15 December 2022
EMA/954956/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Forxiga	dapagliflozin
Edistride	dapagliflozin

Procedure No. EMEA/H/C/xxxx/WS/2299

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation or special term	Explanation
ACEi	Angiotensin converting enzyme inhibitor
AE	Adverse event
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
BP	Blood pressure
CEA	Clinical events adjudication
CI	Confidence interval
CKD	Chronic kidney disease
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
CV	Cardiovascular
DAE	Adverse event leading to discontinuation of IP
DKA	Diabetic ketoacidosis
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FDA	Food and drug administration
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
IP	Investigational product
IQR	Interquartile range
IxRS	Interactive voice or web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
LWYY	Lin Wei Yang Ying
MRA	Mineralocorticoid receptor antagonist

Abbreviation or special term	Explanation
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
PACD	Primary analysis censoring date
SAE	Serious adverse event
SAP	Statistical analysis plan
SGLT2	Sodium glucose co-transporter 2
T2DM	Type 2 diabetes mellitus
TSS	Total symptom score
US	United States
WHO	World Health Organisation

CONVENTIONS

Term	Explanation
Background therapy	Patients included in DELIVER were treated according to local guideline-recommended therapy for HF symptoms (eg, diuretics) and co-morbidities (including treatment for hypertension, ischaemic heart disease, and atrial fibrillation, diabetes, hyperlipidaemia).
HF event	Refers jointly to the 2 primary endpoint components: hospitalisation for HF and an urgent HF visit
HF and LVEF > 40%	LVEF has historically been used to classify patient populations in prior studies of HF, with current guidelines classifying patients with HF as having HF and reduced LVEF (≤ 40%); mildly reduced LVEF (41% to 49%); or preserved LVEF (≥ 50%) (McDonagh et al 2021). For clarity, this document refers to the DELIVER population as patients with HF and LVEF > 40%, a terminology which deviates from that used in the DELIVER study title and CSP.
IP	Refers to randomised treatment (ie, dapagliflozin 10 mg or matching placebo)
Preceding event	Refers to potential risk factor AEs for amputations affecting lower limbs
Recurrent HF events	Refers to the first and recurrent events of HF
Subacute subgroup	Refers to patients randomised during hospitalisation for HF or within 30 days of discharge from hospitalisation for HF

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 12 July 2022 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include population with Heart Failure and LVEF > 40% for Forxiga and its duplicate Edistride, based on final results from study D169CC00001 (DELIVER); The DELIVER study is a category 3, Post-Authorisation Safety Study (PASS) listed in the dapagliflozin RMP to evaluate the potential risk of lower limb amputation; This was an international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled Phase III study in patients with HF and LVEF > 40%, evaluating the effect of dapagliflozin 10 mg compared with placebo, given once daily in addition to background therapy, including treatments to control co-morbidities, in reducing the composite of CV death or an HF event (hospitalisation for HF or urgent HF visit). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet are updated in accordance. Version 27 of the RMP has also been submitted.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0202/2018 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The WSA received Scientific Advice from the CHMP on 14 December 2017 (EMA/CHMP/SAWP/792395/2017). The Scientific Advice pertained to the clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	12 July 2022
Start of procedure:	13 August 2022
CHMP Rapporteur Assessment Report	7 October 2022
PRAC Rapporteur Assessment Report	7 October 2022
PRAC Outcome	27 October 2022
CHMP members comments	27 October 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 November 2022
Request for supplementary information (RSI)	10 November 2022
CHMP Rapporteur Assessment Report	30 November 2022
Updated CHMP Rapporteur Assessment Report	8 December 2022
Opinion	15 December 2022

2. Scientific discussion

2.1. Introduction

Dapagliflozin (FORXIGA/EDISTRIDE) is a potent, selective, and reversible inhibitor of SGLT2.

Dapagliflozin is currently approved for the treatment of T2DM since 2012, HFrEF, and CKD. In addition, it is approved for type 1 diabetes mellitus in Japan.

An indication for the treatment of HFrEF (LVEF ≤ 40%) was based on positive results from the DAPA-HF study (D1699C00001), which demonstrated superiority of dapagliflozin in reducing CV mortality, worsening of HF, and HF symptoms.

This application is based on the single pivotal Phase III study DELIVER (D169CC00001), designed to extend the HF indication of dapagliflozin to include patients with HF and LVEF > 40%.

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 on CV death, a pooled analysis of patient-level data from DELIVER and DAPA-HF is also presented.

2.1.1. Problem statement

Disease or condition

The scope of this application is to extend the current indication "treatment of symptomatic chronic heart failure with reduced ejection fraction" to include heart failure (HF) with mildly reduced or preserved left ventricular ejection fraction (LVEF > 40%).

Claimed therapeutic indication

Heart Failure

Forxiga is indicated in adults for the treatment of symptomatic chronic heart failure ~~with reduced ejection fraction~~.

Epidemiology

An estimated 64 million people are affected by HF worldwide (Groenewegen et al 2020, Lippi and Sanchis-Gomar 2020), with the prevalence of known HF at approximately 1% to 2% of the general adult population (Groenewegen et al 2020). HF with LVEF > 40% accounts for approximately half of all HF cases (Pfeffer et al 2019, Savarese and Lund 2017, Virani et al 2021). Of all hospitalisations in the Westernised countries, 1% to 4% are due to HF (Ponikowski et al 2016), with well over 1 million hospitalisations annually in the US and Europe (Ambrosy et al 2014). Readmissions after hospitalisation for LVEF > 40% are common, ranging from 28% to 45% within the first year (Cheng et al 2014, Cui et al 2020). HF with LVEF > 40% is associated with considerable mortality. Prognosis after hospitalisation for HF with LVEF > 40% is markedly poor, with 1-year and 5-year mortality estimated at 35% and 76%, respectively (Cheng et al 2014, Shah et al 2017) and have remained stable at a high level for the past 2 decades (Tsao et al 2018).

Aetiology and pathogenesis

The aetiology of HF varies according to geography. In Western-type and developed countries, coronary artery disease (CAD) and hypertension are predominant factors (GBD 2017). With regard to ischaemic aetiology, HFmrEF resembles HFrEF, with a higher frequency of underlying CAD compared to those with HFpEF (Koh et al 2017, Vedin et al 2017, Kapoor et al 2016).

The pathophysiology of HFpEF is complex and not completely understood, but it is related to a range of abnormalities. These may include increased left ventricular (LV) mass, LV remodelling, or changes in myocyte structure, as well as diastolic dysfunction related to LV stiffness, interstitial fibrosis, and calcium abnormalities. Systolic function may also be affected despite maintenance of normal EF. Systemic and pulmonary vascular abnormalities include blunted increase in stroke rate, and increased intracardiac and pulse pressure (Butler et al 2014).

Pathology of the valves, pericardium, and endocardium, and abnormalities of heart rhythm and conduction can also cause or contribute to HF (McDonagh et al 2021).

Clinical presentation, diagnosis

Heart failure is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise (McDonagh et al 2021).

Patients with signs and symptoms of HF are categorized, based on measurement of left-ventricular ejection fraction (LVEF), as having HF with reduced LVEF (HFrEF) (typically <40%) or HF with preserved LVEF (HFpEF). HFpEF is typically defined as LVEF ≥50%; HF with LVEF in the 40% to 49% may be characterized as HF with mid-range ejection fraction (HFmrEF) (Yancy et al 2013, Ponikowski et al 2016).

The simplest terminology used to describe the severity of HF is the New York Heart Association (NYHA) functional classification. However, this relies solely on symptoms and there are many other better prognostic indicators in HF (Caraballo et al 2019). Importantly, patients with mild symptoms may still have a high risk of hospitalization and death (Solomon et al 2016).

The diagnosis of HFmrEF requires the presence of symptoms and/or signs of HF, and a mildly reduced EF (41-49%) The presence of elevated NPs (BNP ≥35 pg/mL or NT-proBNP ≥125 pg/mL) and other evidence of structural heart disease [e.g. increased left atrial (LA) size, LVH or echocardiographic measures of LV filling] make the diagnosis more likely but are not mandatory for diagnosis if there is certainty regarding the measurement of LVEF (McDonagh et al 2021).

The diagnosis of HFpEF remains challenging. According to the ESC Guideline (McDonagh et al 2021), the diagnosis should include the following: 1) Symptoms and signs of HF, 2) An LVEF ≥50%, and 3) Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised NPs.

Management

Pharmacotherapy is the cornerstone of treatment for heart failure with reduced ejection fraction (HFrEF). Diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or angiotensin II receptor blocker-neprilysin inhibitor, mineralocorticoid receptor antagonists, and beta-blockers can improve symptoms and haemodynamics as well as reduce hospitalizations and mortality (Iwaz et al 2016). There is some evidence that hospitalization and survival rates for HFrEF but not HFpEF have improved over time, which may relate to the availability of effective treatments for HFrEF (Owan et al 2006, Steinberg et al 2012).

With regards to heart failure with mildly reduced ejection fraction (HFmrEF), the ESC Guideline (McDonagh et al 2021) states that diuretics should be used to control congestion. No substantial prospective RCT has been performed exclusively in patients with HFmrEF. Although the guideline does not make any strong recommendations, treatment with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, or angiotensin II receptor blockers-neprilysin inhibitor may be considered based on subgroup analysis of trials in HFpEF.

There is a lack of approved pharmacotherapy indicated for heart failure with preserved ejection fraction (HFpEF) as reflected in the current HF treatment guidelines. The latest ESC guidelines state that no treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with

HFpEF or HFmrEF (Ponikowski et al 2016, McDonagh et al 2021). However, recently (March 2022), another SGLT2 inhibitor, empagliflozin, was approved for the use in patients with HF and LVEF > 40%.

Considering that HF is a common and serious medical condition with a high risk of repeat hospitalisation for HF and a high mortality, there remains an unmet medical need for new treatment options that reduce morbidity and mortality in patients with HF and LVEF > 40%.

2.1.2. About the product

Dapagliflozin (FORXIGA/EDISTRIDE) is a potent, selective, and reversible inhibitor of SGLT2.

Dapagliflozin is currently approved for the treatment of T2DM since 2012, HFrEF, and CKD. In addition, it is approved for type 1 diabetes mellitus in Japan.

An indication for the treatment of HFrEF (LVEF ≤ 40%) was based on positive results from the DAPA-HF study (D1699C00001), which demonstrated superiority of dapagliflozin in reducing CV mortality, worsening of HF, and HF symptoms.

The primary effect of dapagliflozin—inhibition of SGLT2 in the proximal kidney tubules—leads to changes in sodium, glucose, and fluid handling, which leads to a decrease in volume overload. This off-loading of the heart leads to beneficial effects on cardiac remodelling, which leads to improved diastolic parameters. The decongestive effect and reversal of some of the structural changes in the heart are the likely drivers of the benefit on HF events and mortality

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

This application is based on the single pivotal DELIVER study. DELIVER was a Phase III international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled study in 6263 patients (44% female) with HF and LVEF > 40%. The primary objective was to evaluate the effect of dapagliflozin 10 mg tablets versus placebo, given once daily, in reducing the composite of CV death or an HF event. Two hypotheses were tested for this primary objective simultaneously: in the full study population and in a subpopulation with LVEF < 60%.

DELIVER and DAPA-HF were powered for the primary composite endpoint and not for individual components of the composite. A pooled analysis of patient-level data from DELIVER and DAPA-HF is included in this submission 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 treatment effect of dapagliflozin on CV death.

Scientific advice was sought from EMA (EMA/CHMP/SAWP/792395/2017) in 2017, much of which was focused on a pragmatic register-based study design to evaluate HF with LVEF > 40%. The MAH ultimately decided to perform a traditional randomised controlled trial instead and, in part, relied on relevant advice from the pragmatic design interaction, as well as previous advice from health authority interactions for DAPA-HF in 2016 (EMA/CHMP/SAWP/336742/2016).

Key Advice from the EMA/CHMP

On Pragmatic HFpEF Study (October to December 2017)

- Underscored the need to clarify the mechanism of action in HF with LVEF > 40%.
- Recommended strict inclusion criteria to define population, that characteristics of HF need to be clearly defined and that definitions could include the presence of structural heart disease or documented hospitalisation for HF.

- Recommended subgroup analyses for LVEF subgroups.
- Accepted proposal to study the 10 mg dose but recommended to also include the 5 mg dose.
- Underscored the importance of background therapy.
- Underscored that urgent visit needs to be strictly defined and advised to include all-cause mortality as a component of the primary composite endpoint instead of CV death.
- Advised on safety topics, including to collect also non-serious AEs for amputations and preceding events, and to take volume depletion, hyperkalaemia, and weight loss into consideration.
- Underscored importance of creatinine and eGFR measurements.

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA.

The WSA has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by that the new indication to include adult patients with heart failure with mildly reduced and preserved ejection fraction is considered unlikely to result in any significant increase in the combined sales volumes for all dapagliflozin containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.2.2. Conclusion on the non-clinical aspects

Considering the above data, dapagliflozin is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The application is based on data from the single pivotal DELIVER study (D169CC00001).

To assess whether the treatment effect of dapagliflozin is modified by LVEF and to provide a more precise estimate of CV death in patients with HF, a pooled analysis of patient-level data from DELIVER and DAPA-HF (D1699C00001) is also presented in this submission.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA.

The WSA has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacodynamics

No new pharmacodynamic studies have been provided. The MAH has provided data from literature summarising the current knowledge on the mechanism of action of SGLT2 inhibitors when used in the treatment of heart failure.

Mechanism of action

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal kidney tubules with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Therefore, dapagliflozin increases the delivery of sodium to the distal tubule, which increases tubuloglomerular feedback and reduces intraglomerular pressure, both in patients with T2DM and without diabetes (Cherney et al 2020).

This primary mechanism of action in the kidneys—that dapagliflozin changes the handling of sodium, glucose, and fluid—leads to adaptations in the heart.

A cardinal feature of HF, regardless of ejection fraction, is an increase in left ventricular filling pressures (i.e., increased preload). SGLT2 inhibition has been shown to reduce distal pulmonary artery pressure (which is directly related to left ventricular filling pressure), as measured by an implanted device both in the EMBRACE study, which included HF patients across the LVEF spectrum, with no treatment by LVEF interaction (Nassif et al 2021), and in a study including patients with HFrEF (Mullens et al 2020). Both studies provide direct evidence of a rapid-onset and sustained haemodynamic effect of SGLT2 inhibition in reducing left ventricular preload.

This off-loading of the heart is a likely cause of the longer-term beneficial effects on cardiac remodelling that are evident with SGLT2 inhibition. Two randomised controlled trials have shown beneficial effects on remodelling, as assessed by left ventricular mass: DAPA-LVH, which included patients with T2DM and left ventricular hypertrophy (Brown et al 2020), and EMPA-HEART, which included patients with T2DM and coronary artery disease (Verma et al 2019). These findings of beneficial effects on remodelling from SGLT2 inhibition were further confirmed in an observational study that prospectively included mainly patients with HFpEF and T2DM (Soga et al 2018).

An expected consequence of beneficial effects on remodelling is the improvement in diastolic parameters. Indeed, it was shown that dapagliflozin treatment is associated with improved diastolic parameters, as well as global longitudinal strain (Tanaka et al 2020). This was also confirmed in a large propensity-matched cohort study, in which treatment with SGLT2 inhibitors was associated with: (1) lower end-diastolic dimension, (2) lower left ventricular mass index, (3) improved LVEF, (4) improved global longitudinal strain, (5) lower mitral E/e', and (6) lower pulmonary arterial pressure (Hwang et al 2020).

2.3.3. Discussion on clinical pharmacology

No new pharmacodynamic studies have been provided. In the CHMP scientific advice, the MAH was requested to provide data in support of the mechanism of action for SGLT2 inhibitors when used in the treatment of heart failure. Data from the literature, summarising the current knowledge on the mechanism of action of SGLT2 inhibitors when used in the treatment of heart failure have been provided. The MAH's interpretation of these data is that the primary effect of dapagliflozin—inhibition of SGLT2 in the proximal kidney tubules—leads to changes in sodium, glucose, and fluid handling, which leads to a decrease in volume overload. This off-loading of the heart leads to beneficial effects on cardiac remodelling, which leads to improved diastolic parameters. The MAH concludes that the decongestive effect and reversal of some of the structural changes in the heart are the likely drivers of the benefit on HF events and mortality.

2.3.4. Conclusions on clinical pharmacology

Published data supporting a plausible mechanism of action for SGLT2 inhibitors, when used in the treatment of heart failure, has been provided.

2.4. Clinical efficacy

2.4.1. Dose response study

No formal dose-ranging study has been performed with dapagliflozin in patients with HF because of lack of established biomarkers. Pharmacokinetic and pharmacodynamic data previously showed that 10 mg dose of dapagliflozin near maximally inhibits SGLT2 in the kidney.

Furthermore, in the DAPA-HF study (D1699C00001) which included patients with HFrEF (LVEF ≤ 40%), the 10 mg dose was shown efficient in reducing CV mortality, worsening of HF, and HF symptoms.

2.4.2. Main study

DELIVER - Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure (D169CC00001)

Methods

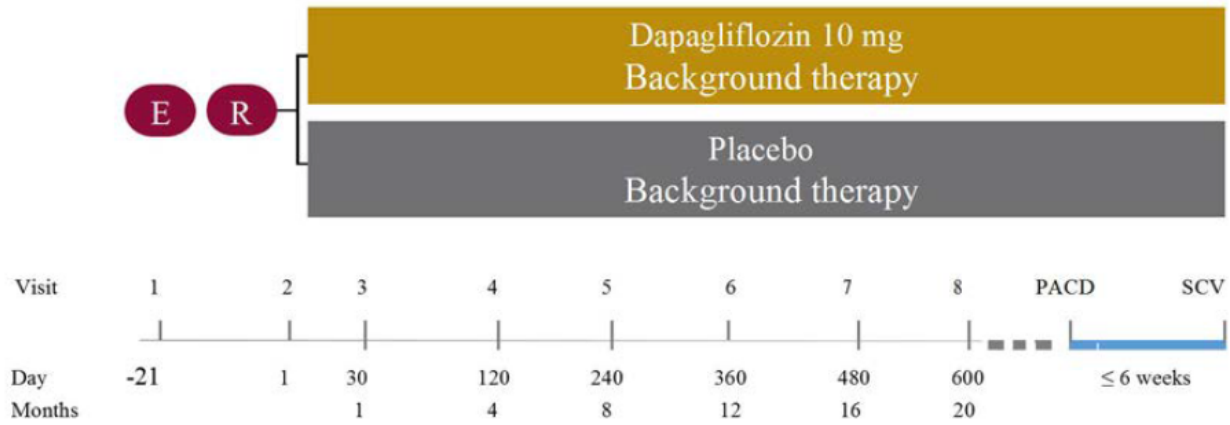
DELIVER was an international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled Phase III study in patients with HF and LVEF > 40%. DELIVER evaluated the effect of dapagliflozin 10 mg compared with placebo, given once daily, in reducing the composite of CV death or an HF event. All primary endpoint events were adjudicated.

The study closure procedures were initiated when the predetermined number of primary endpoints (n = 1117) were predicted to have occurred, i.e., the PACD.

There were no specific dietary or activity restrictions during the study.

In addition to the full study population, data for the subpopulation with LVEF <60% is presented.

Figure 1 Study design



After randomisation, in-person visits were at 30 days, 4 months, and thereafter every 4 months.
E, enrolment; R, randomisation; PACD, primary analysis censoring date; SCV, study closure visit.

Study participants

Key inclusion criteria:

1. Male or female patients aged ≥ 40 years.
2. Documented diagnosis of symptomatic HF (NYHA class II to IV) at enrolment, and a medical history of typical symptoms/signs of HF ≥ 6 weeks before enrolment with at least intermittent need for diuretic treatment.
3. 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 (acute CV event within 12 weeks prior to enrolment), qualifying cardiac imaging assessment at least 12 weeks following the procedure/event is required.
4. 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.
5. Patients may be ambulatory, or hospitalised; patients must be off intravenous HF therapy (including diuretics) for at least 12 hours prior to enrolment and 24 hours prior to randomisation.

Key exclusion criteria were applied to limit bias, ensure patient safety, and reduce the risk of enrolling patients with alternative conditions that could account for the patient's HF symptoms and signs. Hence, patients with anaemia, hypothyroidism, and primary pulmonary hypertension or severe pulmonary disease were not eligible to participate in the study. Patients with hypotension (systolic blood pressure < 95 mmHg) were excluded due to the blood pressure lowering effects of dapagliflozin. Patients with 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 were excluded.

Patients with other conditions likely to prevent participation in the study or greatly limit life expectancy were also excluded as were patients with T1DM.

Treatments

No formal dose-ranging study has been performed with dapagliflozin in patients with HF because of lack of established biomarkers. Pharmacokinetic and pharmacodynamic data previously showed that 10 mg dose of dapagliflozin near maximally inhibits SGLT2 in the kidney.

