rejecting at least one true null hypothesis at the final analysis will be 4.8%. It then follows that if the primary endpoint in the full population at interim analysis is assessed versus a two-sided p-value of 0.2%,

the two-sided probability of rejecting at least one true primary null hypothesis at any analysis can be no larger than 5%. Table 26 provided a summary of the values of α1 depending on the fraction of patients with primary events in the LVEF <60% population relative to the full population.

Table 26. Level of α1 Depending on Proportion of Events in LVEF <60%, DELIVER

Patients with event (LVEF < 60% / overall)	Proportion (95% CI)	Correlation = sqrt of lower confidence limit	Two-sided alpha (%) for primary endpoint		
			Interim analysis Full population	Final analysis (α_2) Full population	Final analysis (α_1) Subpopulation LVEF < 60%
(b) (6)	0.698 (0.671, 0.725)	0.819	0.2	2.4	3.647
	0.707 (0.681, 0.734)	0.825	0.2	2.4	3.674
	0.716 (0.690, 0.743)	0.831	0.2	2.4	3.701
	0.725 (0.699, 0.751)	0.836	0.2	2.4	3.730
	0.734 (0.708, 0.760)	0.842	0.2	2.4	3.758
	0.743 (0.717, 0.769)	0.847	0.2	2.4	3.788

Source: Table 2 of the SAP version 5.0
Abbreviations: LVEF, left ventricular ejection fraction; SAP, statistical analysis plan

Per the SAP, the multiplicity testing alpha splitting procedure at the final analysis is described as follows.

1) If both the primary null hypotheses can be rejected, the following hypotheses in each branch will be tested at 2.4%, in the order described in Figure 2.
2) The following will apply if only one of the tests of the primary endpoint can be rejected at respective levels 2.4% (in the full population) and α1(in the LVEF <60% subpopulation): the remaining hypotheses in the branch where the primary hypothesis was rejected will be tested in fixed sequence at the following two-sided significance levels
3) 4.8% – 2.4% = 2.4% in the left branch only (in case the primary endpoint in the subpopulation was significant at level α1 but not in the full population at level 2.4%)
4) 4.8% – α1 in the right branch only (in case the primary endpoint in the full population was significant at level 2.4% but not in the subpopulation at level α1)
5) If all hypotheses in one branch are rejected, alpha will be recycled to the other branch, where remaining unrejected hypotheses can be tested at full alpha adjusted for interim analysis (i.e., 4.8%) in the order described in Figure 2.
6) If the first secondary hypothesis (recurrent HF events and CV death) in full study population is rejected in one of the branches, it does not have to be re-tested in the other branch. If the primary hypothesis is rejected in both branches and the first secondary hypothesis (recurrent events) is rejected in the LVEF < 60% subpopulation, then the first secondary hypothesis in full population can be tested at full alpha adjusted for interim analysis (4.8%).