The 10 mg dose of dapagliflozin has demonstrated a favourable benefit/risk balance, with superior efficacy and comparable safety to the 5 mg dose, for the treatment of T2DM in an extensive clinical development programme.

The high mortality and morbidity of HF supported studying the highest effective and maximum tolerated dose of dapagliflozin (10 mg), which was assumed to present the greatest benefit-risk in this patient population.

Patients were treated according to local guideline-recommended therapy for HF symptoms and co-morbidities. There are no clinically meaningful drug-drug interactions between dapagliflozin and these background medications and hence, no changes in dose of dapagliflozin were required.

At the time of study initiation, no pharmacological therapy was approved for HF with LVEF > 40%; therefore, placebo was selected as an appropriate comparator.

Objectives/endpoints

Primary Objective	**Endpoint**
To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function, in • full study population • subpopulation with LVEF < 60%	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalisation for HF 3. Urgent HF visit (e.g., emergency department or outpatient visit)

Secondary Objectives	**Endpoints**
To determine whether dapagliflozin is superior to placebo in reducing the total number of HF events (hospitalisations for HF or urgent HF visit) and CV death in • full study population • subpopulation with LVEF < 60%	Total number of HF events (first and recurrent) and CV death
To determine whether dapagliflozin is superior to placebo in improving Patient Reported Outcomes measured by KCCQ	Change from baseline in the TSS of the KCCQ at 8 months

Secondary Objectives	Endpoints
To determine whether dapagliflozin is superior to placebo in reducing CV death	Time to the occurrence of CV death
To determine whether dapagliflozin is superior to placebo in reducing all-cause mortality	Time to the occurrence of death from any cause

Sample size

The study was event-driven. Originally, assuming a true HR of 0.80 between dapagliflozin and placebo, using a two-sided alpha of 5%, 844 primary endpoint events were targeted in order to provide a statistical power of 90% for the test of the primary endpoint.

Assuming 20% of patients from the subacute subgroup with an annual event rate of 24% during the first year and 9% thereafter, the original sample size of 4700 patients was estimated to provide the required target number of 844 patients with a primary event during a recruitment period of 18 months and a minimum follow-up period of 15 months.

Based on the ongoing blinded monitoring of event accrual and with an assumed proportion of 11% patients from the subacute subgroup, the sample size was increased from original 4700 to approximately 6100 randomised patients to obtain the increased target number of 1117 patients with a primary event. The recruitment period was anticipated to increase from the original 18 months to 26 months and a minimum follow-up period of 13.5 months (total study duration 39 months).

Assumptions of effect sizes were based on the empirical studies EMPA-REG OUTCOME, CANVAS, TOPCAT, and I-PRESERVE.

Randomisation

Randomisation of patients was performed using an IxRS in balanced blocks to ensure an approximate balance between treatment groups (1:1). Randomisation was stratified in IxRS based on T2DM status (documented diagnosis of T2DM or HbA1c ≥ 6.5% [48 mmol/mol] shown at central laboratory test at enrolment) at the time of randomisation.

The proportion of patients with T2DM and without diabetes was monitored for potential capping in order to ensure a minimum of 30% within each patient group. Randomisation was also continuously monitored for geographic region, LVEF category, NYHA class, subacute status, and atrial fibrillation status at enrolment, the results of which could have led to capping in the IxRS to avoid over- or underrepresentation of these patient subgroups. During the recruitment period, capping was only used twice in Japan for the atrial fibrillation subgroup.

Blinding (masking)

The blinding of treatment used a double-blind technique using a matching placebo (10mg). Individual treatment codes, indicating the randomised treatment for each patient, were available to the investigator(s) or pharmacists from the IxRS. Instructions for code breaking/unblinding were described in the IxRS user manual that were provided to each site.

The randomisation code was not to be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator was

to document and report the action to AstraZeneca, without revealing the treatment given to the patient to the MAH staff.

The MAH and Investigators remained blinded to the results of the interim analysis.

Statistical methods

General

DELIVER was an international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled Phase III study in patients with HF and LVEF > 40%. DELIVER evaluated superiority of the effect of dapagliflozin 10 mg compared with placebo, given once daily, in reducing the composite of CV death or an HF event.

Estimands

The primary and secondary event-based objectives was evaluated under the treatment policy estimand including differences in outcomes over the entire study period until primary analysis censoring date (PACD) to reflect the effect of the initially assigned randomised study drug, irrespective of exposure to study drug, concomitant treatment as well as subsequent treatment after discontinuation of study drug. The analysis will be performed for the full analysis set including all events that occurred on or prior to PACD, including events following premature discontinuation of study treatment.

The estimand for the change from baseline in KCCQ total symptom score at 8 months will employ a combination of a treatment policy strategy and a composite strategy. For the intercurrent event of death (due to any cause) prior to the KCCQ assessment at 8 months, a composite strategy was used, where death was considered unfavourable and represented by a lowest (worst) rank of a combined outcome variable. For all other types of intercurrent events, including but not limited to a premature discontinuation of randomised treatment, a treatment policy strategy was used.

Analysis sets.

Full Analysis Set (FAS): All patients who have been randomised to study treatment will be included in the full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised IP assignment, irrespective of the treatment actually received. The FAS will be considered the primary analysis set for the intention to treat (ITT) analysis of primary and secondary variables and for the exploratory efficacy variables.

Safety analysis set (SAS): All randomised patients who received at least 1 dose of randomised treatment will be included in the safety analysis set. Patients will be analysed according to the treatment actually received. The Safety analysis set will be considered the primary analysis set for all safety variables.

Endpoints and Analysis

Primary Endpoint. The primary efficacy variable was time from randomisation to the first occurrence of any event in the composite of CV death, hospitalisation for HF or an urgent HF visit, which was analysed using a Cox proportional hazards model. The model was stratified by T2DM status at randomisation and included a factor for treatment group. The analysis of primary composite endpoint was based on the adjudicated events.

Secondary Endpoints. Total number of HF events (first and recurrent) and CV death was analysed using the semi-parametric proportional rates model (known as the LWYY method) (Lin et al 2000).

Change from baseline at 8 months of the Total Symptom Score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ) was transformed to a rank-based endpoint with fractional ranks, using the mean method for ties, and stratified by T2DM status at randomisation. This composite endpoint (including deaths as the worst outcomes) was analysed using rank based ANCOVA (Stokes et al 2012) and adjusted for ranked baseline KCCQ TSS value to test the null hypothesis of no difference in the distributions of ranked outcomes between treatment groups.

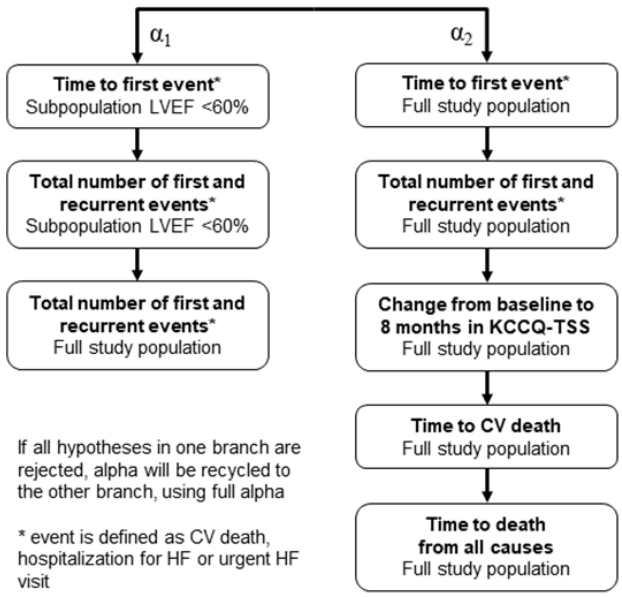
Time to CV death and time to all-cause mortality were analysed using Cox regression in the same manner as the primary composite endpoint, with stratification for T2DM status at randomisation.

Multiple Testing Procedure

To control the overall type I error rate at 5% (two-sided) a closed testing procedure with a pre-specified hierarchical ordering of the primary and secondary endpoints following the principles of alpha-splitting and alpha-recycling. The significance level was adjusted for one planned interim analysis of efficacy with alpha 0.2% allocated to the interim analysis and alpha 4.8% allocated to the final analysis. The primary endpoint was tested parallel in the full study population and in the subpopulation with LVEF < 60% with alpha split between the dual hypotheses.

The primary and secondary endpoints were tested in a hierarchical sequence at a significance level of 4.8% at the final analysis. Statistical significance was assessed simultaneously in 2 branches in the prespecified order of the endpoints and populations as specified in **Figure 2**. The total significance level was split for the dual primary analysis, allocating 3.8% to test the LVEF < 60% subpopulation (alpha 1) and 2.4% to test the full population (alpha 2) taking into account correlation between tests in the total and the subpopulation according to Spiessen and Debois (2010).

Figure 2 Testing Procedure



CV, cardiovascular; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; TSS, total symptom score.

Interim Analysis

An interim analysis assessing superiority of dapagliflozin to placebo was planned to be carried out when approximately 67% of the adjudicated primary events (approximately 748 events) had occurred. The MAH and Investigators remained blinded to the results.

The interim analysis was carried out after the accrual of 70.9% (792 events) of the final target number of 1117 primary events. The primary composite endpoint was tested in the full study population at a nominal two-sided alpha level of 0.2% at the interim. If superiority was achieved for the primary endpoint, then the superiority of dapagliflozin to placebo on CV death was to be tested in the full study population at a two-sided level of 0.2%. The study continued as planned after the interim analysis.

Subgroup Analyses

Exploratory subgroup analyses of the primary composite endpoint were performed for a list of characteristics, e.g., age, sex, race, region, NYHA, LVEF, for both full population and LVEF < 60% subpopulation. The subgroup analyses were repeated for CV death and the HF event (hospitalisation for HF and urgent HF visit) component of the primary composite endpoint.

Missing Data and Imputation

The time-to-first event analysis by Cox proportional hazards regression and the analysis of recurrent events assume that missing data is at random. Sensitivity analysis assuming a conservative missing-not-at-random missing data process was performed (see sensitivity analysis below).

The number of patients with missing vital status at 8 months was expected to be negligible. If a patient was known to have died prior to the 8-month assessment, the patient was considered to have a non-missing composite outcome and was assigned the worst rank. Patients who were alive at 8 months and had missing baseline or 8-month KCCQ assessments had their missing KCCQ-TSS imputed using the multiple imputation under missing-at-random assumption.

Sensitivity Analyses

Sensitivity analyses were performed for the primary analysis: 1) adjudicating undetermined cause of death as CV deaths, 2) imputing missing data of time-to-event for patients with premature censoring including a tipping point analysis to assess violations of informative censoring (which was replaced by a "worst case" analysis post-hoc), and 3) censoring patients and events at the onset data of AE associated with a Covid-19 infection (MAR).

In addition, various sensitivity analyses were performed on secondary endpoints, e.g., to evaluate any bias because of the Covid-19 pandemic. Potential bias because of competing risks of events (incl. HF events and CV death) included in the composite primary endpoint was assessed using a joint modelling approach (frailty model) (Rogers et al., 2016) for the analysis of individual components and non-parametric estimates of HF event rates over time allowing for death as terminal event (Ghosh & Lin, 2000).

Governance

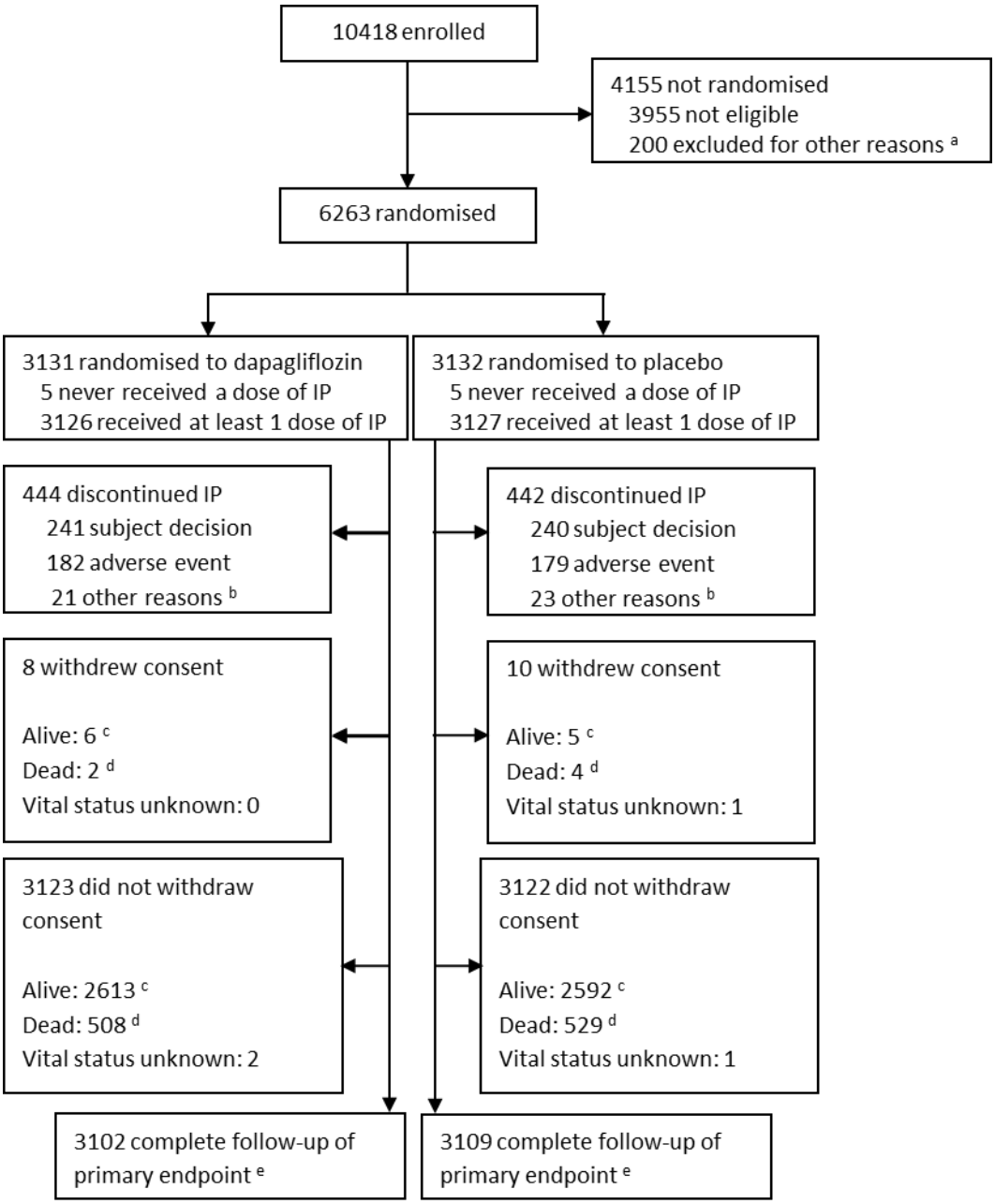
The final Statistical Analysis Plan (V5.0, 2021-12-08) outlining all planned analyses was prepared before database lock on 2022-04-22 and unblinding (Last patient, last visit: 2022-03-27), while blinding was maintained during sample size re-estimation and interim analysis.

Results

Participant flow

A total of 6263 patients were randomised from 350 study sites in 20 countries. The median time in study until PACD was 28.0 months (range 0.1 to 42.1 months) and median time until last visit was 28.5 months (range 0.1 to 42.2 months). There were 6211 patients (99.2%) with complete follow-up of the primary composite endpoint (**Figure 3**). A total of 18 patients withdrew consent, withdrawals were balanced between treatment groups. Vital status was unknown for 4 patients in total. The frequency of discontinuation of IP was low and balanced between treatment groups. The most common reasons for discontinuation of IP were patient decision in 481 cases (7.7%) and AE in 361 cases (5.8%).

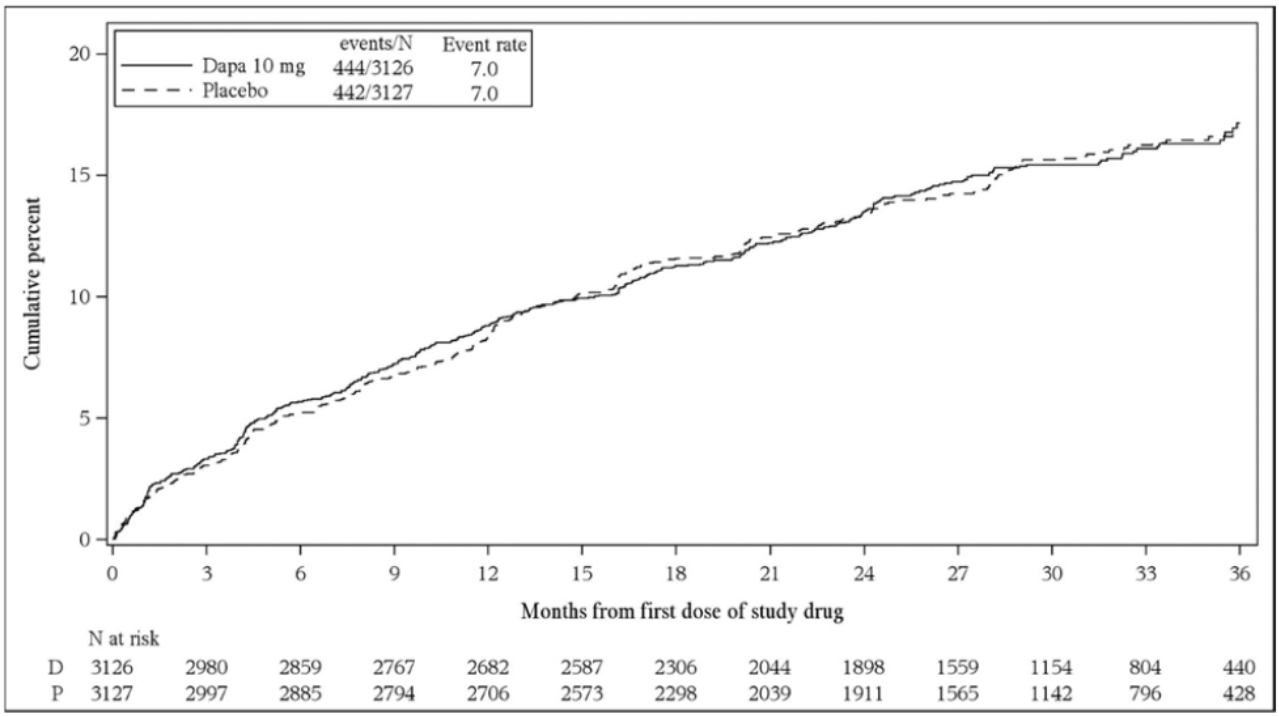
Figure 3 Patient Disposition



a Other possible reasons for exclusion of enrolled subjects: withdrawal by subject, adverse event, death, other
b Other possible reasons for discontinuing IP: confirmed DKA, other.
c Confirmed alive on or after PACD.
d Dead at any time during study.
e Subjects with a primary event or censored due to death or at PACD in the analysis of the primary endpoint.
DKA, diabetic ketoacidosis; IP, investigational product; PACD, primary analysis censoring date.

In the full study population, the frequency of discontinuation of IP was low and balanced between treatment groups (**Figure 4**).

Figure 4 Kaplan-Meier Plot of the Cumulative Percentage of Patients with Premature Permanent Discontinuation of IP (SAS)



N at risk is the number of subjects at risk at the beginning of the period. One month corresponds to 30 days.
Two-sided p-value is displayed.
Dapa, dapagliflozin; D, dapa 10 mg; IP, investigational product; N, number of subjects; P, placebo; SAS, safety analysis set.

Recruitment

This international, multi-centre study of 6263 randomised patients was conducted at 353 sites across 20 countries.

EU countries involved: Belgium, Bulgaria, Czech Republic, Hungary, Netherlands, Poland, Romania, Spain

Non-EU countries involved: Argentina, Brazil, Canada, China, Japan, Mexico, Peru, Russian Federation, Saudi Arabia, Taiwan, United States, Vietnam

First subject enrolled: 27 August 2018

Last subject last visit: 27 March 2022

Conduct of the study

Protocol amendments

The original CSP was dated 24 April 2018. There were 3 amendments to the CSP: Version 2.0 was dated 9 May 2018, Version 3.0 was dated 16 December 2019, and Version 4.0 was dated 12 November 2020. All protocol amendments were approved by AstraZeneca before being submitted to Health Authorities and/or an IRB/IEC.

Protocol deviations

Important protocol deviations were balanced between treatment groups with respect to frequency and type (**Table 1**). Overall, 3.7% of patients had at least one important protocol deviation. All the important protocol deviations were reviewed and agreed before clinical data lock.