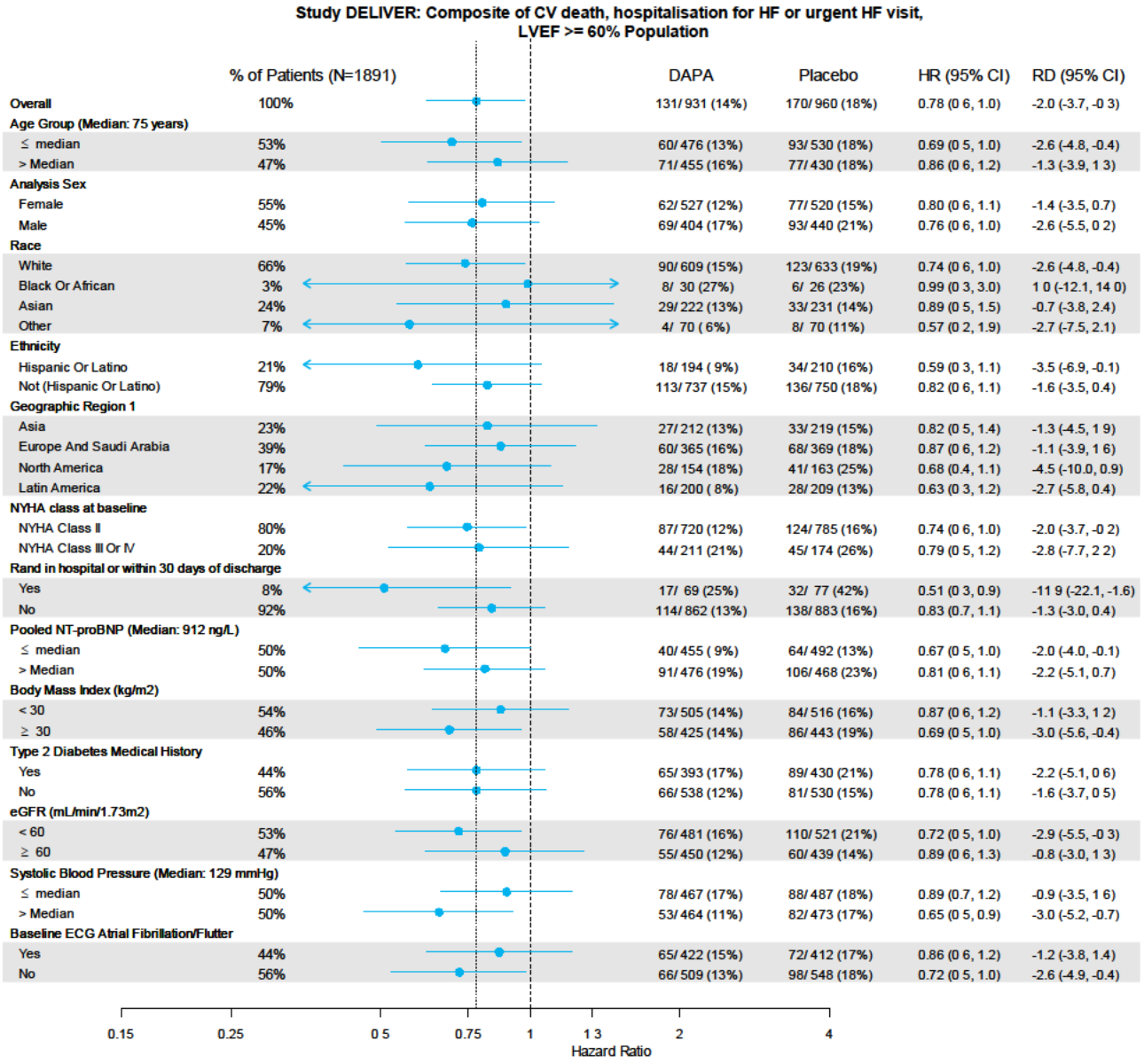
The Applicant included the programming code for calculating the significance level in the Appendix of the SAP.