Table 1 Summary of Important Protocol Deviations (FAS)

	Number (%) of subjects		
Important protocol deviation	**Dapa 10 mg (N = 3131)**	**Placebo (N = 3132)**	**Total (N = 6263)**
Number of subjects with at least one important deviation	107 (3.4)	125 (4.0)	232 (3.7)
Randomised but did not fulfil all inclusion and exclusion criteria	76 (2.4)	83 (2.7)	159 (2.5)
Received IP not allocated by IxRS	3 (0.1)	3 (0.1)	6 (0.1)
Received prohibited concomitant medication [a]	20 (0.6)	32 (1.0)	52 (0.8)

[a] SGLT2 inhibitor taken concomitantly with the IP

Note that the same subject may have had more than one important protocol deviation.

Dapa, dapagliflozin; FAS, full analysis set; IP, investigational product; IxRS, interactive response system; N, number of subjects in treatment group; SGLT2, sodium-glucose cotransporter 2.

A total of 36 patients were randomised despite failing the inclusion criteria of LVEF > 40% and evidence of structural heart disease within the last 12 months prior to enrolment. Of these 36 patients, 4 patients had LVEF ≤ 40%: 3 in the dapagliflozin group and 1 in the placebo group.

A total of 46 patients were randomised despite failing the inclusion criteria of documented diagnosis of symptomatic HF (NYHA class II to IV) at enrolment, and a medical history of typical symptoms/signs of HF ≥ 6 weeks before enrolment with at least intermittent need for diuretic treatment. Of these 46 patients, 2 patients (1 in each treatment group) did not have a documented diagnosis of symptomatic HF.

A total of 140 patients (2.2%) were treated with open-label SGLT2 inhibitors during the study, of which 54 (0.9%) cases were classified as prohibited medication use (ie, taken concomitantly with the IP). Reported use of concomitant SGLT2 inhibitors was reviewed by the study teams/study physicians. Following review of the 54 cases, 52 cases were confirmed as prohibited medication use and reported as important protocol deviations. The cases of prohibited medication use were balanced between treatment groups.

Protocol Deviations Related to COVID-19

There were 2571 patients (41.1%) with at least one COVID-19 related non-important protocol deviation. The most common non-important protocol deviation was related to study procedures and

assessments. Only 5 patients (0.1%) had at least one important protocol deviation: 4 in the dapagliflozin group and 1 in the placebo group.

Baseline data

Demographic Characteristics

In the full study population, patient demographic characteristics were balanced between treatment groups (**Table 2**). In total, 43.9% of patients were female. The mean age was 71.7 years.

Table 2 Demographic Characteristics (FAS)

		Dapa 10 mg (N = 3131)	Placebo (N = 3132)	Total (N = 6263)
Demographic characteristic				
Age (years)	n	3131	3132	6263
	Mean	71.8	71.5	71.7
	SD	9.6	9.5	9.6
	Median	73.0	72.0	72.0
	Min	40	40	40
	Max	99	99	99
Age group (years) n (%)	≤ 50	85 (2.7)	74 (2.4)	159 (2.5)
	> 50	3046 (97.3)	3058 (97.6)	6104 (97.5)
	≤ 65	743 (23.7)	761 (24.3)	1504 (24.0)
	> 65-75	1184 (37.8)	1228 (39.2)	2412 (38.5)
	> 75	1204 (38.5)	1143 (36.5)	2347 (37.5)
Sex n (%)	Male	1767 (56.4)	1749 (55.8)	3516 (56.1)
	Female	1364 (43.6)	1383 (44.2)	2747 (43.9)
Race n (%)	White	2214 (70.7)	2225 (71.0)	4439 (70.9)
	Black or African American	81 (2.6)	78 (2.5)	159 (2.5)
	Asian	630 (20.1)	644 (20.6)	1274 (20.3)
	Native Hawaiian or other Pacific Islander	0	0	0
	American Indian or Alaska Native	93 (3.0)	96 (3.1)	189 (3.0)
	Other	113 (3.6)	89 (2.8)	202 (3.2)
Ethnic group n (%)	Hispanic or Latino	632 (20.2)	598 (19.1)	1230 (19.6)
	Not Hispanic or Latino	2499 (79.8)	2534 (80.9)	5033 (80.4)
Region n (%)	Asia	607 (19.4)	619 (19.8)	1226 (19.6)
	Europe and Saudi Arabia	1494 (47.7)	1511 (48.2)	3005 (48.0)
	North America	428 (13.7)	423 (13.5)	851 (13.6)
	Latin America	602 (19.2)	579 (18.5)	1181 (18.9)

Dapa, dapagliflozin; FAS, full analysis set; Max, maximum; Min, minimum; N, number of subjects in treatment group; n, number of subjects included in analysis; SD, standard deviation.

In the subpopulation with LVEF < 60%, patient demographic characteristics were balanced between treatment groups, and were generally consistent with those of the full study population.

Baseline Patient Characteristics

Baseline patient characteristics, including vital signs, were balanced between treatment groups. There were similar proportions of patients with T2DM (defined as medical history of T2DM): 44.7% in the dapagliflozin group and 44.9% in the placebo group. Mean body mass index was similar between treatment groups.

Baseline Heart Failure Characteristics

Most patients were diagnosed with HF < 5 years before enrolment. A total of 2539 patients (40.5%) had been hospitalised for HF prior to study enrolment. The subacute subgroup included 654 patients (10.4%).

HF characteristics were balanced between treatment groups (**Table 3**). Overall, 4713 patients (75.3%) were classified as NYHA class II at enrolment. The median (IQR) LVEF was 54.0% (47.0% to 60.0%). The median (IQR) NT-proBNP was 1011.0 pg/mL (623.0 to 1751.0 pg/mL).

Table 3 Heart Failure Characteristics at Baseline (FAS)

		Dapa 10 mg (N = 3131)	**Placebo (N = 3132)**	**Total (N = 6263)**
Subject characteristic				
NYHA class at enrolment [a] n (%)	n	3131	3132	6263
	I	0	1 (0.0)	1 (0.0)
	II	2314 (73.9)	2399 (76.6)	4713 (75.3)
	III	807 (25.8)	724 (23.1)	1531 (24.4)
	IV	10 (0.3)	8 (0.3)	18 (0.3)
LVEF (%)	n	3131	3132	6263
	Q1	46.0	47.0	47.0
	Median	54.0	54.0	54.0
	Q3	60.0	60.0	60.0
LVEF group (%) n (%)	n	3131	3132	6263
	≤ 40	3 (0.1)	1 (0.0)	4 (0.1)
	≥ 41-49	1064 (34.0)	1048 (33.5)	2112 (33.7)
	≥ 50-59	1133 (36.2)	1123 (35.9)	2256 (36.0)
	≥ 60	931 (29.7)	960 (30.7)	1891 (30.2)
Left ventricular hypertrophy	n	3130	3130	6260
	Yes	2103 (67.2)	2080 (66.5)	4183 (66.8)

Table 3 Heart Failure Characteristics at Baseline (FAS)

		Dapa 10 mg (N = 3131)	Placebo (N = 3132)	Total (N = 6263)
Subject characteristic				
Left atrial enlargement	n	3128	3128	6256
	Yes	2792 (89.3)	2797 (89.4)	5589 (89.3)
Atrial fibrillation or flutter at enrolment ECG	n	3130	3131	6261
	Yes	1327 (42.4)	1317 (42.1)	2644 (42.2)
NT-proBNP (pg/mL) [a]	n	3131	3131	6262
	Q1	625.0	620.0	623.0
	Median	1021.0	1005.0	1011.0
	Q3	1777.0	1735.0	1751.0

[a] The last value on or prior to date of first dose of IP.

[b] n is the number of patients with non-missing data and the denominator for percentages.

[c] Dapa, dapagliflozin; ECG, electrocardiogram; FAS, full analysis set; IP, investigational product; LVEF, left ventricular ejection fraction; N, number of subjects in treatment group; n, number of subjects included in analysis; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; Q1, first quartile; Q3, third quartile.

The baseline characteristics based on clinical laboratory measurements were balanced between treatment groups (**Table 4**). Overall, 49.0% of patients had an eGFR < 60 mL/min/1.73 m2.

Table 4 Baseline Characteristics Based on Clinical Laboratory Measurements (FAS)

		Dapa 10 mg (N = 3131)	Placebo (N = 3132)	Total (N = 6263)
Subject characteristic				
Serum creatinine (µmol/L) [a]	n	3131	3131	6262
	Min	29	34	29
	Median	96.4	97.2	97.2
	Max	251	253	253
eGFR (mL/min/1.73 m^2) [a]	n	3131	3131	6262
	Min	23	22	22
	Median	60.0	60.0	60.0
	Max	147	121	147
	Mean	61.2	60.9	61.0
	SD	19.0	19.3	19.1
eGFR category (mL/min/1.73 m^2) [a]	n	3131	3131	6262
	< 25	2 (0.1)	2 (0.1)	4 (0.1)

Table 4 Baseline Characteristics Based on Clinical Laboratory Measurements (FAS)

		Dapa 10 mg (N = 3131)	Placebo (N = 3132)	Total (N = 6263)
Subject characteristic				
	25- < 30	89 (2.8)	99 (3.2)	188 (3.0)
	30- < 45	599 (19.1)	622 (19.9)	1221 (19.5)
	45- < 60	826 (26.4)	831 (26.5)	1657 (26.5)
	< 60	1516 (48.4)	1554 (49.6)	3070 (49.0)
	≥ 60	1615 (51.6)	1577 (50.4)	3192 (51.0)

[a] The last value on or prior to date of first dose of IP.

n is the number of subjects with non-missing data and the denominator for percentages.

Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; FAS, full analysis set; IP, investigational product; Max, maximum; Min, minimum; N, number of subjects in treatment group; n, number of subjects included in analysis; SD, standard deviation.

In the full study population, KCCQ-TSS data at baseline was available for 92.6% of patients. Mean KCCQ-TSS at baseline was 68.8 in the dapagliflozin group and 69.8 in the placebo group (range 0 to 100; a higher score indicates less/milder symptoms). Missing KCCQ-TSS data at baseline was balanced between treatment groups.

Medical History

The medical and relevant surgical history of the patients, as well as the smoking history, was balanced between treatment groups. Hypertension was reported by 89%, dyslipidaemia by 64%, coronary artery stenosis by 30%, CKD by 28%, valvular heart disease by 27%, myocardial infarction by 26% and stable angina pectoris by 21% of patients.

Use of Concomitant Medication

Concomitant Medication at Randomisation

At randomisation, treatment of HF symptoms and co-morbidities was balanced between treatment groups. In total, 97.8% of patients were treated with a diuretic, most commonly a loop diuretic, 82.7% with a beta blocker, 77.2% with an ACEi/ARB/ARNI, and 42.6% with an MRA (**Table 5**).

Table 5 Heart Failure and CV Medication at Randomisation (FAS)

	Number (%) of subjects		
	Dapa 10 mg (N = 3131)	**Placebo (N = 3132)**	**Total (N = 6263)**
Treatments			
ACEi	1144 (36.5)	1151 (36.7)	2295 (36.6)
ARB	1133 (36.2)	1139 (36.4)	2272 (36.3)
ARNI	165 (5.3)	136 (4.3)	301 (4.8)
Beta blocker	2592 (82.8)	2585 (82.5)	5177 (82.7)

Table 5 Heart Failure and CV Medication at Randomisation (FAS)

	Number (%) of subjects		
	Dapa 10 mg (N = 3131)	**Placebo (N = 3132)**	**Total (N = 6263)**
Calcium channel blockers	939 (30.0)	976 (31.2)	1915 (30.6)
ACEi or ARB	2262 (72.2)	2281 (72.8)	4543 (72.5)
ACEi, ARB, or ARNI	2420 (77.3)	2412 (77.0)	4832 (77.2)
(ACEi, ARB, or ARNI) and beta blocker	2036 (65.0)	2023 (64.6)	4059 (64.8)
(ACEi, ARB, or ARNI) and beta blocker and MRA	933 (29.8)	898 (28.7)	1831 (29.2)
Diuretics	3061 (97.8)	3062 (97.8)	6123 (97.8)
MRA	1340 (42.8)	1327 (42.4)	2667 (42.6)
Loop diuretics	2403 (76.7)	2408 (76.9)	4811 (76.8)
Other (non-loop non-MRA) diuretics	654 (20.9)	689 (22.0)	1343 (21.4)
Digitalis glycosides	150 (4.8)	146 (4.7)	296 (4.7)
Vasodilators	271 (8.7)	286 (9.1)	557 (8.9)
Lipid lowering drugs	2061 (65.8)	2096 (66.9)	4157 (66.4)
Statins	2004 (64.0)	2035 (65.0)	4039 (64.5)
Antithrombotic agents	2708 (86.5)	2731 (87.2)	5439 (86.8)

This table includes medication with at least one dose taken before date of randomisation and with no stop date before date of randomisation.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CV, cardiovascular; Dapa, dapagliflozin; FAS, full analysis set; MRA, mineralocorticoid receptor antagonist; N, number of subjects in treatment group.

Concomitant Medication after Randomisation

The use of diuretics remained high and balanced between treatment groups throughout the study. The use of ACEi, ARB, ARNI, and MRA also remained balanced between treatment groups throughout the study.

The use of prohibited medications was balanced between treatment groups. A total of 140 patients (2.2%) were treated with open-label SGLT2 inhibitors during the study, of which 54 cases (0.9%) were classified as prohibited medication use (i.e., taken concomitantly with the IP). Reported use of concomitant SGLT2 inhibitors was reviewed by the study teams/study physicians. Following review of the 54 cases, 52 cases were confirmed as prohibited medication use and reported as important protocol deviations.

Study Treatment Compliance

Treatment compliance was high and balanced between treatment groups. Compliance > 90% was observed in 90.3% of subjects in the dapagliflozin treated group and in 90.9% in the placebo treated group.

Summary of Demographic and Other Baseline Patient Characteristics in the Subpopulation with LVEF < 60%

In the subpopulation with LVEF < 60%, treatment compliance was high and balanced between treatment groups, while the frequency of discontinuation of IP was low and balanced. Demographic and baseline patient characteristics, including background therapy and medical history, were balanced between treatment groups.

Demographic and baseline patient characteristics in the subpopulation with LVEF < 60% were generally consistent with those of the full study population, except for minor expected differences in the proportion of patients with myocardial infarction, stable angina pectoris, and coronary artery stenosis, which tended to be higher in the subpopulation with LVEF < 60%.

Numbers analysed

The analysis sets and the number of patients in each analysis set are summarised in **Table 6**.

Table 6 Analysis Sets

	Number of subjects	
	Dapa 10 mg	**Placebo**
Subjects randomised	3131	3132
Subjects included in full analysis set	3131	3132
Subjects included in full analysis set with LVEF < 60%	2200	2172
Subjects included in safety analysis set [a,b]	3126	3127
Subjects excluded from safety analysis set [a] (Patients who did not receive at least one dose of IP)	5	5

All randomised subjects who received at least one dose of IP.

No subjects randomised to placebo incorrectly received Dapa (only). No subjects randomised to Dapa incorrectly received placebo (only).

Dapa, dapagliflozin; FAS, full analysis set; IP, investigational product; LVEF, left ventricular ejection fraction; SAS, safety analysis set.

Outcomes and estimation

Summary of Testing Hierarchy and Overall Efficacy Results

Dapagliflozin was superior to placebo in reducing the incidence of primary composite endpoint of CV death or an HF event in the full study population and in the subpopulation with LVEF < 60% (**Table 7**). Detailed results will be presented only for the full study population.

Demonstration of superiority for the primary composite endpoint initiated sequential testing of secondary endpoints. An alpha of 2.4% and 3.8% was used to test the primary composite endpoint in the full study population and in the subpopulation with LVEF < 60%, respectively. Since both primary null hypotheses were rejected, the subsequent hypotheses in each branch (**Table 7**) were tested at 2.4%, in the order of the testing hierarchy. Further, because all hypotheses in branch II were rejected, alpha was recycled to branch I, where remaining unrejected hypotheses were re-tested at full alpha adjusted for interim analysis (i.e., 4.8%).

In the full study population, dapagliflozin was superior to placebo in reducing the incidence of composite of CV death and recurrent HF events, and in providing symptom benefit as measured by KCCQ TSS.

The benefit of dapagliflozin on primary composite endpoint was consistent across the key prespecified subgroups in the full study population, including those defined by baseline LVEF (≤ 49%, 50% to 59%, ≥ 60%), age and sex. A nominal interaction p-value < 0.05 was observed for the subgroup analysis by median systolic BP (≤ 128.0 mmHg, > 128.0 mmHg), but the point estimates for both subgroups were below unity.

Table 7 Overview of Confirmatory Analysis of Primary and Secondary Endpoint Hierarchy (FAS)

		Dapa 10 mg (N = 3131)	**Placebo (N = 3132)**			
Variable	**Type of estimate**	**n [a]**	**n [a]**	**Comparison between groups**	**95% CI**	**p-value**
Branch I: Full population		**(N = 3131)**	**(N = 3132)**			
Composite of CV death, hospitalisation for HF or urgent HF visit	Hazard ratio	512	610	0.82	(0.73, 0.92)	0.0008 [s]
Composite of CV death and recurrent HF events [b]	Rate ratio	815	1057	0.77	(0.67, 0.89)	0.0003 [s]
Change from baseline at 8 months in the KCCQ total symptom score [c]	Win ratio	1273	1276	1.11	(1.03, 1.21)	0.0086 [s]
CV death	Hazard ratio	231	261	0.88	(0.74, 1.05)	0.1678
All-cause mortality	Hazard ratio	497	526	0.94	(0.83, 1.07)	0.3425
Branch II: LVEF < 60% subpopulation and full population		**(N = 2200)**	**(N = 2172)**			
Composite of CV death, hospitalisation for HF or urgent HF visit in LVEF < 60% subpopulation	Hazard ratio	381	440	0.83	(0.73, 0.95)	0.0085 [s]
Composite of CV death and recurrent HF events [b] in LVEF < 60% subpopulation	Rate ratio	605	782	0.77	(0.65, 0.90)	0.0017 [s]
Composite of CV death and recurrent HF events [b]	Rate ratio	815	1057	0.77	(0.67, 0.89)	0.0003 [s]

a n is the number of subjects with event for time to first event analysis (hazard ratio estimate), total number of events for recurrent event analysis (rate ratio estimate), and number of subjects included in analysis (win ratio analysis).

b An HF event includes hospitalisations for HF and urgent HF visits.

c Analysis performed in the population with Visit 5 (8 months) planned or performed prior to 11 March 2020, when COVID 19 was declared a pandemic by the WHO.

s Indicates statistical significance. Statistical testing is performed in sequence in 2 branches with split alpha, until first non-significant result is observed. An alpha of 2.4% and 3.8% was used to test the primary endpoint in the full population and in the subpopulation with LVEF < 60%, respectively. Because all hypotheses in branch II were rejected, alpha was recycled to branch I, where remaining unrejected hypotheses were re-tested at full alpha adjusted for interim analysis (ie, 4.8%).

A hazard ratio < 1, a rate ratio < 1, or a win ratio > 1 favours Dapa 10 mg.

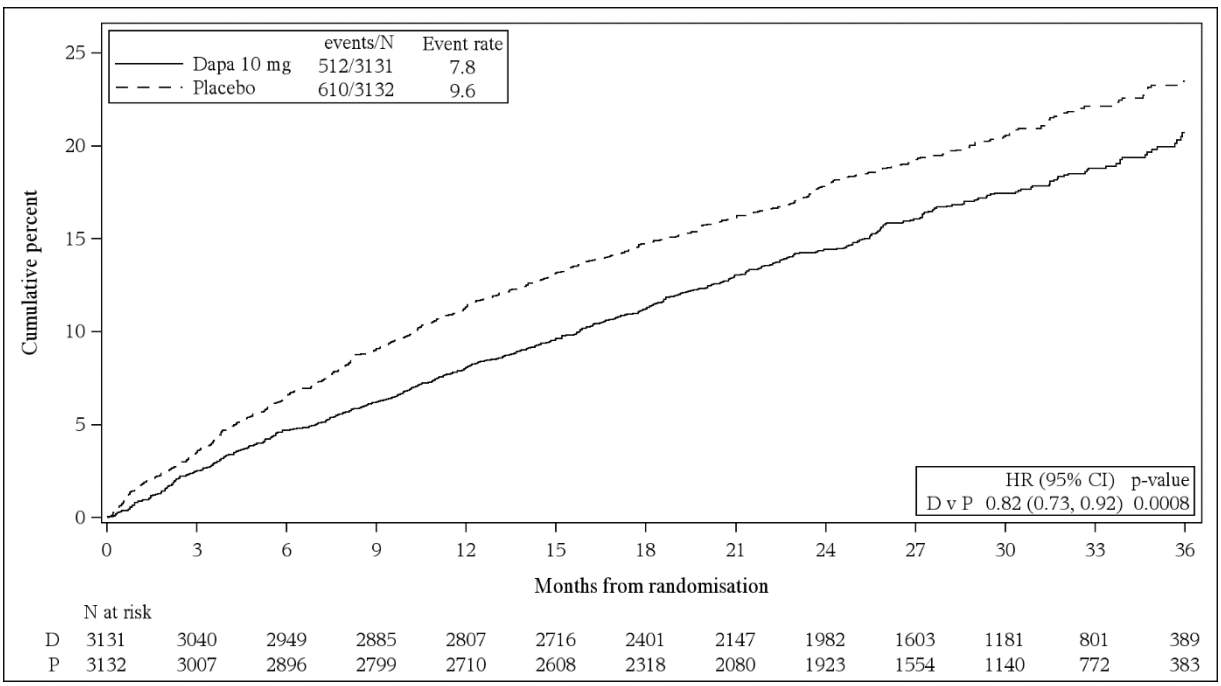
CI, confidence interval; COVID 19, coronavirus disease 2019; CV, cardiovascular; Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; N, number of subjects in treatment group.

Primary Efficacy Endpoint – Composite of CV death or an HF Event

Dapagliflozin was superior to placebo in reducing the incidence of primary composite endpoint of CV death or an HF event (HR 0.82 [95% CI 0.73, 0.92], p = 0.0008) (**Figure 5**). There were 512 and 610 patients with CV death or an HF event in the dapagliflozin group and in the placebo group, respectively, corresponding to event rates per 100 patient-years of 7.8 and 9.6. Of a total of 1122 patients with a composite event, 300 patients had CV death as their first event.

A Kaplan-Meier analysis of the composite of CV death or an HF event is presented in **Figure 5**. The curves diverged early, and the separation was maintained throughout the study.

Figure 5 Kaplan-Meier Plot of the Primary Composite Endpoint (CV Death/HF Hospitalisation/Urgent HF Visit) (FAS)

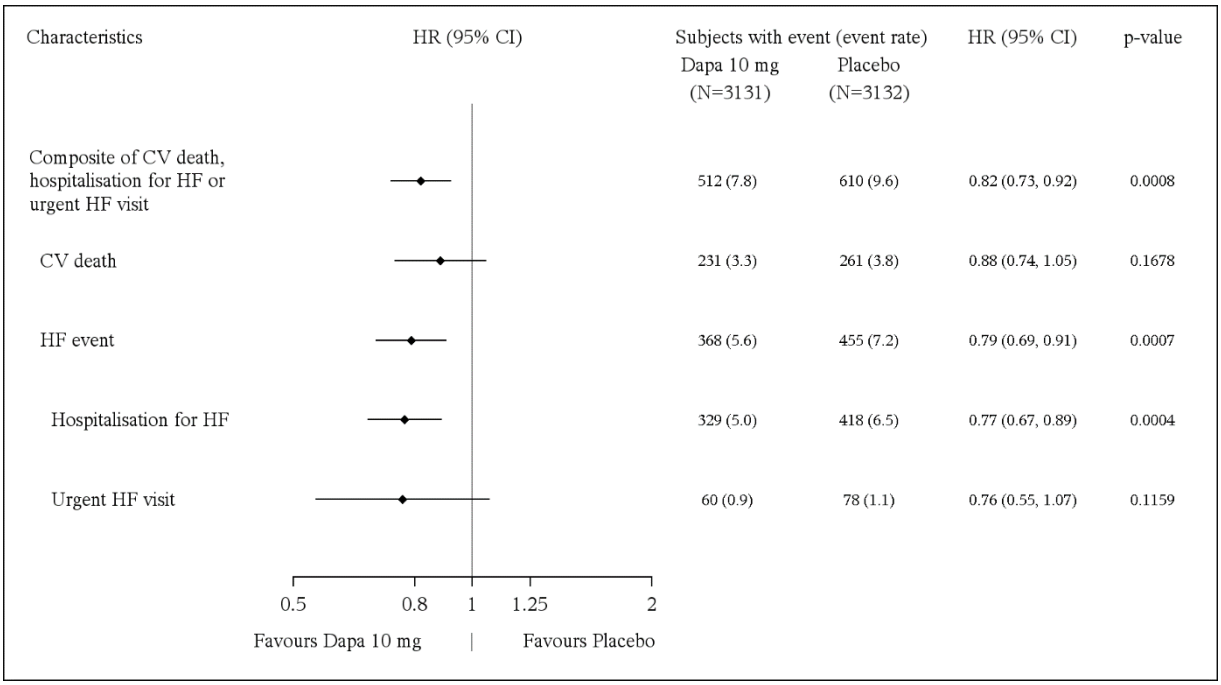


N at risk is the number of subjects at risk at the beginning of the period. One month corresponds to 30 days. Two-sided p-value is displayed. HR, CI, and p-value are from the Cox proportional hazards model.

CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; D, dapa 10 mg; FAS, full analysis set; HF, heart failure; HR, hazard ratio; N, number of subjects; P, placebo.

Results from analyses of individual components of the primary composite endpoint are summarised in **Figure 6**. All components individually contributed to the treatment effect.

Figure 6 Forest Plot of the Primary Composite Endpoint (CV Death/HF Hospitalisation/Urgent HF Visit) and the Individual Components (FAS)



The number of events for the individual components are the actual number of first events for each component and their sum exceeds the number of events for the composite endpoint. Event rates are presented as the number of subjects with event per 100 patient-years of follow-up. Hazard ratio for Dapa 10 mg vs placebo, CIs, and 2-sided p-value are calculated from Cox proportional hazards model (Wald statistic) stratified by T2DM status at randomisation. An HF event includes hospitalisations for HF and urgent HF visits.

CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure; HR, hazard ratio; N, number of subjects in treatment group; T2DM, type 2 diabetes mellitus.

Subpopulation with LVEF < 60%

Consistent with the results in the full study population, dapagliflozin was superior to placebo in reducing the incidence of primary composite endpoint of CV death or an HF event in the subpopulation with LVEF < 60% (HR 0.83 [95% CI 0.73, 0.95], p = 0.0085.

Sensitivity Analyses of the Primary Variable

Sensitivity analyses were performed to assess the robustness of the results of primary composite endpoint. Results of the sensitivity analysis, in which deaths adjudicated as 'undetermined cause of death' were considered CV deaths and included as endpoint events, were consistent with those of the main analysis.

Results of the COVID-19 sensitivity analysis, in which patients were censored at the onset date of the first AE associated with COVID-19 infection, were consistent with those of the main analysis.

The extent of incomplete follow-up of the primary composite endpoint, defined in terms of incomplete event assessment or withdrawal of consent, was low and balanced between treatment groups. In the dapagliflozin group and in the placebo group, respectively, 0.9% and 0.7% of patients were censored

prior to PACD due to incomplete follow-up. Incomplete follow-up of the primary composite endpoint accounted for 0.5% of total patient time in both treatment groups. A tipping point analysis was prespecified to assess the robustness of the statistical significance of primary analysis with respect to prematurely censored patients. In light of the magnitude of the observed treatment effect and the low frequency of incomplete follow-up, the tipping point analysis was replaced by a post-hoc "worst case analysis". This rendered in total 29 new events in the dapagliflozin group. Patients in the placebo group censored before PACD were considered event-free until PACD. While this constitutes the most unfavourable scenario for dapagliflozin with regards to the outcome in the censored patients, the resulting treatment effect estimate remained statistically significant.

Subpopulation with LVEF < 60%

Results of the sensitivity analysis, in which deaths adjudicated as 'undetermined cause of death' were considered CV deaths and included as endpoint events, were consistent with those of the main analysis in the subpopulation with LVEF < 60%.

Secondary Efficacy Endpoints

Composite of CV Death and Recurrent HF Events

Dapagliflozin was superior to placebo in reducing the incidence of composite of CV death and recurrent HF events (**Table 8**). There were 815 and 1057 events of the composite endpoint in the dapagliflozin group and in the placebo group, respectively, corresponding to event rates per 100 patient-years of 11.8 and 15.3.

Table 8 Analysis of the Composite of CV Death and Recurrent HF Events (FAS)

	Dapa 10 mg (N = 3131)		**Placebo (N = 3132)**				
Variable	**Number of events**	**Event rate**	**Number of events**	**Event rate**	**Rate/ hazard ratio [a]**	**95% CI**	**p-value**
Composite of CV death and recurrent HF events	815	11.8	1057	15.3	0.77	(0.67, 0.89)	0.0003
Recurrent HF events [b]	584	8.4	796	11.5	0.73	(0.62, 0.87)	0.0003
CV death [a]	231	3.3	261	3.8	0.88	(0.74, 1.05)	0.1678

[a] Hazard ratio for CV death as an individual component is derived from Cox proportional hazards regression.

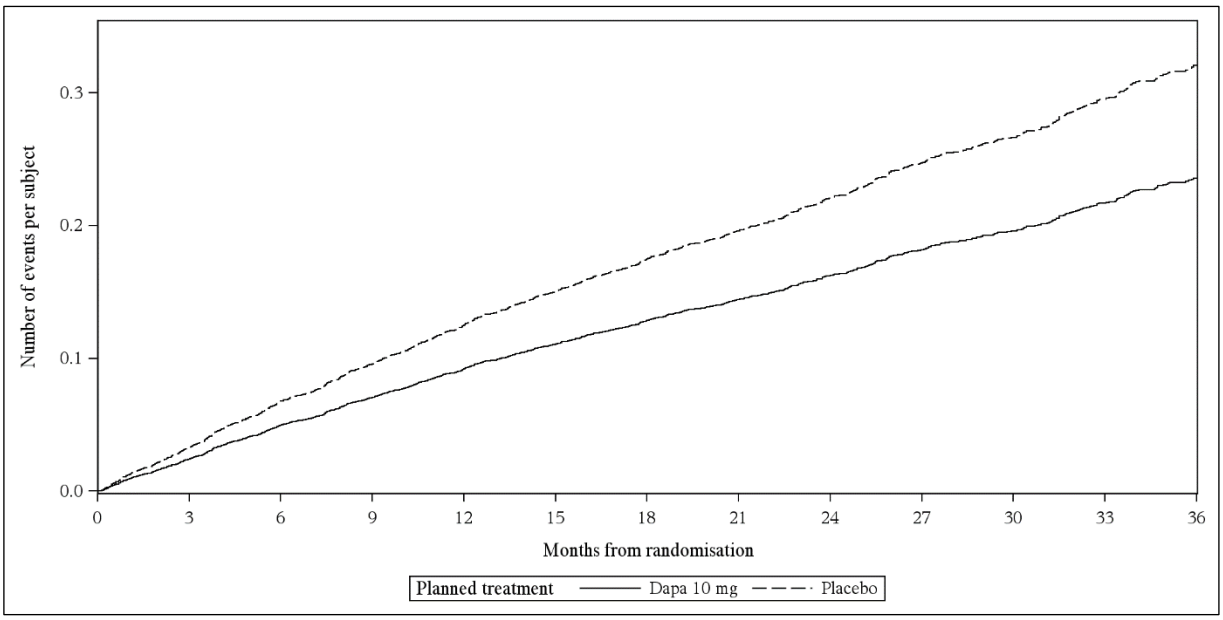
[b] An HF event includes hospitalisations for HF and urgent HF visits.

Event rates are presented as the number of events per 100 patient-years of follow-up. 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 randomisation, with a factor for treatment group as a covariate. If HF events and CV death occurred on the same day, then only CV death is counted in this table.

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.

Results of a supportive analysis, using a joint frailty model, were consistent with those of the main analysis. Rates of hospitalisation events per patient over the course of the study are displayed in **Figure 7**.

Figure 7 Non-parametric Estimates (Ghosh and Lin) of HF Event Rates Over Time (FAS)



Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure.

Results of the COVID-19 sensitivity analysis, in which patients were censored at the onset date of the first AE associated with COVID-19 infection, were consistent with those of the main analysis.

Subpopulation with LVEF < 60%

Consistent with the results in the full study population, dapagliflozin was superior to placebo in reducing the incidence of composite of CV death and recurrent HF events in the subpopulation with LVEF < 60% (rate ratio 0.77 [95% CI 0.65, 0.90], p = 0.0017). The numbers of patients with ≥ 1 and ≥ 2 events of the composite endpoint were lower in the dapagliflozin group compared with the placebo group. Results of a supportive analysis, using a joint frailty model, were consistent with the main analysis of the endpoint.

A post-hoc analysis of composite of CV death and recurrent HF events showed consistent treatment effect in the complement subpopulation with LVEF ≥ 60%.

Change from Baseline at 8 Months in the Total Symptom Score of KCCQ

To mitigate the potential impact of COVID-19 pandemic, the main analyses of KCCQ-TSS were conducted in patients who had the 8-month assessment (Visit 5) planned or performed prior to 11 March 2020 (when COVID-19 was declared a pandemic by the WHO).

Dapagliflozin was superior to placebo in providing symptom benefit as measured by KCCQ-TSS (**Table 9**). A rank-based ANCOVA (including deaths as the worst outcomes) was used to analyse KCCQ-TSS. Both the symptom frequency and the symptom burden subdomains contributed to the overall treatment effect. Results of a sensitivity analysis with an alternative ranking of death were consistent with those of the main analysis.

Table 9 Rank-Based Analysis of Change From Baseline in KCCQ Scores (FAS)

		Dapa 10 mg (N = 1316)	Placebo (N = 1311)	Difference between treatment groups		
Time point	**KCCQ score**	**n**	**n**	**Win ratio**	**95% CI**	**p-value [a]**
8 Months	Total Symptom Score	1273	1276	1.11	(1.03, 1.21)	0.0086
	Symptom Frequency	1273	1276	1.09	(1.01, 1.18)	0.0286
	Symptom Burden	1273	1276	1.11	(1.02, 1.21)	0.0159
	Clinical Summary Score	1273	1276	1.12	(1.03, 1.22)	0.0087
	Overall Summary Score	1273	1276	1.12	(1.02, 1.22)	0.0130

[a] The p-value is obtained from a rank-based ANCOVA adjusted for baseline KCCQ score, stratified by T2DM status at randomisation.

Including subjects with the 8-month assessment (Visit 5) planned or performed prior to 11 March 2020, when COVID-19 was declared a pandemic by the WHO. Subjects with planned but not performed assessment prior to 11 March 2020 were imputed. Change from baseline at the respective assessment time point is converted to ranks. Subjects who died prior to the assessment are assigned worst ranks. Among the deceased, the relative ranking is based on the last value while alive.

ANCOVA, analysis of covariance; CI, confidence interval; COVID-19, coronavirus disease 2019; Dapa, dapagliflozin; FAS, full analysis set; KCCQ, Kansas City Cardiomyopathy Questionnaire; N, number of subjects in treatment group; n, number of subjects alive at time point; T2DM, type 2 diabetes mellitus.

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.

For the DELIVER study, the MAH extensively investigated the clinically meaningful individual levels of change from baseline at 8 months in KCCQ-TSS using an anchor-based approach, in accordance with the guidelines from the FDA workshop (see FDA 2019). The results of these responder analyses showed that a smaller proportion of patients in the dapagliflozin group compared with the placebo group deteriorated by ≥ 5 points (reflecting moderate deterioration) or ≥ 14 points (reflecting large deterioration) on the KCCQ-TSS at 8 months (**Table 10**). The responder analysis of improvement did not show a significant difference between treatment groups.

Table 10 KCCQ Total Symptom Score - Responder Analysis of Improvement and Deterioration (FAS)

Change from baseline at 8 months	**Dapa 10 mg N = 1316**	**Placebo N = 1311**		
Deterioration	**n [a] (%) deteriorated**	**n [a] (%) deteriorated**	**Odds ratio [b] (95% CI)**	**p-value**
≥ 5 points (moderate deterioration)	264 (24.1)	317 (29.1)	0.78 (0.64, 0.95)	0.0127
≥ 14 points (large deterioration)	148 (13.5)	201 (18.4)	0.70 (0.55, 0.88)	0.0026
Improvement	**n [c] (%) improved**	**n [c] (%) improved**	**Odds ratio [d] (95% CI)**	**p-value**

Table 10 KCCQ Total Symptom Score - Responder Analysis of Improvement and Deterioration (FAS)

Change from baseline at 8 months	**Dapa 10 mg N = 1316**	**Placebo N = 1311**		
≥ 13 points (small to moderate improvement)	531 (48.4)	498 (45.6)	1.13 (0.95, 1.33)	0.1608
≥ 17 points (large improvement)	486 (44.3)	478 (43.8)	1.06 (0.89, 1.26)	0.5137

[a] Number of subjects who died prior to the given time point or had an observed deterioration from baseline equal to or exceeding the given threshold. Subjects with a KCCQ-TSS at baseline that was too low to possibly experience a deterioration were defined as deteriorated if their score at 8 months was not higher than baseline

[b] Odds ratio < 1 favours Dapa 10 mg

Number of subjects who had an observed improvement from baseline equal to or exceeding the given threshold. Subjects who died prior to the given timepoint are counted as not improved. Subjects with a KCCQ-TSS at baseline that was too high to possibly experience an improvement were defined as improved if their score at 8 months was not lower than baseline

Odds ratio > 1 favours Dapa 10 mg

Including subjects with the 8-month assessment (Visit 5) planned or performed prior to 11 March 2020, when COVID-19 was declared a pandemic by the WHO. Subjects with planned but not performed assessment prior to 11 March 2020 will be imputed. Odds ratios are obtained from logistic regression with treatment group, baseline KCCQ-TSS and T2DM status at randomisation as covariates.

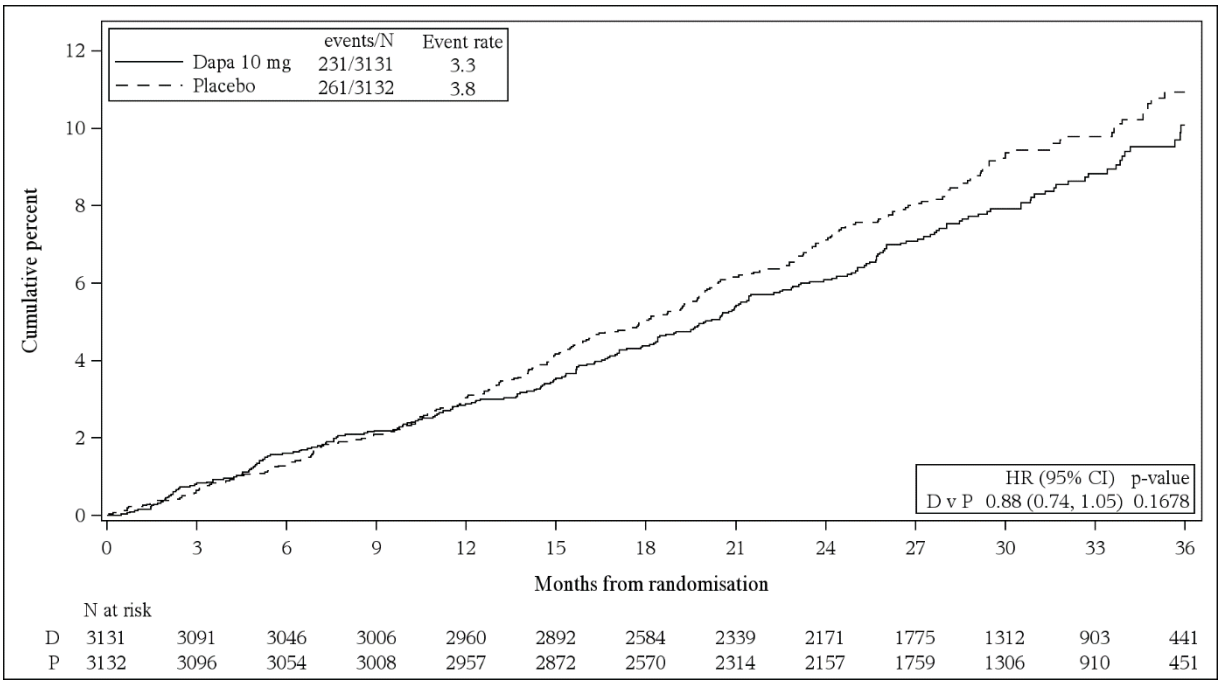
CI, confidence interval; COVID-19, coronavirus disease 2019; Dapa, dapagliflozin; FAS, full analysis set; KCCQ, Kansas City Cardiomyopathy Questionnaire; N, number of subjects in treatment group; T2DM, type 2 diabetes mellitus; TSS, total symptom score.

In addition to the anchor-based analyses at the pre-defined cut-offs, the effect of dapagliflozin compared with placebo was also assessed across the full range of possible cut-points in cumulative distribution function plots of change in KCCQ-TSS.

Time to the Occurrence of CV Death

There were fewer CV deaths in the dapagliflozin group compared with the placebo group (231 vs 261), not reaching statistical significance (HR 0.88 [95% CI 0.74, 1.05]) (**Figure 8**).

Figure 8 Kaplan-Meier Plot of CV Death (FAS)



N at risk is the number of subjects at risk at the beginning of the period. One month corresponds to 30 days. Two-sided p-value is displayed. The HR, CI, and p-value are from the Cox proportional hazards model.