17. Efficacy Assessment Additional Information and Assessment

Applicability of Foreign Data

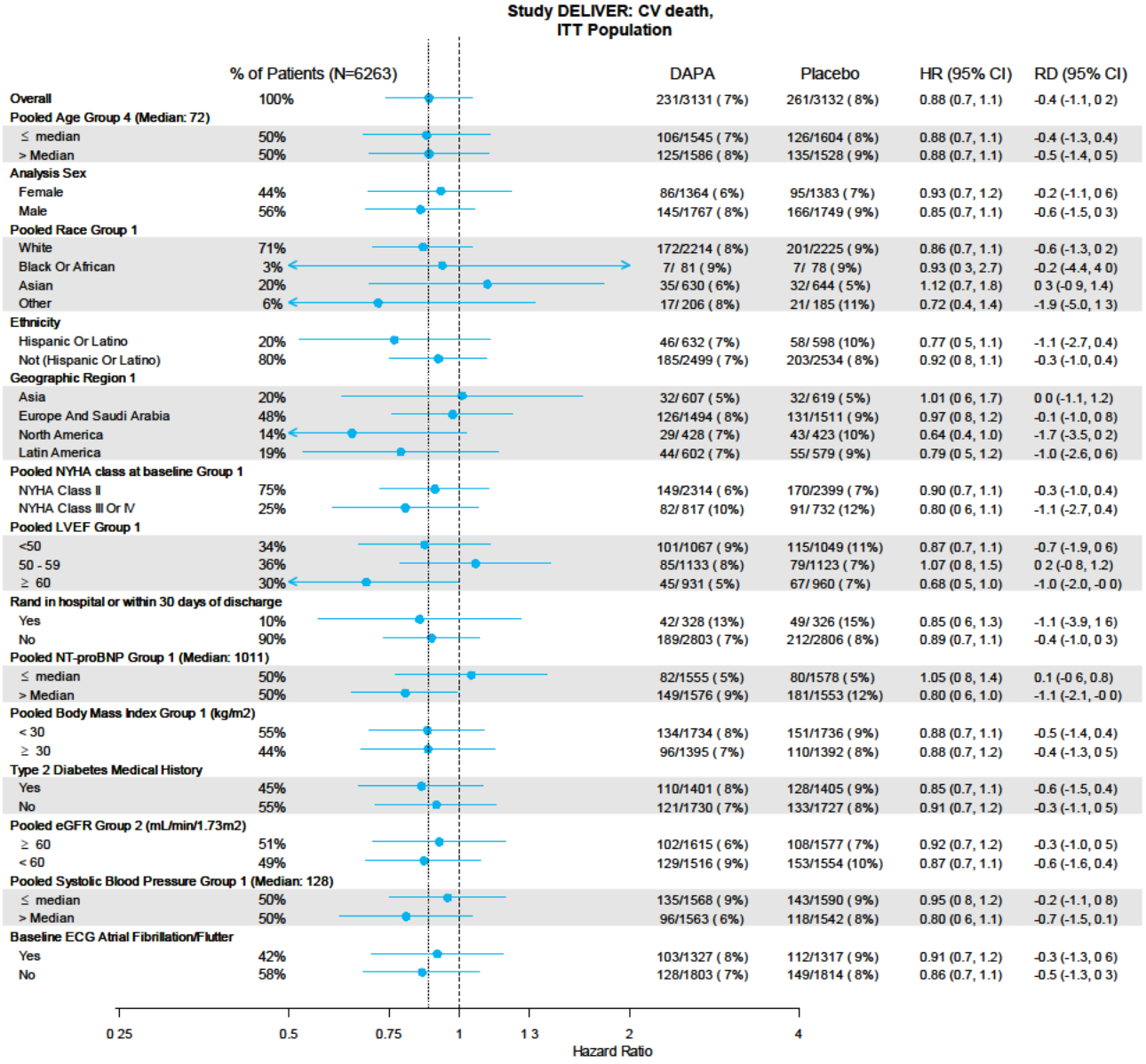
The clinical study supporting this sNDA application used good clinical practices (GCP) in compliance with the Institutional Review Board (IRB) requirements in 21 Code of Federal Regulations (CFR)56 and
informed consent requirement in 21CFR50. Furthermore, all foreign clinical sites were conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the laws and regulations of the country in which the study was conducted.
All US investigational sites were filed to IND 136809 and Form FDA 1572 were collected from US investigators. Non-US investigational sites were not conducted under the IND and therefore, not filed. All non-US sites followed ICH-GCP guidelines, 21CFR312.120, appropriate AstraZeneca standards, and other relevant country regulations.

Figure 8. Subgroup Analysis for the Primary Composite Endpoint, LVEF ≥60%, DELIVER