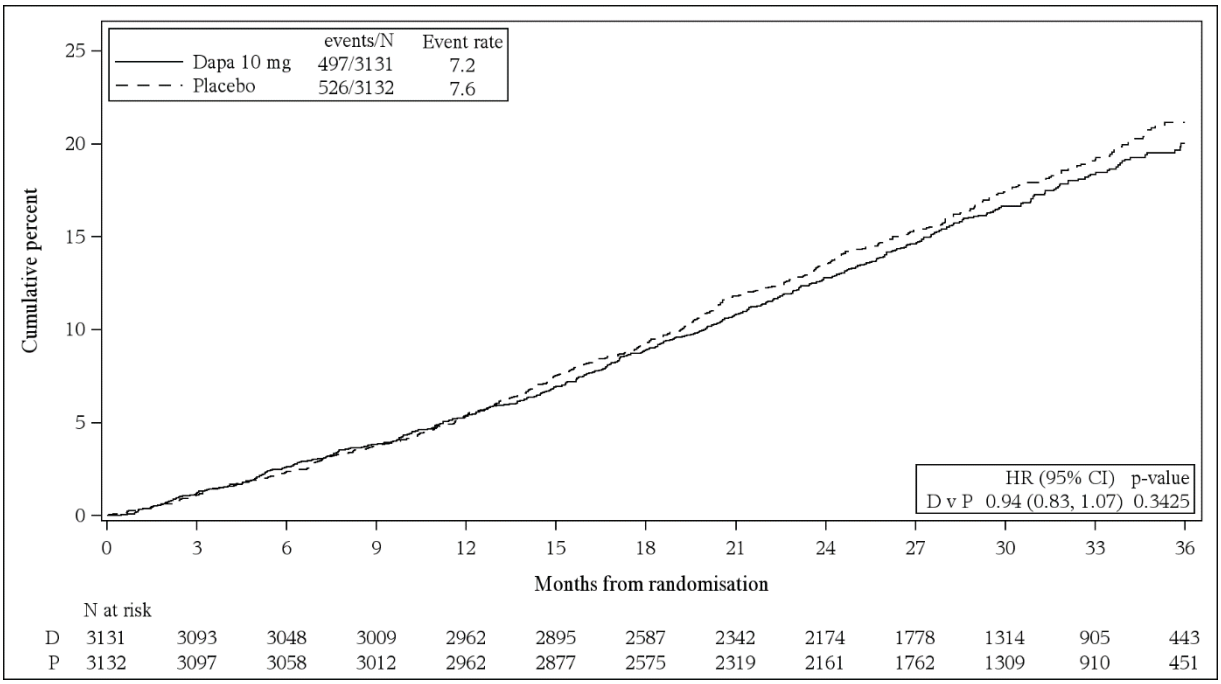
CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; D, dapa 10 mg; FAS, full analysis set; HR, hazard ratio; N, number of subjects; P, placebo.

Time to the Occurrence of Death From Any Cause

The hierarchical testing sequence stopped before the endpoint of time to death from any cause could be assessed. Hence, the analysis of this endpoint was not conducted as part of the confirmatory testing sequence.

There were 497 and 526 deaths from any cause in the dapagliflozin group and in the placebo group, respectively, corresponding to event rates per 100 patient-years of 7.2 and 7.6 (**Figure 9**).

Figure 9 Kaplan-Meier Plot of All-Cause Mortality (FAS)



N at risk is the number of subjects at risk at the beginning of the period. One month corresponds to 30 days. Two-sided p-value is displayed. The HR, CI, and p-value are from the Cox proportional hazards model.

CI, confidence interval; Dapa, dapagliflozin; D, dapa 10 mg; FAS, full analysis set; HR, hazard ratio; N, number of subjects; P, placebo.

In the dapagliflozin group and in the placebo group, respectively, there were 231 and 261 deaths adjudicated as CV death, 197 and 188 deaths adjudicated as non-CV death, and 67 and 73 deaths adjudicated as death due to an undetermined cause. Deaths occurring after withdrawal of consent were not adjudicated. There were 2 deaths in the dapagliflozin group and 4 deaths in the placebo group occurring after withdrawal of consent.

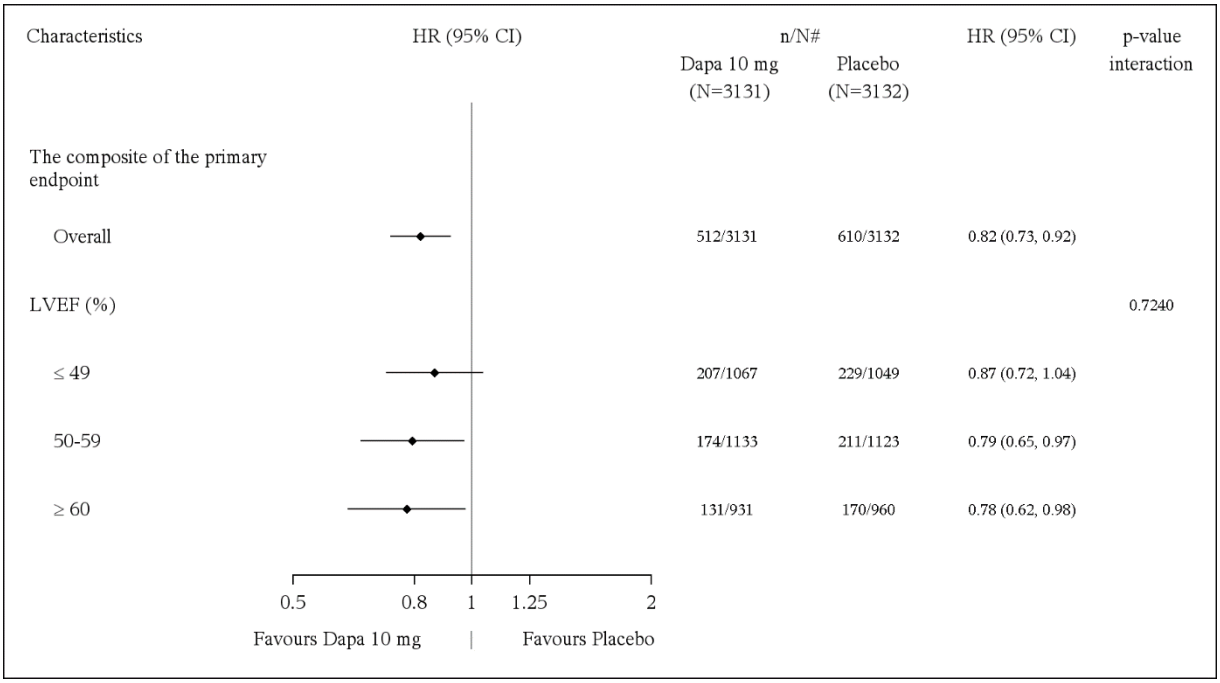
Ancillary analyses

Subgroup Analyses of the Primary Composite Endpoint

Efficacy by Baseline LVEF

The benefit of dapagliflozin on primary composite endpoint was consistent across the prespecified subgroups defined by baseline LVEF (≤ 49%, 50% to 59%, and ≥ 60%) (**Figure 10**).

Figure 10 Forest Plot of the Primary Composite Endpoint (CV death/HF Hospitalisation/Urgent HF Visit) by Baseline LVEF Group (FAS)



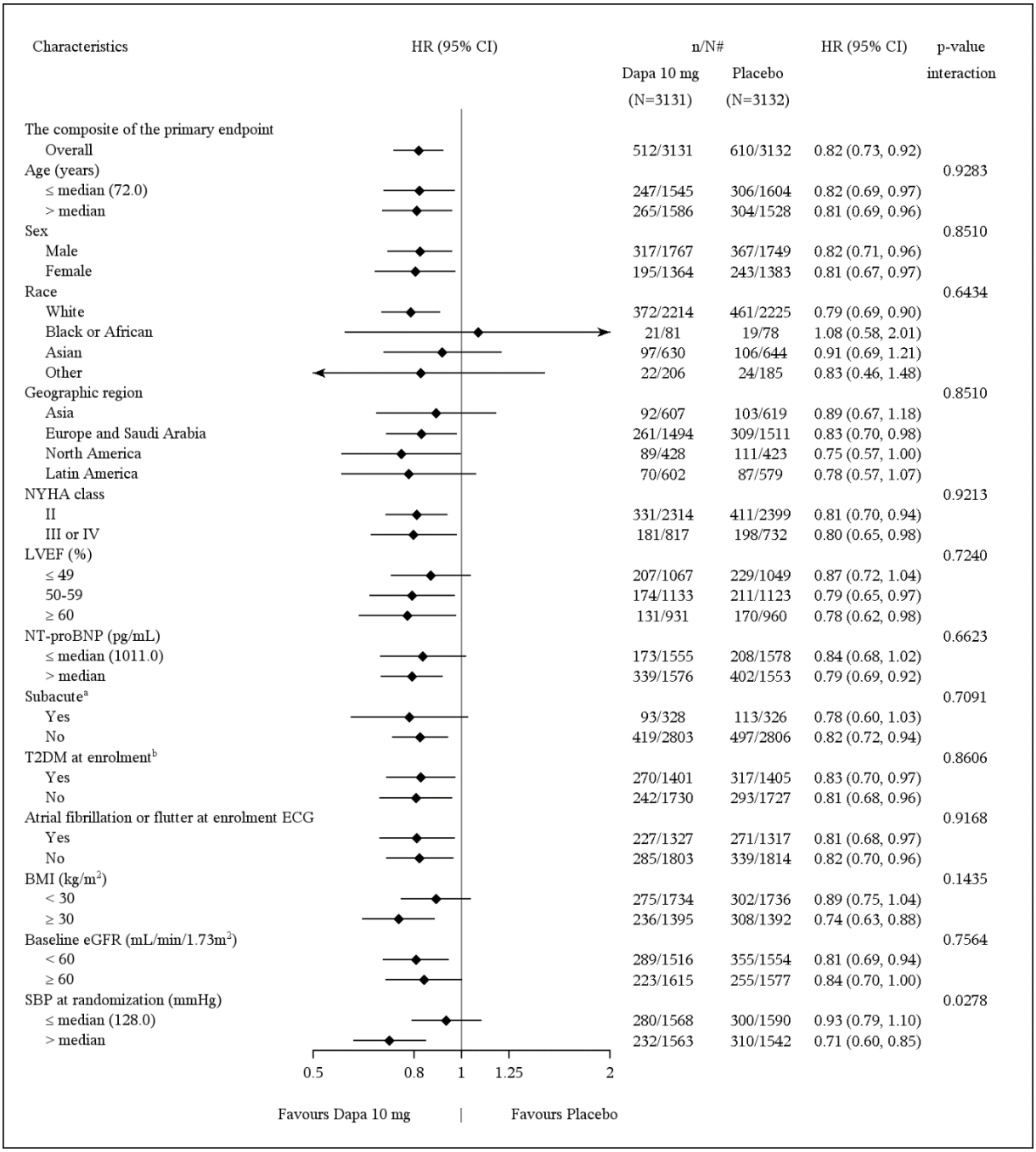
Hazard ratio for Dapa 10 mg vs placebo, CIs, and 2-sided p-value are calculated from Cox proportional hazards model (Wald statistic) stratified by T2DM status at randomisation with factor for treatment group, and when calculating the interaction p-value also including factor for subgroup variable and subgroup by treatment interaction. Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both treatment groups combined.

CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N, number of subjects in treatment group; N#, number of subjects in the subgroup; n, number of subjects with event; T2DM, type 2 diabetes mellitus.

Efficacy by Demographic and Other Baseline Patient Characteristics

The benefit of dapagliflozin on primary composite endpoint was consistent across the key prespecified subgroups, including those defined by age and sex (**Figure 11**). A nominal interaction p-value < 0.05 was observed for subgroup analysis by median systolic BP (≤ 128.0 mmHg, > 128.0 mmHg), but the point estimates for both subgroups were below unity.

Figure 11 Forest Plot of the Primary Composite Endpoint (CV Death/HF Hospitalisation/Urgent HF Visit) by Subgroups (FAS)



Defined as randomised during hospitalisation for HF or within 30 days of discharge

Defined as history of T2DM. This analysis does not include T2DM as a stratification factor

Hazard ratio for Dapa 10 mg vs placebo, CIs, and 2-sided p-value are calculated from Cox proportional hazards model (Wald statistic) stratified by T2DM status at randomisation with factor for treatment group, and when calculating the interaction p-value also including factor for subgroup variable and subgroup by treatment interaction. Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both treatment groups combined.

BMI, body mass index; CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FAS, full analysis set; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; N, number of subjects in treatment group; N#, number of subjects in the subgroup; n, number of subjects with event; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Subpopulation with LVEF < 60%

The benefit of dapagliflozin on the primary composite endpoint was consistent across the prespecified subgroups in the subpopulation with LVEF < 60%.

Impact of COVID-19 on DELIVER

On 11 March 2020, the WHO declared the global COVID-19 outbreak a pandemic. In DELIVER, majority of patients (81.7%) were randomised prior to the start of the pandemic, whereas the majority of follow-up (75.9% of total patient-years until last visit) was during the pandemic phase.

The results of the sensitivity analyses for the primary composite endpoint and the first secondary composite endpoint, in which patients were censored at the onset date of the first AE associated with COVID-19 infection, showed consistency with the main analyses. Therefore, the overall impact of COVID-19 pandemic on efficacy evaluation was assessed as low, and the COVID-19 pandemic was judged to not have meaningfully impacted the interpretation of results.

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11. Summary of Efficacy for trial DELIVER

Title: Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure **(DELIVER)**			
Study identifier	D169CC00001		
Design	DELIVER was an international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled Phase III study conducted at 353 sites in 20 countries with 6263 randomised patients. It was designed to evaluate the effect of dapagliflozin 10 mg compared with placebo on the primary composite endpoint of CV death or an HF event in patients with HF and LVEF > 40%.		
	Duration of main phase:		The median time in study until primary analysis censoring date was 28.0 months (range 0.1 to 42.1 months) and median time until last visit was 28.5 months (range 0.1 to 42.2 months) (event-driven study)
Hypothesis	Superiority		
Treatments groups	Dapagliflozin 10 mg		3131
	Placebo		3132
Endpoints and definitions	Primary endpoint		Composite of CV death, hospitalisation for HF or urgent HF visit
	Secondary endpoint	CV death + rHF	Composite of CV death and recurrent HF events
	Secondary endpoint	KCCQ	Change from baseline at 8 months in the KCCQ total symptom score (TSS)

	Secondary endpoint	CV death	CV death
	Secondary endpoint	AC mort	All-cause mortality
Database lock	22 April 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set		
Descriptive statistics and estimate variability	Treatment group	Dapagliflozin	Placebo
	Number of subjects	3131	3132
	Primary (event rates per 100 PY)	7.8	9.6
	CV death + rHF (event rates per 100 PY)	11.8	15.3
	KCCQ (mean change from baseline)	8.3	5.2
	CV death (event rates per 100 PY)	3.3	3.8
	AC mort (event rates per 100 PY)	7.2	7.6

Effect estimate per comparison	Primary endpoint	Comparison groups	Dapa vs placebo
		Hazard ratio	0.82
		95% CI	(0.73, 0.92)
		P-value	0.0008
	Secondary endpoint CV death + rHF	Comparison groups	Dapa vs placebo
		Rate ratio	0.77
		95% CI	(0.67, 0.89)
		P-value	0.0003
	Secondary endpoint KCCQ (TSS)	Comparison groups	Dapa vs placebo
		Win ratio	1.11
		95% CI	(1.03, 1.21)
		P-value	0.0086
	Secondary endpoint CV death	Comparison groups	Dapa vs placebo
		Hazard ratio	0.88
		95% CI	(0.74, 1.05)
		P-value	0.1678
	Secondary endpoint AC mortality	Comparison groups	Dapa vs placebo
		Hazard ratio	0.94
		95% CI	(0.83, 1.07)
		P-value	0.3425

Analysis performed across trials (pooled analyses and meta-analysis)

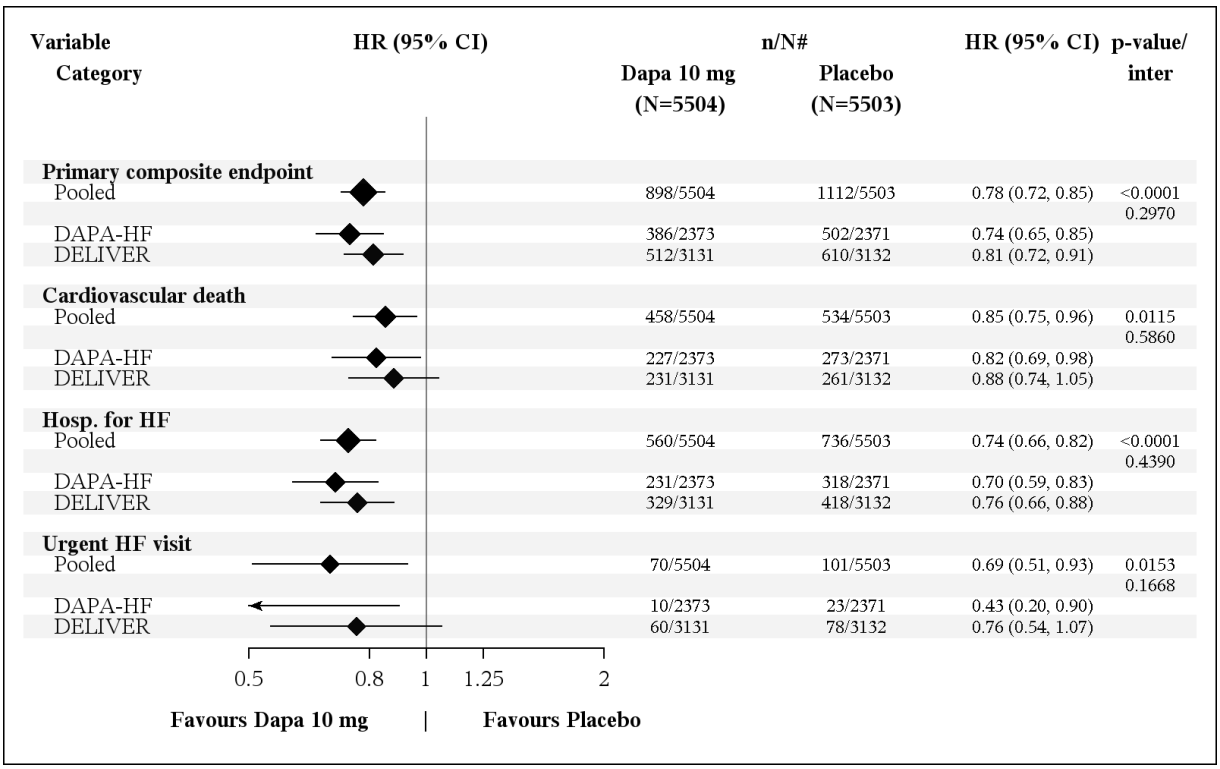
Pooled Analysis of DELIVER and DAPA-HF

This section summarises the results from the pooled analysis of patient-level data from DELIVER and DAPA-HF.

Primary Composite Endpoint of CV Death or an HF Event

Treatment with dapagliflozin resulted in a statistically significant and clinically meaningful reduction in the primary composite endpoint of CV death or an HF event, when compared with placebo, in both DELIVER and DAPA-HF (**Figure 12**). This benefit was also observed for the individual components in both studies. An interaction p-value of 0.2970 for the primary composite endpoint provided no evidence of heterogeneity between studies. This supports the consistent treatment effect observed across the prespecified LVEF subgroups in both DELIVER and in DAPA-HF.

Figure 12 Forest Plot of the Primary Composite Endpoint and the Components by Studies (FAS)



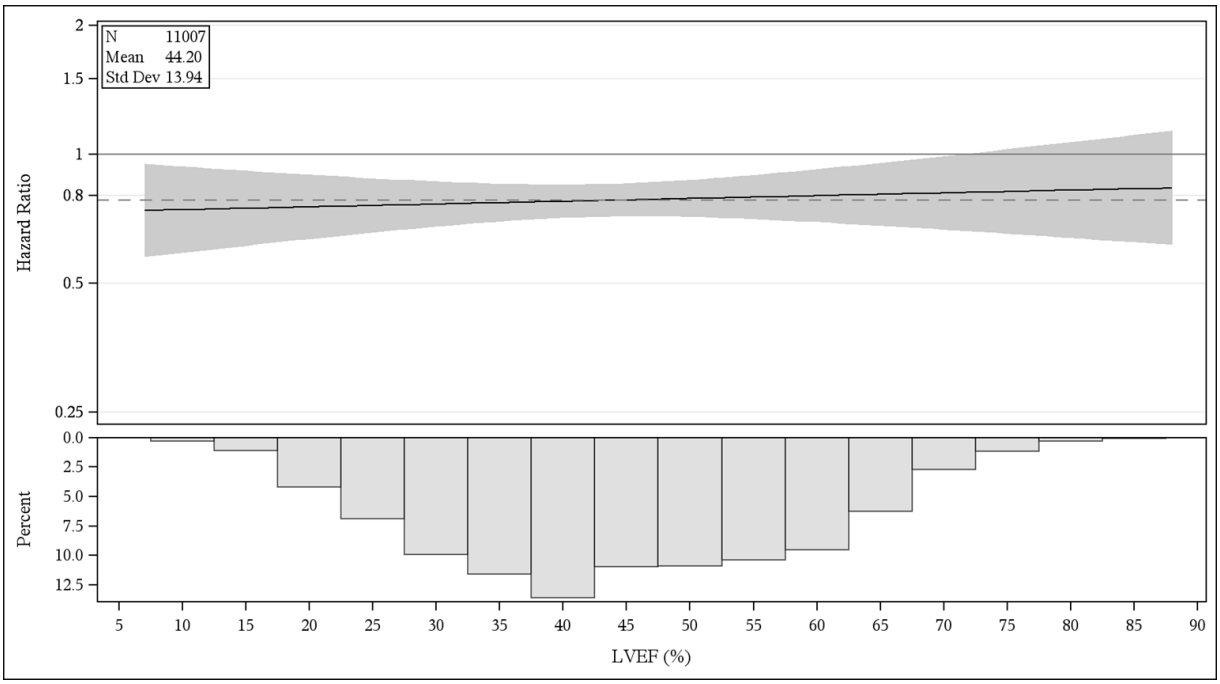
Definitions of the primary composite endpoints from each study are used. In DAPA-HF the primary composite endpoint included death with undetermined cause of death. Hazard ratio for Dapa 10 mg vs placebo, CIs, and 2-sided p-value are calculated from Cox proportional hazards model stratified by study and T2DM status at randomisation, and adjusted for history of hospitalisation for HF. The interaction p-value is calculated from the same model and including a term for the study by treatment interaction.

CI, confidence interval; Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure; HR, hazard ratio; inter, interaction; N, number of subjects in treatment group; N#, number of subjects in the study; n, number of subjects with event; T2DM, type 2 diabetes mellitus.

A fitted linear model, that includes the horizontal reference line of the overall treatment effect in the pooled dataset (HR = 0.78), illustrates the consistency of treatment effect across LVEF, as the difference in slope between the 2 lines is negligible (**Figure 13**). An absence of modification of

treatment effect by LVEF is further supported by a restricted cubic spline plot, which shows no apparent trend or tendency of non-linearity.

Figure 13 Linear Plot of Hazard Ratio of the Primary Composite Endpoint by Baseline LVEF (%) - Pooled (FAS)



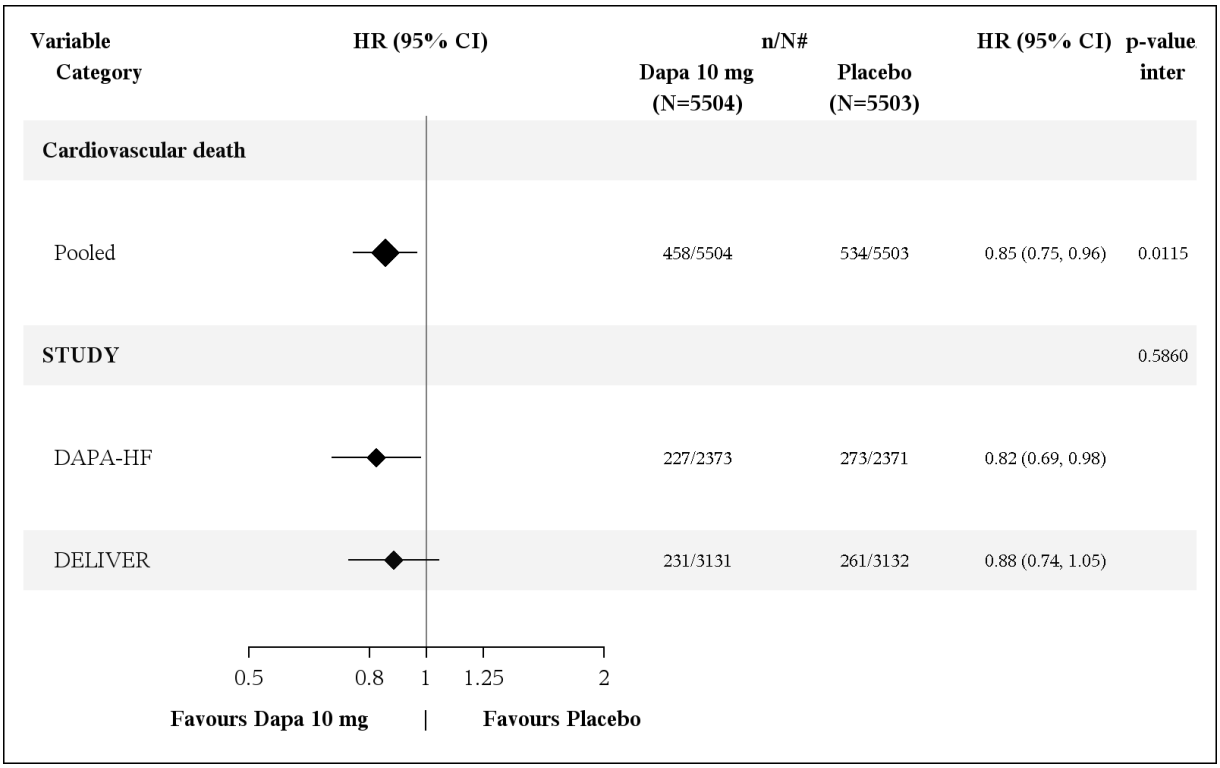
Definitions of the primary composite endpoints from each study are used. In DAPA-HF the primary composite endpoint included death with undetermined cause of death. The dotted line represents the overall HR. Hazard ratios for Dapa 10 mg vs placebo and confidence intervals are calculated from Cox proportional hazards model stratified by study and T2DM status at randomisation, and adjusted for history of hospitalisation for HF, including in the model the continuous variable LVEF, the treatment group, and the interaction between treatment group and the continuous variable LVEF.

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.

CV Death and All-Cause Mortality

The pooled analysis, using the respective study definitions of CV death, demonstrated a relative risk reduction of 15% (95% CI 4 to 25%, p = 0.0115) in CV death, with both studies contributing to the result, and with an interaction p-value of 0.5860, providing no evidence of heterogeneity between studies (**Figure 14**). Results of a sensitivity analysis, that included 'undetermined cause of death' as CV death in both studies, were consistent with those of the main analysis.

Figure 14 Forest Plot of CV Death by Studies (FAS)

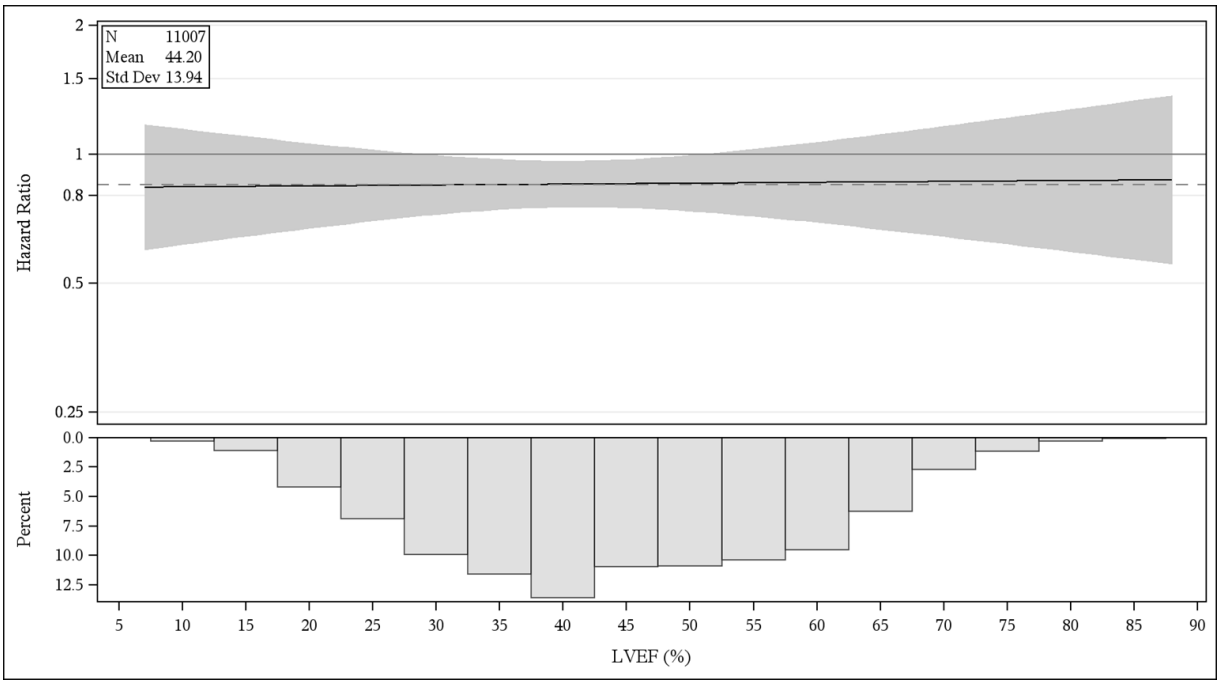


Definitions of CV death from each study is used. In DAPA-HF CV death included death with undetermined cause of death. Hazard ratio for Dapa 10 mg vs placebo, CIs, and 2-sided p-value are calculated from Cox proportional hazards model stratified by study and T2DM status at randomisation, and adjusted for history of hospitalisation for HF. The interaction p-value is calculated from the same model and including a term for the study by treatment interaction.

CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; FAS, full analysis set; HF, heart failure; HR, hazard ratio; inter, interaction; N, number of subjects in treatment group; N#, number of subjects in the study; n, number of subjects with event; T2DM, type 2 diabetes mellitus.

A fitted linear model, that includes the horizontal reference line of the overall treatment effect in the pooled dataset (HR = 0.85), illustrates the consistency of treatment effect across LVEF, as the difference in slope between the 2 lines is negligible (**Figure 15**). This is further supported by a restricted cubic spline plot, which shows no apparent trend or tendency of non-linearity.

Figure 15 Linear Plot of Hazard Ratio of CV Death by Baseline LVEF (%) – Pooled (FAS)

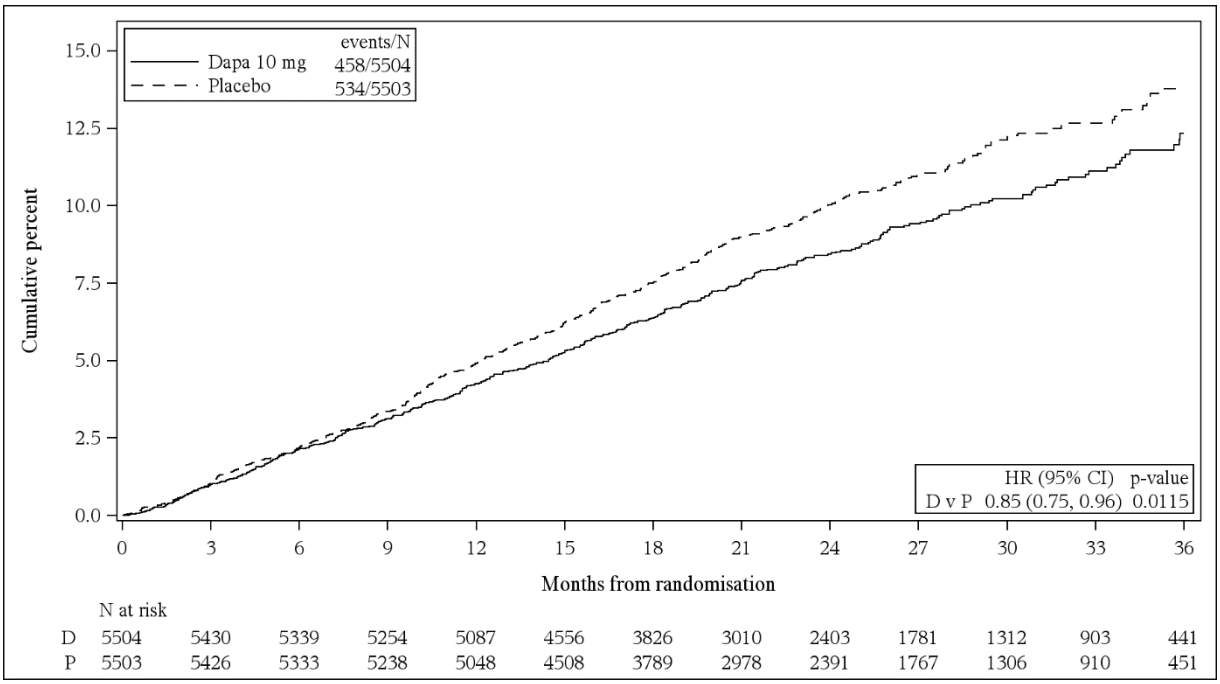


Definitions of CV death from each study are used. In DAPA-HF CV death included death with undetermined cause of death. The dotted line represents the overall HR. Hazard ratios for Dapa 10 mg vs placebo and confidence intervals are calculated from Cox proportional hazards model stratified by study and T2DM status at randomisation, and adjusted for history of hospitalisation for HF, including in the model the continuous variable LVEF, the treatment group, and the interaction between treatment group and the continuous variable LVEF.

CV, cardiovascular; 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.

A Kaplan-Meier plot of the pooled analysis of CV death in DELIVER and DAPA-HF is presented in **Figure 16**.

Figure 16 Kaplan-Meier Plot of CV Death - Pooled (FAS)



Definitions of CV death from each study is used. In DAPA-HF CV death included death with undetermined cause of death. Hazard ratio for Dapa 10 mg vs placebo, CIs, and 2-sided p-value are calculated from Cox proportional hazards model stratified by study and T2DM status at randomisation, and adjusted for history of hospitalisation for HF.

CI, confidence interval; CV, cardiovascular; Dapa, dapagliflozin; D, Dapa 10 mg; FAS, full analysis set; HF, heart failure; HR, hazard ratio; N, number of subjects; P, placebo; T2DM, type 2 diabetes mellitus.

A treatment effect of dapagliflozin on CV death is further supported by a reduction of all-cause mortality in the pooled analysis (HR 0.90 [95% CI 0.82, 0.99]), with no evidence of heterogeneity in treatment effect by study (interaction p-value 0.2143).

Clinical studies in special populations

No studies were conducted in special populations. The DELIVER study included a large group of patients aged > 75 years with a maximum age of 99 years.

Table 12 Number (%) of Subjects by Age Category (SAS)

Age (years)	Dapa 10 mg (N = 3126)	Placebo (N = 3127)	Total (N = 6253)
< 65	668 (21.4)	675 (21.6)	1343 (21.5)
65-74	1134 (36.3)	1189 (38.0)	2323 (37.2)
75-84	1096 (35.1)	1041 (33.3)	2137 (34.2)
≥ 85	228 (7.3)	222 (7.1)	450 (7.2)

Dapa, dapagliflozin; N, number of subjects in treatment group; SAS, safety analysis set.

The treatment effect of dapagliflozin on primary composite endpoint was consistent across all age groups, with the observed point estimate below 1 and a non-significant nominal p-value for interaction (**Table 13**).

Table 13 Analysis of Primary Composite Endpoint by Age Categories (FAS)

	Dapa 10 mg (N = 3131)			Placebo (N = 3132)						
Subject characteristic Category	Number of subjects	Subjects with event n (%)	Event rate	Number of subjects	Subjects with event n (%)	Event rate	Hazard ratio	95% CI	p-value	Interaction p-value
Age (years)										
< 65	668	105 (15.7)	7.6	677	121 (17.9)	8.9	0.86	(0.66, 1.11)	0.2490	0.8589
65-74	1136	179 (15.8)	7.5	1190	234 (19.7)	9.4	0.78	(0.65, 0.95)	0.0143	
75-84	1098	177 (16.1)	7.7	1042	205 (19.7)	9.8	0.79	(0.65, 0.97)	0.0251	
≥ 85	229	51 (22.3)	11.1	223	50 (22.4)	11.8	0.94	(0.64, 1.39)	0.7663	

Event rates are presented as the number of subjects with event per 100 patient years of follow-up. Number and proportion of subjects with events calculated within subgroup.
Hazard ratio for Dapa 10 mg versus placebo, CIs, and 2-sided p-value are calculated from Cox proportional hazards model (Wald statistic) stratified by T2DM status at randomisation with factor for treatment group, and when calculating the interaction p-value also including factor for subgroup variable and subgroup by treatment interaction.
Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both treatment groups combined.
CI, confidence interval; Dapa, dapagliflozin; FAS, full analysis set; N, number of subjects in treatment group; T2DM, type 2 diabetes mellitus.

2.4.1. Discussion on clinical efficacy

Design and conduct of the clinical study

DELIVER was an international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled Phase III study in patients with HF and LVEF > 40%. DELIVER evaluated the effect of dapagliflozin 10 mg compared with placebo, given once daily, in reducing the composite of CV death or an HF event.

No dose finding study has been performed. The dose of 10 mg was chosen, justified by data supporting that this dose maximally inhibits SGLT2 in the kidney. Previous experience has not shown any apparent difference in safety profile between doses. In the scientific advice given in 2017, the CHMP recommended that more than one dose should be investigated as "*the Mode of Action for HF treatment has not been established, and the dose-effect relationship with regard to PD parameters is still uncertain*". Lower doses therefore could be efficacious in HF. The MAH has provided a summary of published data supporting a plausible mechanism of action for SGLT2 inhibitors when used in the treatment of heart failure, but this data does not provide any information on the dose-effect relationship. It should however be noted that only the 10 mg dose was investigated in the DAPA-HF study. The DAPA-HF study included patients with heart failure and reduced LVEF, i.e., a potentially more vulnerable population. In this study, dapagliflozin 10 mg dose was superior to placebo in reducing the incidence of the composite of CV death or a HF event with an acceptable safety profile. Thus, the choice of dose can be accepted.

The inclusion criteria were adequate and aimed at including a population with symptomatic HF (NYHA class II to IV) and preserved LVEF (LVEF > 40%; HFpEF). Characteristics of HF were clearly defined in line with the given scientific advice. Exclusion criteria were adequate. In the scientific advice, it was suggested that for normotensive HFpEF patients the 5 mg doses could be more appropriate; lowering BP in these normotensive patients could be of concern. In this context, it should be noted that patients with SBP < 95 mmHg were not included due to the blood pressure lowering effect of dapagliflozin. Patients with eGFR <25 were also excluded. Known causes for HFpEF are infiltrative diseases, such as amyloidosis, however, patients with these diseases were excluded from participation in the study. The lack of data in this population has been reflected in the product information (section 4.4).

Patients with T1DM were also excluded. Currently the recommendation not to use dapagliflozin in patients with T1DM is given in relation to the information on diabetic ketoacidosis in section 4.4. Taking into consideration that dapagliflozin is approved in other indications than the treatment of diabetes, i.e., HF and CKD, the warning against the use in T1DM has been included in the beginning of section 4.4.

The primary objective was to determine whether dapagliflozin 10 mg is superior to placebo in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) and the primary variable was time from randomisation to the first event included in the composite endpoint. All primary endpoint events were adjudicated. The secondary endpoints included the composite of CV death and HF events (first and recurrent), change from baseline in the TSS of the KCCQ at 8 months, time to CV death and time to all-cause mortality. The objectives and endpoints are acceptable and in line with the "Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure" (CPMP/EWP/235/95, Rev.2). Although the scientific advice recommended to consider all-cause death for the primary endpoint, the use of CV death has been accepted for the DAPA-HF trial.

The statistical methods including study design and statistical analysis are in general considered adequate. The applicant has supported the results of the primary and secondary analysis sufficiently with sensitivity analyses to assess the robustness of results regarding any bias caused by intercurrent

or competing events and missingness considering that such events were well balanced between treatment groups and missingness (due to incomplete follow-up) at a low level. The method used for alpha splitting between the total and subpopulation adjusting for the correlation is not well known and an analytical proof was not provided. Given the results in this study, there is, however, no concern for the robustness of the results. The subgroup analysis in the populations with LVEF<60%, which was included in the multiple testing procedure, and additional analysis in the complementary subgroup with LVEF ≥60% in the DELIVER study and pooled analysis in the DELIVER and DAPA-HF studies are considered sufficient to resolve concerns regarding differential treatment effects depending on LVEF.

Concerns were raised regarding study integrity and the maintenance of blinding considering the interim analysis and the multiple amendments of the clinical study protocol and statistical analysis plan. On request, the MAH provided more detailed information on measures taken to maintain the blind of the study, as well as the timeline for changes to the CSP and the SAP in relation to the interim analysis. All the important changes were made before the DMC session for the interim analysis. The clarifications are deemed acceptable.