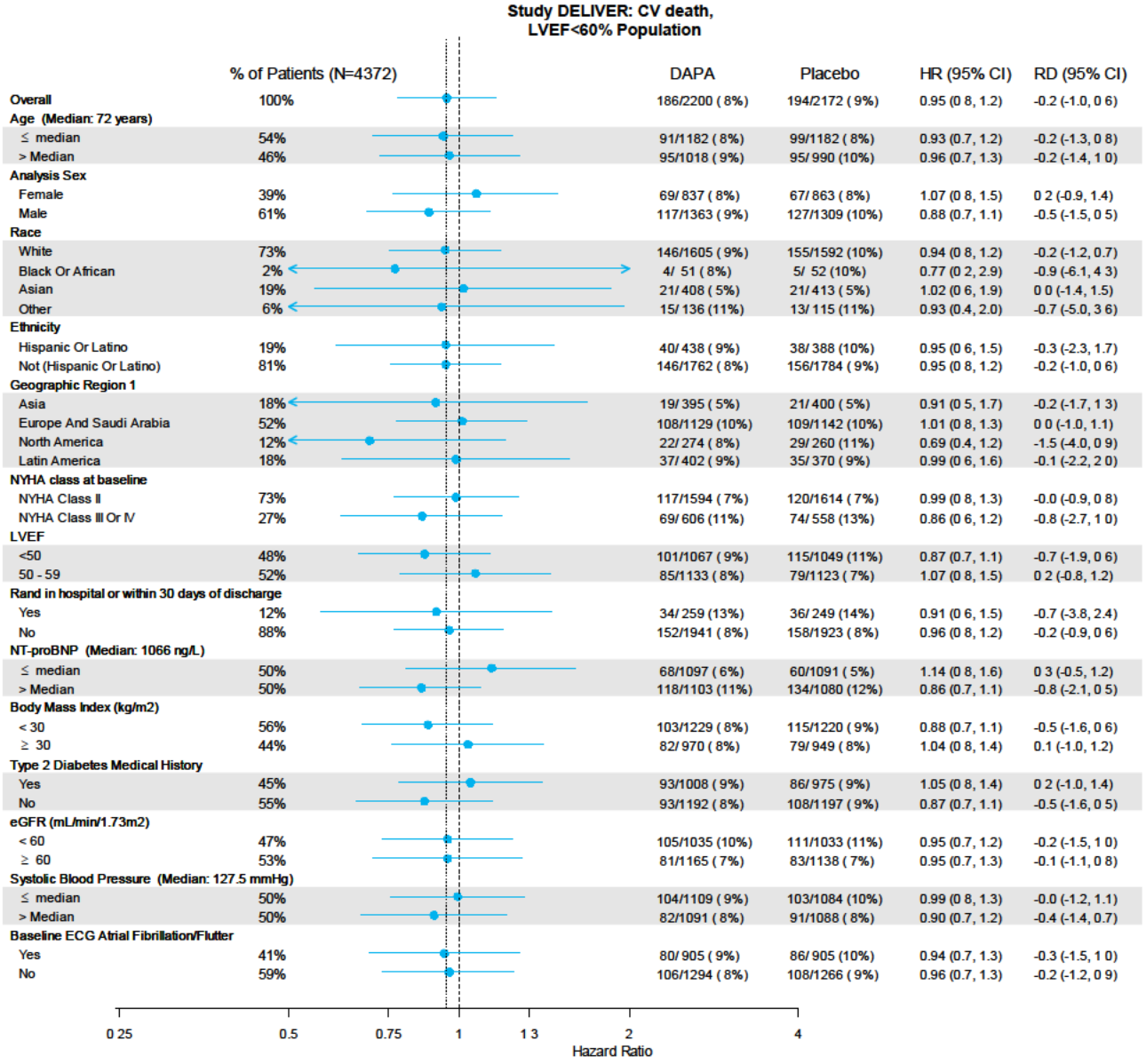
Source: Statistical Reviewer
Ethnicity was included by the Statistical Reviewer
In the Applicant's clinical study report, patients who were randomized in hospital or within 30 days of discharge were labelled as subacute hospitalization for the subgroup analysis.
Abbreviations: FAS, full analysis set; NYHA, New York Heart Association; CV, cardiovascular; LVEF, left ventricular ejection fraction; HF, heart failure; NT-proBNP, N-terminal pro–B-type natriuretic peptide, eGFR, estimated glomerular filtration rate; ECG, electrocardiography; DAPA, dapagliflozin, HR, hazard ratio; CI, confidence intervals; RD, risk difference

Figure 9. Subgroup Analysis for the CV Death, FAS, DELIVER



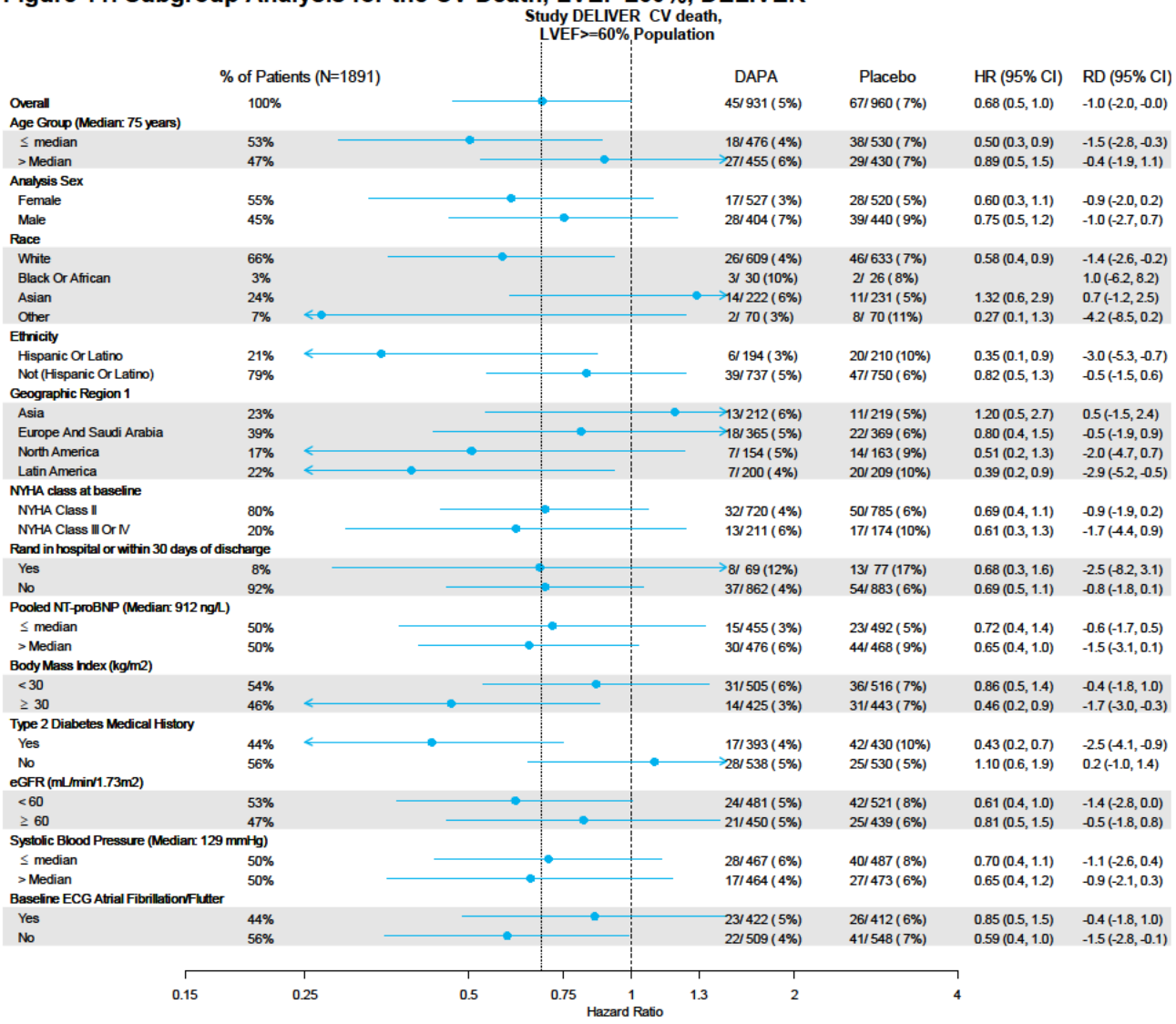
Source: Statistical Reviewer
Ethnicity was included by the Statistical Reviewer
In the Applicant's clinical study report, patients who were randomized in hospital or within 30 days of discharge were labelled as subacute hospitalization for the subgroup analysis.
Abbreviations: FAS, full analysis set; NYHA, New York Heart Association; CV, cardiovascular; LVEF, left ventricular ejection fraction; HF, heart failure; NT-proBNP, N-terminal pro–B-type natriuretic peptide, eGFR, estimated glomerular filtration rate; ECG, electrocardiography; DAPA, dapagliflozin, HR, hazard ratio; CI, confidence intervals; RD, risk difference