The protocol was amended four times. With the second amendment the sample size was increased, and the recruitment period was extended. With the third amendment, changes were made to the endpoints and analyses: 1) Addition of urgent HF visits in addition to hospitalisations for HF to be evaluated for the first secondary endpoint. 2) Introduction of dual primary analysis (of the full study population and subpopulation with LVEF < 60%). 3) CV death was added as secondary objective. 4) The secondary objective (change in NYHA class) was moved to exploratory. None of the amendments are deemed to have affected the outcome or interpretation of the study.

In total 3.7% of patients had an important protocol deviation, the patient being randomised without fulfilling inclusion/exclusion criteria was the most common. 36 patients were included without fulfilling the inclusion criterion of LVEF > 40% and evidence of structural heart disease within the last 12 months prior to enrolment. Thus, the important protocol deviations were relatively few and balanced between groups and are therefore not considered to have affected the outcome or interpretation of the study. COVID-19 related protocol deviations were common (41.1% of patients) but only 0.1% had important protocol deviations. These protocol deviations are not considered to have affected the outcome of the study.

Among the 10418 patients enrolled, 4155 were not randomised, the main reason being not eligible. The most common reason for not being eligible was failure to fulfil the NT-pro BNP criteria (3373 subjects, 32.4%). This pattern was observed and discussed during the assessment of the DAPA-HF study. As in the DAPA-HF study, this criterion aimed at ensuring that the patients indeed had HF. The subgroup analysis show that the outcome was not affected by the level of NT-pro BNP, as was also observed in the DAPA-HF study. The observation is not considered to compromise the representativeness of the study population. The number of patients discontinuing treatment (in total 886 patients) was balanced between groups, as was the reasons for discontinuation. Only 18 subjects withdrew consent (also balanced between groups), and vital status was known for all but four patients. Treatment compliance was high and balanced between treatment groups.

Efficacy data and additional analyses

A total of 6263 patients were randomised from 350 study sites in 20 countries. The median time in study until PACD was 28.0 months and median time until last visit was 28.5 months. The mean age of the study population was 71.7 years and 43.9% of patients were female. 48% of patients were recruited in Europe/Saudi Arabia (only 190 out of 3005 patients were recruited from Saudi Arabia).

Almost 45% of patients had a medical history of T2DM. About 75% of patients were in NYHA class II and about 24% were in NYHA class III. 30% of patients had a LVEF ≥ 60%. Most patients were diagnosed with HF < 5 years before enrolment and 40.5% of patients had been hospitalised for HF prior to study enrolment. The median LVEF was 54.0% and the median NT-proBNP was 1011.0 pg/mL. Four subjects had eGFR<25, i.e., had an eGFR below the cut-off in the exclusion criterion. Overall, 49% had eGFR<60. The medical and relevant surgical history of the patients, as well as the smoking history, was balanced between treatment groups. Hypertension and CVD were commonly reported. The study population appears representative for the proposed target population.

Demographic and baseline patient characteristics in the subpopulation with LVEF < 60% were generally balanced and consistent with those of the full study population. Compared to the full population where about 30% had a LVEF >60%, the proportion of patients with myocardial infarction, stable angina pectoris, and coronary artery stenosis tended to be higher in patients with LVEF <60%.

Almost all patients (97.8%) were on diuretics at randomisation. The majority of patients (64.8%) were on dual combination therapy with ACEi/ARB/ARNI and a betablocker whereas 29.2% were on triple therapy with ACEi/ARB/ARNI, beta blocker and MRA. The proportion of patients on ARNI (4.8%) was about half of that reported in the DAPA-HF study (10.7%). At the time of the initiation of the study, no medicinal product was approved for the treatment of HFpEF, but the high use of medication may be explained by the medical history of the patients, e.g., a high reporting of hypertension and CV diseases. During the study, no imbalances were observed with regards to the use of ACEi, ARB, ARNI, and MRA between groups. 2.2% of subjects were on concomitant SGLT2i during the study. Baseline treatment seems to have been adequate and according to treatment guidelines.

The study met the primary endpoint as dapagliflozin was superior to placebo in reducing the incidence of primary composite endpoint of CV death or an HF event (HR 0.82 [95% CI 0.73, 0.92], p = 0.0008). The event rates per 100 patient-years of 7.8 for dapagliflozin and 9.6 for placebo. All components of the composite endpoint contributed to the outcome, although CI overlapped for CV-death and urgent HF visits. The performed sensitivity analyses are considered sufficient to support the robustness of the primary results considering the balance of intercurrent events between treatment arms and the balance and overall low frequency of incomplete follow-up.

The outcome in the subgroup with LVEF < 60% was in line with that if the overall population. The sensitivity analysis is considered sufficient regarding the evaluation of bias caused by "undetermined cause of death". No complementary analysis of the population with LVEF > 60% has been provided, however, the subgroup analysis by LVEF showed a comparable outcome in this group.

The composite secondary endpoint of recurrent HF events and CV death was also met (RR 0.77 [95% CI 0.67, 0.89], p = 0.0003), again the outcome was mainly driven by the recurrent HF events. The outcome in the subgroup with LVEF < 60% was in line with that if the overall population.

Due to the COVID-19 pandemic, the main analysis for the change from baseline in TSS of KCCQ was conducted in patients who had their 8-month assessment performed prior to 11 March 2020. After that time-point phone collection of KCCQ was introduced as an alternative solution. The change from baseline in KCCQ Scores was significantly greater in the dapagliflozin treated group (WR1.11 [95% CI 1.03, 1.21], p = 0.0086). The responder analysis showed that the proportion of patients who experienced a moderate (≥ 5 points) or large (≥ 14 points) deterioration in KCCQ Scores was significantly lower in the dapagliflozin treated group (moderate: 24% vs 29% and large: 13.5% vs 18.4%), whereas no differences were observed for patients reporting an improvement.

CV deaths were numerically fewer in the dapagliflozin treated group (231 vs 261), but the difference was not statistically significant. The events of all-cause death were also numerically fewer in the dapagliflozin treated group (497 vs 526), but again the difference was not statistically significant.

Subgroup analysis of the primary composite endpoint showed that the outcome was consistent across all prespecified subgroups by LVEF, including the subgroup with LVEF > 60%, as well as across all prespecified demographic subgroups. The only divergent findings were observed in one very small subgroup, i.e., Black or African. The subgroup analysis performed on the subpopulation with LVEF <60% was consistent with the overall population.

Analysis of the data to evaluate the impact of the COVID-19 pandemic did not reveal any inconsistencies compared to the main analysis.

No studies were conducted in special populations. The DELIVER study included a large group of patients aged ≥ 75 years (2587 patients, 41.4% of the study population) with a maximum age of 99 years. On request, the MAH provided a subgroup analysis for the age groups <65, 65-74, 75-84 and ≥ 85 years, which showed that the outcome of the primary composite endpoint was consistent across the age groups.

A pooled analysis of patient-level data from the two studies DELIVER and DAPA-HF was conducted. The studies were of similar design, but the DAPA-HF study included patients with reduced LVEF (<40%). There was no evidence of heterogeneity between studies. Analysis of the pooled data for the primary composite endpoint resulted in a HR of 0.78 (95% CI 0.72, 0.85). The analysis further showed a consistent effect over the entire range of LVEF observed at baseline, with a stable HR of about 0.8. In a subject level pooled analysis of the two studies, a significant effect on CV death (HR 0.85 [95% CI 0.75, 0.96]) and all-cause mortality (HR 0.90 [95% CI 0.82, 0.99]) is observed. The effect on CV death was consistent across the range of observed LVEF at baseline.

2.4.2. Conclusions on the clinical efficacy

With this application the MAH seek to extend the heart failure indication to include patients with preserved LVEF to the currently approved heart failure indication. To support the claim, data from a large, well conducted study, DELIVER, has been submitted. Dapagliflozin was superior to placebo in reducing the incidence of primary composite endpoint of CV death or an HF event with a 18 % relative risk reduction (HR 0.82 [95% CI 0.73, 0.92], p = 0.0008). This is considered a clinically relevant effect. The effect was consistent across subgroups. A pooled analysis including data from DELIVER and the previously assessed study, DAPA-HF, showed a consistent effect irrespective of baseline LVEF. Furthermore, a subject level pooled analysis of the two studies showed a significant effect on CV and all-cause mortality.

2.5. Clinical safety

Introduction

Forxiga is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction. The main evidence of efficacy and safety submitted to support the indication was the DAPA-HF study in patients with heart failure (HF) and reduced left ventricular ejection fraction (HFrEF) and included subjects with and without T2DM. The current safety evaluation is based on data from the completed DELIVER study. The target population had a documented diagnosis of symptomatic HF with LVEF >40% in patients with T2DM and without diabetes.

No subgroup analysis regarding the effect of T2DM has been provided in the DELIVER study; however, this was performed in the HF-DAPA study. In subjects with HFrEF, the safety profile with regards to

SAEs did not differ in any substantial way between patients with and without diabetes and HbA1c was not reduced in non-diabetic subjects. Also, based on the mechanism of action, dapagliflozin is not expected to pose an unwarranted risk of hypoglycaemia in subjects without diabetes.

Patient exposure

In the DELIVER study, in total 6,253 patients were treated with dapagliflozin (n=3,126) or placebo (n=3,127). In the study, there were 6,426 patient-years of exposure to dapagliflozin.

Duration of exposure

The duration of exposure ranged from 0 to 42.2 months (**Table 14**). The median duration of exposure to was similar between the dapagliflozin group (26.9 months) and the placebo group (27.0 months).

Table 14 Duration of exposure and cumulative exposure over time (SAS)

Characteristic	Statistic	Dapa 10 mg (N=3126)	Placebo (N=3127)
Duration of exposure (months)[a]	n	3126	3127
	Mean	24.7	24.7
	SD	10.6	10.4
	Minimum	0.0	0.0
	Q1	17.5	17.5
	Median	26.9	27.0
	Q3	33.2	33.2
	Maximum	42.2	42.0
	Total treatment years	6426	6440
Cumulative exposure over time, n (%)[b]	≥ 1 day	3126 (100.0)	3127 (100.0)
	≥ 1 month	3070 (98.2)	3066 (98.0)
	≥ 6 months	2859 (91.5)	2885 (92.3)
	≥ 12 months	2682 (85.8)	2706 (86.5)
	≥ 18 months	2306 (73.8)	2298 (73.5)
	≥ 24 months	1898 (60.7)	1911 (61.1)
	≥ 36 months	440 (14.1)	428 (13.7)
Actual exposure (months)[c]	n	3126	3127
	Mean	24.5	24.5
	SD	10.6	10.4
	Minimum	0.0	0.0
	Q1	17.4	17.2
	Median	26.7	26.7
	Q3	32.9	32.9
	Maximum	41.4	42.0
	Total treatment years	6372	6384

Source: Table 14.3.1.1, D169CC00001 CSR

Interruptions of investigational product

The proportions of patients with interruptions of IP were balanced between treatment groups: 585 patients (18.7%) in the dapagliflozin group and 622 patients (19.9%) in the placebo group. Most patients had only one period of interruption of IP. The median number of days per interruption was 11 days in the dapagliflozin group and 10 days in the placebo group. Reasons for interruption were comparable between treatment groups. The most common reason for interruption of IP was AE: 426 patients (13.6%) in the dapagliflozin group and 484 patients (15.5%) in the placebo group.

The most common AE, by PT, that led to interruption of IP was cardiac failure: 46 patients (1.5%) in the dapagliflozin group and 64 patients (2.0%) in the placebo group.

Demographic and other characteristics of study population

Demographic and baseline patient characteristics, including background therapy and medical history, were balanced between treatment groups.

Adverse events

An overall summary of AEs for patients on treatment and on and off treatment is presented in **Table 15**. Non-serious AEs were only collected for the following reasons: DAE, Amputations, AEs leading to amputation, 'Preceding events', Potential DKA, Major hypoglycaemic events, Cardiac ischaemic events (MI, unstable angina) and stroke, and AEs leading to interruption of IP.

Table 15 Number of Subjects with AEs in Any Category (SAS)

	Number (%) of subjects			
	On treatment		On and off treatment	
AE Category	Dapa 10 mg (N = 3126)	Placebo (N = 3127)	Dapa 10 mg (N = 3126)	Placebo (N = 3127)
Any AE with outcome = death	401 (12.8)	421 (13.5)	507 (16.2)	529 (16.9)
Any SAE (including events with outcome = death)	1361 (43.5)	1423 (45.5)	1454 (46.5)	1508 (48.2)
Any AE leading to discontinuation of IP	182 (5.8)	181 (5.8)	183 (5.9)	181 (5.8)
Any AE leading to interruption of IP	436 (13.9)	494 (15.8)	436 (13.9)	494 (15.8)
Any AE possibly related to IP	273 (8.7)	235 (7.5)	276 (8.8)	240 (7.7)
Any SAE or DAE suggestive of volume depletion	42 (1.3)	32 (1.0)	49 (1.6)	37 (1.2)
Any renal SAE or DAE	73 (2.3)	79 (2.5)	84 (2.7)	91 (2.9)
Any definite or probable DKA	2 (0.1)	0	2 (0.1)	0
Any major hypoglycaemic event	6 (0.2)	7 (0.2)	8 (0.3)	7 (0.2)
Any amputation	19 (0.6)	25 (0.8)	19 (0.6)	26 (0.8)

Source: Table 14.3.2.1 and Table 14.3.2.2, D169CC00001 CSR

Serious adverse event/deaths/other significant events

Deaths

During the on- and off-treatment period, the proportions of patients who had an AE with outcome of death were balanced between treatment groups: 507 patients (16.2%) in the dapagliflozin group and 529 patients (16.9%) in the placebo group. During the on-treatment period, there were 401 patients (12.8%) in the dapagliflozin group and 421 patients (13.5%) in the placebo group who had an AE with outcome of death. Deaths by SOC and PT were generally balanced between treatment groups. Most deaths occurred in the SOCs of cardiac disorders and infections and infestations in both treatment groups.

On and off treatment, there were 132 AEs associated with COVID-19 infection with an outcome of death: 74 (2.4%) in the dapagliflozin group and 58 (1.9%) in the placebo group. The results from the on-treatment period were consistent with the results from the on- and off-treatment period.

Other serious adverse events

On treatment, the proportions of patients with SAEs were balanced between treatment groups: 1361 patients (43.5%) in the dapagliflozin group and 1423 patients (45.5%) in the placebo group. The 3 most reported SAEs by PT, were cardiac failure, COVID-19, and pneumonia in both treatment groups (**Table 16**). The proportions of patients with SAEs in the SOC of infections and infestations were balanced between treatment groups. Number of subjects with SAEs, by system organ class and preferred term - on treatment (**Table 17**).

All confirmed COVID-19 infections (based on a positive COVID-19 test result) were requested to be reported as SAEs.

Table 16 Number of Subjects with SAEs (≥ 0.5%) by PT – On Treatment (SAS)

Preferred term	Number (%) of subjects	
	Dapa 10 mg (N = 3126)	Placebo (N = 3127)
Subjects with any SAE	1361 (43.5)	1423 (45.5)
Cardiac failure	262 (8.4)	343 (11.0)
COVID-19	165 (5.3)	131 (4.2)
Pneumonia	97 (3.1)	96 (3.1)
COVID-19 pneumonia	78 (2.5)	81 (2.6)
Ischaemic stroke	66 (2.1)	60 (1.9)
Atrial fibrillation	57 (1.8)	47 (1.5)
Acute myocardial infarction	51 (1.6)	58 (1.9)
Cardiac failure congestive	51 (1.6)	73 (2.3)
Cardiac failure acute	47 (1.5)	55 (1.8)
Acute kidney injury	46 (1.5)	50 (1.6)
Angina unstable	43 (1.4)	59 (1.9)
Death	36 (1.2)	38 (1.2)
Cellulitis	31 (1.0)	18 (0.6)
Urinary tract infection	30 (1.0)	32 (1.0)
Sudden cardiac death	23 (0.7)	30 (1.0)
Cardiac failure chronic	22 (0.7)	24 (0.8)
Peripheral arterial occlusive disease	22 (0.7)	14 (0.4)
Asymptomatic COVID-19	21 (0.7)	19 (0.6)
Sudden death	20 (0.6)	18 (0.6)
Angina pectoris	17 (0.5)	19 (0.6)
Chronic obstructive pulmonary disease	17 (0.5)	16 (0.5)

Source: Table 14.3.4.3, D169CC00001 CSR

Table 17 Number of subjects with SAEs, by SOC and preferred term - on treatment (SAS)

System organ class	Number (%) of subjects	
	Dapa 10 mg (N = 3126)	Placebo (N = 3127)
Infections and infestations	512 (16.4)	506 (16.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	113 (3.6)	116 (3.7)
Blood and lymphatic system disorders	28 (0.9)	34 (1.1
Immune system disorders	4 (0.1)	0
Endocrine disorders	2 (0.1)	2 (0.1)
Metabolism and nutrition disorders	62 (2.0)	72 (2.3)
Psychiatric disorders	10 (0.3)	16 (0.5)
Nervous system disorders	151 (4.8)	154 (4.9)
Eye disorders	19 (0.6)	12 (0.4)
Ear and labyrinth disorders	5 (0.2)	6 (0.2)
Cardiac disorders	577 (18.5)	664 (21.2)
Vascular disorders	81 (2.6)	64 (2.0)
Respiratory, thoracic and mediastinal disorders	84 (2.7)	101 (3.2)
Gastrointestinal disorders	75 (2.4)	128 (4.1)
Hepatobiliary disorders	31 (1.0)	27 (0.9)
Skin and subcutaneous tissue disorders	12 (0.4)	16 (0.5)
Musculoskeletal and connective tissue disorders	36 (1.2)	46 (1.5)
Renal and urinary disorders	84 (2.7)	89 (2.8)
Reproductive system and breast disorders	8 (0.3)	8 (0.3)
Congenital, familial and genetic disorders	0	3 (0.1)
General disorders and administration site conditions	112 (3.6)	120 (3.8)
Investigations	8 (0.3)	5 (0.2)
Injury, poisoning and procedural complications	83 (2.7)	86 (2.8)
Social circumstances	0	1 (0.0)
Product issues	5 (0.2)	0 (0.0)

Source: Table 14.3.4.1, D169CC00001 CSR

Adverse events of special interest and other analysis

Volume depletion, renal events, adjudicated DKAs, major hypoglycaemic events, amputations, AEs leading to amputations, 'preceding events', ischaemic cardiac events, strokes, Fournier's gangrene, genital infections, and urinary tract infections were presented.

Volume depletion

On treatment, the proportions of patients with SAEs suggestive of volume depletion were low and balanced between treatment groups: 35 patients (1.1%) in the dapagliflozin group and 31 patients (1.0%) in the placebo group (**Table 18).** Three SAEs suggestive of volume depletion (2 patients in the dapagliflozin group and 1 patient in the placebo group) were fatal. All 3 patients had multiple severe

underlying conditions and were on IP for at least one year before the fatal event occurred. The 3 most commonly reported SAEs suggestive of volume depletion by PT, were syncope, hypotension, and dehydration in both treatment groups. DAEs suggestive of volume depletion were few and numerically higher in the dapagliflozin group: 9 patients (0.3%) in the dapagliflozin group and 3 patients (0.1%) in the placebo group.

Table 18 Summary of SAEs and DAEs Suggestive of Volume Depletion – On Treatment (SAS)

	Number (%) of subjects	
AE category	**Dapa 10 mg (N = 3126)**	**Placebo (N = 3127)**
Subjects with any SAE suggestive of volume depletion	35 (1.1)	31 (1.0)
With outcome death	2 (0.1)	1 (0.0)
Any SAE leading to interruption of IP	10 (0.3)	7 (0.2)
Any SAE possibly related to IP	4 (0.1)	3 (0.1)
Subjects with any DAE suggestive of volume depletion	9 (0.3)	3 (0.1)
Any DAE possibly related to IP	8 (0.3)	1 (0.0)

Source: Table 14.3.11.3, D169CC00001 CSR

Renal events

On treatment, the proportions of patients with renal SAEs and DAEs were balanced between treatment groups. There were 57 patients (1.8%) with renal SAEs in the dapagliflozin group and 68 patients (2.2%) in the placebo group (**Table 19**). There were 23 patients (0.7%) with renal DAEs in the dapagliflozin group and 18 patients (0.6%) in the placebo group. Number of subjects with SAEs in the SOC Renal and urinary disorders is presented in **Table 20**.