Figure 10. Subgroup Analysis for the CV Death, LVEF <60%, DELIVER



Source: Statistical Reviewer
Ethnicity was included by the Statistical Reviewer
In the Applicant's clinical study report, patients who were randomized in hospital or within 30 days of discharge were labelled as subacute hospitalization for the subgroup analysis.
Abbreviations: FAS, full analysis set; NYHA, New York Heart Association; CV, cardiovascular; LVEF, left ventricular ejection fraction; HF, heart failure; NT-proBNP, N-terminal pro–B-type natriuretic peptide, eGFR, estimated glomerular filtration rate; ECG, electrocardiography; DAPA, dapagliflozin, HR, hazard ratio; CI, confidence intervals; RD, risk difference

Figure 11. Subgroup Analysis for the CV Death, LVEF ≥60%, DELIVER



Source: Statistical Reviewer
Ethnicity was included by the Statistical Reviewer
In the Applicant's clinical study report, patients who were randomized in hospital or within 30 days of discharge were labelled as subacute hospitalization for the subgroup analysis.
Abbreviations: FAS, full analysis set; NYHA, New York Heart Association; CV, cardiovascular; LVEF, left ventricular ejection fraction; HF, heart failure; NT-proBNP, N-terminal pro–B-type natriuretic peptide, eGFR, estimated glomerular filtration rate; ECG, electrocardiography; DAPA, dapagliflozin, HR, hazard ratio; CI, confidence intervals; RD, risk difference

Table 27. Number of Events Per Patient for the CV Death and Recurrent HF Events or HF Events Only, LVEF <60%, DELIVER

	CV Death and Recurrent HF events		HF Events	
Outcomes	Dapa 10 Mg N=2200	Placebo N=2172	Dapa 10 Mg N=2200	Placebo N=2172
With 0 Events	1939	1848	1819	1732
With 1 Events	176	197	256	271
With 2 Events	43	66	70	93
With 3 Events	29	29	31	38
With 4 Events	7	16	16	16
With 5 Events	1	8	3	10
With >5 Events	5	8	5	12

Source: Statistical Reviewer
Abbreviations: Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure; CV, cardiovascular

18. Clinical Safety Assessment Additional Information and Assessment

None

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

None

20. Other Drug Development Considerations Additional Information

None

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

None

22. Labeling Summary of Considerations and Key Additional Information

In DELIVER, a key secondary efficacy variable was the change from baseline at 8 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS). The observed between-group difference change in KCCQ-TSS from baseline at 8 months in DELIVER was 8.3 in

the dapagliflozin group (n = 1273) and 5.2 in the placebo group (n = 1276). The estimated win ratio was 1.11 (95% confidence interval (CI): 1.03, 1.21; p-value from the ranked ANCOVA test = 0.009

(b) (4)

As part of a general revision across the SGLT2 inhibitor class of agents, the contraindication for use in patients on dialysis has been removed. When SGLT-2 inhibitor products were initially approved for glycemic control, a contraindication in patients on dialysis seemed appropriate given the available data and our understanding of drug's mechanism of action as well as perceived benefits. Based on the current data and evolution in our understanding of this class of agents, we no longer think that a contraindication in patients on dialysis is appropriate.

23. Postmarketing Requirements and Commitments

None

24. Financial Disclosure

Table 28. Covered Clinical Studies: DELIVER

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: ~1800		
Number of investigators who are Applicant employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
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: Enter text here. Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Applicant 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 ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

The number of subjects recruited at the sites controlled by the investigators with disclosable financial interests/arrangements were low (less than 1%) and this reduces any bias that possibly could affect the outcome of the study.

25. References

N/A

26. Review Team Acknowledgements

Table 29. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Manager	Alexis Childers
Nonclinical Reviewer	N/A
Nonclinical Team Leader	N/A
Office of Clinical Pharmacology Reviewer(s)	N/A
Office of Clinical Pharmacology Team Leader(s)	N/A
Clinical Reviewer	Rosalyn Adigun/ Tejas Patel
Clinical Team Leader	Fortunato Senatore
Statistical Reviewer	William Koh
Statistical Team Leader	Jialu Zhang
Cross-Disciplinary Team Leader	Fortunato Senatore
Division Director/ Signatory	Norman Stockbridge

Table 30. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Parvin Akther,
Microbiology	NA
OPDP	Meena Savani
OSI	NA
OSE/DEPI	NA
OSE/DMEPA	Devin Kane
OSE/DRISK	NA
Other - DMPP	Sharon Mills

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
DMPP=Division of Medical Policy Programs

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/

ROSALYN O ADIGUN
05/05/2023 03:55:07 PM

TEJAS PATEL
05/05/2023 06:30:10 PM

WILLIAM J KOH
05/06/2023 10:26:36 PM

JIALU ZHANG
05/08/2023 08:25:43 AM

FORTUNATO F SENATORE
05/08/2023 08:53:29 AM

NORMAN L STOCKBRIDGE
05/08/2023 08:59:07 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s026

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 31, 2023

To: Alexis Childers, Senior Regulatory Project Manager
Division of Cardiology and Nephrology (DCN)

Michael Monteleone, MS, RAC
Associate Director for Labeling, DCN

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Ankur Kalola, Regulatory Review Officer, OPDP

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for FARXIGA® (dapagliflozin) tablets, for oral use

NDA: 202293, S-026

Background:

In response to DCN's consult request dated February 8, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for supplement 26 for Farxiga. This supplement proposes to expand the heart failure indication based on data from the outcome trial, DELIVER, to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit in adults with heart failure.

PI and Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 24, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on March 29, 2023.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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ANKUR S KALOLA
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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:	March 29, 2023
To:	Alexis Childers, RAC, CQIA Senior Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Sevani, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)** Ankur Kalola, 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/S-026
Supplement Number:	S-026
Applicant:	Astrazeneca AB c/o Astrazeneca Pharmaceuticals LP

1 INTRODUCTION

On July 8, 2022, Astrazeneca AB c/o Astrazeneca Pharmaceuticals LP submitted for the Agency's review a Prior Approval Supplement- Efficacy to their approved New Drug Application (NDA) 202293/S-026 for FARXIGA (dapagliflozin) tablets. According to their cover letter dated July 8, 2022, the Applicant submitted S-026 based on the recently completed Phase III study, D169CC00001 (DELIVER), NCT03619213 entitled: "*An International, Double-blind, Randomised, Placebo-Controlled Phase III Study to Evaluate the Effect of Dapagliflozin on Reducing Cardiovascular Death or Worsening Heart Failure in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)*." With this supplement, the Applicant seeks the following new indication for FARXIGA (dapagliflozin) tablets: "*To reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit in adults with heart failure*."

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 Cardiology and Nephrology (DCN) on September 2, 2022, 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 July 8, 2022, and received by DMPP on March 24, 2023.
- Draft FARXIGA (dapagliflozin) tablets Prescribing Information (PI) received on July 8, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on March 24, 2023.
- Approved FARXIGA (dapagliflozin) tablets labeling dated October 13, 2022.

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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LASHAWN M GRIFFITHS
03/29/2023 07:13:15 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	February 1, 2023
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 202293/S-026
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 (AstraZeneca)
FDA Received Date:	July 8, 2022 and October 26, 2022
TTT ID #:	2022-512
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

AstraZeneca AB (AstraZeneca) submitted a prior approval supplement (PAS) for Farxiga (dapagliflozin) tablets on July 8, 2022 under NDA 202293/S-026. AstraZeneca is proposing the expansion of the indication for Farxiga to include "reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit in adults with heart failure". We reviewed the proposed Farxiga prescribing information (PI) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

Farxiga (dapagliflozin) was approved on January 8, 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. On October 18, 2019 it was approved in type 2 diabetes mellitus patients 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. On May 5, 2020 it was approved 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). On April 30, 2021 it was approved for chronic kidney disease. It is available in 5 mg and 10 mg tablets.

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 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

AstraZeneca AB (AstraZeneca) submitted this prior approval supplement (PAS) to propose an expansion of the Farxiga indication to include "reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit in adults with heart failure". We note the recommended dose is based on estimated glomerular filtration rate (eGFR) for the currently approved indications as well as the proposed indication. The recommended starting dosage for patients with eGFR 45 or greater is 5 mg once daily with increase to 10 mg once daily if needed, for patients with eGFR 25 to less than 45 is 10 mg once daily, and initiation is not recommended in patients eGFR less than 25 however, patients may continue 10 mg orally once daily. Thus, we do not have concerns with the proposed expansion of the Farxiga indication from a medication error perspective. We defer to the Division of Cardiology and Nephrology (DCN) regarding the acceptability of the proposed indication for Farxiga.

We performed a risk assessment of the proposed prescribing information (PI) for Farxiga to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed PI for Farxiga did not identify any unique areas of vulnerability that may lead to medications errors. Thus, we have no concerns or recommendations for the PI at this time.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Farxiga prescribing information (PI) did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time for the Farxiga PI.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Farxiga received on October 26, 2022 from AstraZeneca AB.

Table 2. Relevant Product Information for Farxiga	
Initial Approval Date	January 8, 2014
Active Ingredient	dapagliflozin
Indication	***Current***: • 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 either established cardiovascular disease or multiple cardiovascular risk factors • 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) • to reduce the risk of sustained eGFR decline, end stage kidney disease cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk of progression ***Proposed:*** • to reduce the risk of cardiovascular death and hospitalization for heart failure and ***urgent heart failure visit*** in adults with heart failure (b) (4) (b) (4)
Route of Administration	Oral
Dosage Form	tablets
Strength	5 mg and 10 mg
Dose and Frequency	For eGFR 45 mL/min/1.73 m^2 or greater: • to improve glycemic control, the recommended starting dose is 5 mg once daily and can be increased to 10 mg once daily for additional glycemic control • for all other indications, the recommended starting dose is 10 mg once daily For eGFR 25 to less than 45: • 10 mg once daily For eGFR less than 25:

<table>
<tr><td></td><td>
Initiation not recommended; however, may continue 10 mg once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF
<u>On dialysis</u>:
Contraindicated
</td></tr>
<tr><td>How Supplied</td><td>
<table>
<tr><th>Tablet Strength</th><th>Film-Coated Tablet Color/Shape</th><th>Tablet Markings</th><th>Package Size</th><th>NDC Code</th></tr>
<tr><td>5 mg</td><td>Yellow, biconvex, round</td><td>“5” engraved on one side and “1427” engraved on the other side</td><td>Bottles of 30</td><td>0310-6205-30</td></tr>
<tr><td>10 mg</td><td>Yellow, biconvex, diamond-shape</td><td>“10” engraved on one side and “1428” engraved on the other side</td><td>Bottles of 30</td><td>0310-6210-30</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>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].</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 27, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Farxiga and NDA 202293. Our search identified 7 previous reviews[a,b,c,d,e,f,g], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Conrad, A. Label and Labeling Review for Farxiga (NDA 202293/S-027). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 SEP 13. TTT ID: 2022-623.

[b] Aidoo, M. Label and Labeling Review for Farxiga (NDA 202293/S-024). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Mar 2. RCM No.: 2020-2566.

[c] Aidoo, M. Label and Labeling Review for Farxiga (NDA 202293/S-020). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 17. RCM No.: 2019-2293.

[d] Conrad, A. Labeling Review for Farxiga (NDA 202293/S-018) and Xigduo XR (NDA 205649/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jun 7. RCM No.: 2018-2812.

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

[f] Agustin, R. Label, Labeling, and Packaging Review for Farxiga (NDA 202293). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Nov 18. RCM No.: 2013-1640.

[g] Owen, L. Label and Labeling Review for Farxiga (NDA 202293). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 Dec 9. RCM No.: 2011-241.

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,[h] along with postmarket medication error data, we reviewed the following Farxiga labels and labeling submitted by AstraZeneca AB.

- Prescribing Information (Image not shown) received on October 26, 2022, available from \\CDSESUB1\EVSPROD\nda202293\1186\m1\us\annotated-draft-label-deliver.pdf

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

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