Table 19 Summary of Renal SAEs and DAEs – On Treatment (SAS)

	Number (%) of subjects	
AE category	**Dapa 10 mg (N = 3126)**	**Placebo (N = 3127)**
Subjects with any renal SAE	57 (1.8)	68 (2.2)
With outcome death	5 (0.2)	6 (0.2)
Any SAE leading to interruption of IP	12 (0.4)	23 (0.7)
Any SAE possibly related to IP	9 (0.3)	9 (0.3)
Subjects with any renal DAE	23 (0.7)	18 (0.6)
Any DAE possibly related to IP	9 (0.3)	4 (0.1)

Source: Table 14.3.11.7, D169CC00001 CSR

Table 20 Number of subjects with SAEs, in the SOC Renal disorders, preferred terms - on treatment (SAS)

System organ class / Preferred term	Number (%) of subjects[a] Dapa 10 mg (N=3126)	Placebo (N=3127)
Renal and urinary disorders	84 (2.7)	89 (2.8)
Acute kidney injury	46 (1.5)	50 (1.6)
Chronic kidney disease	8 (0.3)	7 (0.2)
Renal failure	6 (0.2)	11 (0.4)
Renal impairment	4 (0.1)	7 (0.2)
Haematuria	3 (0.1)	6 (0.2)
End stage renal disease	2 (0.1)	2 (0.1)
Nephrolithiasis	2 (0.1)	3 (0.1)
Tubulointerstitial nephritis	2 (0.1)	0
Urinary retention	2 (0.1)	0
Calculus urinary	1 (0.0)	1 (0.0)
Cystitis glandularis	1 (0.0)	0
Nephropathy toxic	1 (0.0)	1 (0.0)
Nephrotic syndrome	1 (0.0)	1 (0.0)
Obstructive nephropathy	1 (0.0)	0
Polyuria	1 (0.0)	0
Prerenal failure	1 (0.0)	1 (0.0)
Renal cyst	1 (0.0)	0
Renal haemorrhage	1 (0.0)	0
Urinary fistula	1 (0.0)	0
Urinary tract inflammation	1 (0.0)	0
Cystitis haemorrhagic	0	1 (0.0)
Renal colic	0	1 (0.0)
Renal cyst ruptured	0	1 (0.0)
Urinary tract obstruction	0	2 (0.1)

Source: Table 14.3.4.1, D169CC00001 CSR

Diabetic ketoacidosis

On treatment, there were 2 patients with definite DKA events in the dapagliflozin group compared with none in the placebo group. Both patients had T2DM and were treated with insulin; neither of them had a fatal outcome. None of the patients with DKA had an AE associated with COVID-19 infection.

For a summary of adjudicated potential events of DKA on and off treatment, see **Table 21** and **Table 22**.

Table 21 Summary of adjudicated potential events of diabetic ketoacidosis - on and off treatment (SAS)

	Number (%) of subjects[a] Dapa 10 mg (N=3126)	Placebo (N=3127)
Number of subjects with event[a]		
Subjects with a potential DKA event sent for adjudication	15 (0.5)	20 (0.6)
Subjects with an event adjudicated as definite DKA	2 (0.1)	0
Subjects with an event adjudicated as probable DKA	0	0
Subjects with an event adjudicated as possible DKA	2 (0.1)	2 (0.1)
Subjects with an event adjudicated as not a DKA event	11 (0.4)	18 (0.6)
Number of events[b]		
Potential DKA events sent for adjudication	17	20
Event adjudicated as definite DKA	3 (17.6)	0
Event adjudicated as probable DKA	0	0
Event adjudicated as possible DKA	2 (11.8)	2 (10.0)
Event adjudicated as not a DKA event	12 (70.6)	18 (90.0)

Source: Table 14.3.6.3, D169CC00001 CSR

Table 22 Potential events of diabetic ketoacidosis sent for adjudication by preferred term - on and off treatment (SAS)

Preferred term	Number (%) of subjects[a] Dapa 10 mg (N=3126)	Placebo (N=3127)
Subjects with a potential DKA event sent for adjudication	15 (0.5)	20 (0.6)
Metabolic acidosis	8 (0.3)	8 (0.3)
Diabetic ketoacidosis	3 (0.1)	3 (0.1)
Lactic acidosis	2 (0.1)	1 (0.0)
Hyperglycaemic hyperosmolar nonketotic syndrome	1 (0.0)	3 (0.1)
Ketosis	1 (0.0)	0
Blood bicarbonate decreased	0	1 (0.0)
Diabetes mellitus inadequate control	0	1 (0.0)
Hyperglycaemia	0	3 (0.1)

Source: Table 14.3.6.4, D169CC00001 CSR

Major hypoglycaemic events

On treatment, the proportions of patients with major hypoglycaemic events were low and balanced between treatment groups: 6 patients (0.2%) in the dapagliflozin group and 7 patients (0.2%) in the placebo group, corresponding to event rates of 0.1 and 0.1 per 100 patient-years, respectively (**Table 23**). No major hypoglycaemic events were reported for patients without T2DM.

Patients with major hypoglycaemic events in both treatment groups were treated with sulfonylureas or insulin, or in combination, at the time of the event, except for 1 patient in the placebo group who was only treated with biguanides.

Table 23 Summary of major hypoglycaemic events – on treatment (SAS)

AE category	Number (%) of subjects[a] Dapa 10 mg (N=3126)	Placebo (N=3127)
Subjects with any major hypoglycaemic event[b]	6 (0.2)	7 (0.2)
Event rate per 100 subject years	0.1	0.1
Any SAE	4 (0.1)	1 (0.0)
With outcome death	0	0
SAE excluding death	4 (0.1)	1 (0.0)
Any DAE	0	0
Any SAE leading to discontinuation of IP	0	0
Any AE leading to interruption	0	1 (0.0)
Maximum intensity[c]		
Mild	0	1 (0.0)
Moderate	5 (0.2)	4 (0.1)
Severe	1 (0.0)	2 (0.1)
Any AE possibly related to IP[d]	1 (0.0)	2 (0.1)

Source: Table 14.3.7.1, D169CC00001 CSR

Amputations and adverse events leading to amputation

On and off treatment, the proportions of patients with amputations were balanced between treatment groups. There were 19 patients (0.6%) in the dapagliflozin group and 26 patients (0.8%) in the placebo group who underwent at least one amputation, corresponding to event rates of 0.3 and 0.4 per 100 patient-years, respectively. All but 4 patients in each treatment group had T2DM at baseline.

Most patients with surgical amputations had one amputation; all but one was lower limb amputations. The numbers of patients with major amputations (below knee and above knee) were the same in both treatment groups (8 patients in each treatment group) (**Table 24**).

AEs leading to amputation were balanced between treatment groups. The most common AE, by PT, leading to amputation was osteomyelitis, occurring in 3 patients (0.1%) in the dapagliflozin group and 6 patients (0.2%) in the placebo group.

Table 24 Amputation by Type of Event and Location – On and Off Treatment (SAS)

Category	Number (%) of subjects	
	Dapa 10 mg (N = 3126)	Placebo (N = 3127)
Subjects with any amputation	19 (0.6)	26 (0.8)
1 amputation	12 (0.4)	15 (0.5)
2 amputations	6 (0.2)	6 (0.2)
3 amputations	1 (0.0)	1 (0.0)
> 3 amputations	0	4 (0.1)
Type of event		
Trauma by accident	0	0
Surgical amputation	19 (0.6)	25 (0.8)
Spontaneous/non-surgical amputation	0	1 (0.0)
Anatomic localisation		
Lower limb amputation	19 (0.6)	26 (0.8)
Big toe	3 (0.1)	8 (0.3)
Index toe	4 (0.1)	8 (0.3)
Middle toe	1 (0.0)	8 (0.3)
Fourth toe	1 (0.0)	7 (0.2)
Little toe	1 (0.0)	5 (0.2)
Transmetatarsal	6 (0.2)	0
Foot	1 (0.0)	2 (0.1)
Below knee	3 (0.1)	3 (0.1)
Above knee	5 (0.2)	5 (0.2)
Other	1 (0.0)	1 (0.0)
Upper limb amputation	1 (0.0)	0

Source: Table 14.3.8.6, D169CC00001 CSR

Potential risk factor AEs for amputations affecting lower limbs ('Preceding Events')

On and off treatment, the proportions of patients with 'preceding events' were balanced between treatment groups: 206 patients (6.6%) in the dapagliflozin group and 218 patients (7.0%) in the placebo group. Of patients with 'preceding events', 18 patients (0.6%) in the dapagliflozin group and 25 patients (0.8%) in the placebo group had subsequent amputations.

Subjects with preceding events	Dapagliflozin 10 mg (n=3,126) Number (%) of subjects	Placebo (n=3,127) Number (%) of subjects
Subjects with any preceding event	188 (6.0)	199 (6.4)
Diabetic foot related AEs	98 (3.1)	104 (3.3)
Nervous system disorders	12 (0.4)	17 (0.5)
Vascular AEs	66 (2.1)	47 (1.5)
Volume depletion	27 (0.9)	23 (0.7)
Wound/infection	12 (0.4)	18 (0.6)

Source: Table 14.3.9.3, D169CC00001 CSR

Cardiac Ischaemic Events and Stroke

On treatment, the proportions of patients who had MIs were balanced between treatment groups: 68 patients (2.2%) in the dapagliflozin group and 71 patients (2.3%) in the placebo group. The proportions of patients who had unstable angina were balanced between treatment groups: 53 patients (1.7%) in the dapagliflozin group and 70 patients (2.2%) in the placebo group.

The proportions of patients who had stroke of any cause were balanced between treatment groups: 106 patients (3.4%) in the dapagliflozin group and 101 patients (3.2%) in the placebo group.

Table 25 Cardiac ischaemic AEs by investigator diagnosis - on treatment (SAS

Investigator diagnosis[b]	Number (%) of subjects[a] Dapa 10 mg (N=3126)	Placebo (N=3127)
Subjects with any unstable angina or myocardial infarction AE	120 (3.8)	133 (4.3)
Unstable angina	53 (1.7)	70 (2.2)
Myocardial infarction[c]	68 (2.2)	71 (2.3)

Source: Table 14.3.10.1, D169CC00001 CSR

Fournier's gangrene

SAEs or DAEs indicating genital area infections or necrotising fasciitis were identified based on a prespecified list of PTs. The identified events were then medically assessed by the MAH using pre-defined criteria to confirm cases of Fournier's gangrene. All assessments were made prior to unblinding of treatment allocation.

On- and off-treatment, 4 SAEs were identified for internal blinded medical assessment: 1 patient in the dapagliflozin group and 3 patients in the placebo group. None of these events were confirmed as Fournier's gangrene.

Genital infections

On treatment, SAEs and DAEs of genital infections were rare. There were 2 SAEs of genital infection; 1 patient in each treatment group. There were 3 patients with a DAE of genital infection in the dapagliflozin group compared with none in the placebo group.

Urinary tract infections

On treatment, the proportions of patients with SAEs and DAEs of urinary tract infections were balanced between treatment groups. There were 78 patients with SAEs of urinary tract infection: 41 (1.3%) in the dapagliflozin group and 37 (1.2%) in the placebo group. The most common SAE of urinary tract infection, by PT, was urinary tract infection, occurring in 30 patients (1.0%) in the dapagliflozin group and 32 patients (1.0%) in the placebo group. There were 22 patients with a DAE of urinary tract infection: 13 (0.4%) in the dapagliflozin group and 9 (0.3%) in the placebo group.

Laboratory findings

Clinical chemistry

Creatinine/ eGFR

There was an initial slight increase in mean serum creatinine, which was more pronounced in the dapagliflozin group compared with the placebo group. At 24 months, the mean changes from baseline in serum creatinine were similar in both treatment groups (**Table 26**). In line with the findings for serum creatinine, there was an initial decrease in mean eGFR, which was more pronounced in the dapagliflozin group compared with the placebo group. At 24 months, change in eGFR from baseline was similar in both treatment groups (**Table *27***).

There were more patients with a marked abnormality in serum creatinine (defined as ≥ 1.5 times baseline value) in the dapagliflozin group compared with the placebo group, whereas the proportions of patients with a marked abnormality in serum creatinine (defined as ≥ 2 times baseline value) were balanced between treatment groups (**Table *28***).

Table 26 Creatinine values over time in SI units - on treatment

			Result						Change from baseline					
Laboratory variable (SI-unit)	Group	Time point	n	Mean	SD	Q1	Median	Q3	n	Mean	SD	Q1	Median	Q3
Creatinine (umol/L)	Dapa 10 mg (N=3126)	Baseline	3126	102.2	31.2	79.6	96.8	117.6						
		1 Month	2887	109.2	37.0	84.0	101.7	127.3	2887	7.3	19.8	-2.7	6.2	15.0
		4 Months	2528	107.9	36.2	83.1	99.9	124.6	2528	6.1	21.1	-4.4	4.4	15.0
		12 Months	2051	106.9	36.2	83.1	99.9	122.0	2051	6.2	21.9	-5.3	4.4	15.0
		24 Months	1314	106.7	37.2	82.2	99.0	122.0	1314	7.6	25.5	-5.3	5.3	16.8
		36 Months	266	102.6	31.7	79.6	97.2	119.3	266	5.3	23.9	-6.2	3.5	14.1
	Placebo (N=3127)	Baseline	3126	102.7	30.9	79.6	97.2	119.3						
		1 Month	2894	104.2	35.4	80.4	97.2	119.3	2893	1.5	20.3	-7.1	0.9	8.8
		4 Months	2554	104.6	35.3	81.3	97.2	119.3	2553	2.6	20.8	-7.1	1.8	10.6
		12 Months	2050	105.6	37.2	82.2	97.7	120.2	2049	4.2	25.4	-7.1	2.7	12.4
		24 Months	1343	105.6	44.2	79.6	97.2	118.5	1342	6.3	33.7	-7.1	3.5	15.9
		36 Months	271	108.9	38.1	84.0	99.9	123.8	271	9.6	26.1	-5.3	7.1	18.6

Source: Table 14.3.14.1, D169CC00001 CSR

Table 27 eGFR values over time in SI units - on treatment

			Result						Change from baseline					
Laboratory variable (SI-unit)	Group	Time point	n	Mean	SD	Q1	Median	Q3	n	Mean	SD	Q1	Median	Q3
eGFR (mL/min/1.73m²)	Dapa 10 mg (N=3126)	Baseline	3126	61.2	19.0	47.0	60.0	75.0						
		1 Month	2887	57.6	19.4	43.0	56.0	71.0	2887	-3.7	9.8	-9.0	-4.0	1.0
		4 Months	2528	58.6	19.5	44.0	58.0	72.0	2528	-3.0	10.9	-9.0	-3.0	3.0
		12 Months	2051	58.9	19.4	45.0	58.0	72.0	2051	-3.3	11.3	-10.0	-3.0	3.0
		24 Months	1314	58.7	19.5	44.0	57.0	73.0	1314	-4.2	12.8	-11.0	-4.0	2.0
		36 Months	266	60.2	18.7	45.0	58.0	74.0	266	-3.9	13.8	-10.0	-3.0	3.0
	Placebo (N=3127)	Baseline	3126	60.9	19.2	46.0	60.0	75.0						
		1 Month	2894	60.5	19.6	45.0	60.0	75.0	2893	-0.4	10.1	-6.0	-1.0	5.0
		4 Months	2554	60.3	19.6	45.0	59.0	75.0	2553	-1.1	10.7	-7.0	-1.0	4.0
		12 Months	2050	59.5	19.3	45.0	58.0	74.0	2049	-2.1	11.9	-9.0	-2.0	5.0
		24 Months	1343	59.7	19.9	45.0	59.0	74.0	1342	-3.2	13.7	-11.0	-3.0	4.0
		36 Months	271	56.8	19.9	41.0	54.0	73.0	271	-5.6	13.0	-12.0	-5.0	2.0

Source: Table 14.3.14.1, D169CC00001 CSR

Table 28 Marked laboratory abnormalities - on treatment (SAS)

	Number (%) of subjects[a]	
	Dapa 10 mg (N=3126)	Placebo (N=3127)
Serum Creatinine (umol/L)		
Number of subjects with any on-treatment value	3042	3046
≥ 1.5x baseline creatinine	238 (7.8)	174 (5.7)
≥ 2x baseline creatinine	32 (1.1)	38 (1.2)

Source: Table 14.3.15.1, D169CC00001 CSR

Vital signs and physical findings

Body weight

There was a decrease in body weight in the dapagliflozin group compared with the placebo group (mean change -1.37 kg in the dapagliflozin group and 0.12 kg in the placebo group) at month 24 (**Table 29**).

Table 29 Vital signs variables over time, body weight - on treatment (SAS)

			Result						Change from baseline					
Vital sign variable (Unit)	Group	Time point	n	Mean	SD	Q1	Median	Q3	n	Mean	SD	Q1	Median	Q3
Weight (kg)	Dapa 10 mg (N=3126)	Baseline	3124	81.76	20.34	67.00	80.00	94.10						
		12 Months	2134	79.89	19.90	65.30	78.00	91.60	2134	-1.10	5.02	-3.10	-1.00	1.10
		24 Months	1491	81.14	20.45	66.00	79.70	93.70	1491	-1.37	6.14	-4.00	-1.00	1.60
		36 Months	435	78.76	21.34	62.80	77.80	92.80	435	-2.45	5.44	-5.70	-2.20	1.00
	Placebo (N=3127)	Baseline	3126	81.55	20.17	67.00	79.50	93.50						
		12 Months	2134	80.99	20.31	66.10	79.00	92.70	2133	0.01	4.57	-2.00	0.00	2.20
		24 Months	1529	82.44	21.01	68.00	80.10	94.10	1528	0.12	7.06	-2.55	0.00	3.00
		36 Months	420	80.39	20.95	65.00	78.05	92.00	420	-0.27	5.85	-3.00	0.00	3.00

Source: Table 14.3.13, D169CC00001 CSR

Blood pressure

Systolic BP decreased in the dapagliflozin group compared with the placebo group (mean change -1.1 mmHg in the dapagliflozin group and 0.3 mmHg in the placebo group at month 24). There were no clinically relevant mean changes in diastolic BP or pulse rate in either treatment group (**Table *30***).

Table 30 Vital signs variables over time, blood pressure - on treatment (SAS)

			Result						Change from baseline				
Vital sign variable (Unit)	Group	Time point	n	Mean	SD	Q1	Median	Q3	n	Mean	SD	Q1	Median	Q3
Diastolic blood pressure (mmHg)	Dapa 10 mg (N=3126)	Baseline	3126	73.9	10.3	67.5	74.0	80.5						
		1 Month	2918	72.9	10.6	66.0	73.0	80.0	2918	-0.9	9.2	-6.5	-1.0	4.0
		12 Months	2149	74.1	11.1	67.0	74.5	81.0	2149	-0.1	10.5	-6.5	0.0	6.5
		24 Months	1505	74.4	10.6	67.5	74.5	81.0	1505	-0.1	10.9	-7.0	0.0	6.5
		36 Months	437	74.7	11.4	68.0	75.0	81.5	437	-0.1	11.2	-7.5	0.0	7.5
	Placebo (N=3127)	Baseline	3127	74.0	10.4	67.0	74.0	81.0						
		1 Month	2936	73.6	10.8	66.5	73.0	80.5	2936	-0.4	9.1	-6.0	0.0	5.0
		12 Months	2141	74.2	11.1	67.0	74.5	81.5	2141	0.1	10.4	-6.0	0.0	6.5
		24 Months	1536	74.8	10.6	68.0	75.0	82.0	1536	0.2	10.8	-6.5	0.0	6.5
		36 Months	423	73.6	11.3	66.0	74.0	81.5	423	-1.9	10.9	-9.0	-1.0	5.0
Systolic blood pressure (mmHg)	Dapa 10 mg (N=3126)	Baseline	3126	128.2	15.4	117.5	128.0	138.5						
		1 Month	2918	126.0	16.3	115.0	126.0	136.0	2918	-2.3	14.2	-10.0	-2.0	5.0
		12 Months	2149	127.9	16.4	117.5	128.0	138.0	2149	-0.2	15.7	-10.0	0.0	9.0
		24 Months	1505	127.7	16.0	118.5	127.5	137.0	1505	-1.1	16.6	-11.5	-1.5	10.0
		36 Months	437	129.0	17.6	119.5	129.0	137.5	437	0.2	17.2	-9.5	0.5	9.5
	Placebo (N=3127)	Baseline	3127	128.2	15.3	117.5	128.0	138.5						
		1 Month	2936	127.7	16.3	116.5	127.5	138.0	2936	-0.4	13.8	-8.0	-0.5	7.5
		12 Months	2141	128.9	17.0	119.0	128.5	139.0	2141	0.9	15.9	-9.0	0.0	10.0
		24 Months	1536	129.9	15.8	120.0	129.5	139.0	1536	0.3	16.1	-9.5	0.0	10.0
		36 Months	423	130.3	17.6	117.5	129.5	140.0	423	-0.5	16.7	-11.5	-0.5	9.5

Source: Table 14.3.13, D169CC00001 CSR

Safety in special populations

Intrinsic factors

Effect by renal function

The effect of renal function at baseline was summarised for SAEs, AEs with outcome of death, DAEs, temporary interruption of IP, AEs possibly related to IP, SAEs and DAEs suggestive of volume depletion, renal SAEs and DAEs, and amputations (**Table *31***, **Table *32***, **Table *33***).

Table 31 Number of subjects with AEs in any category - eGFR at baseline <45 mL/min/1.73m^2 - on treatment (SAS)

	Number (%) of subjects[a]	
AE Category	Dapa 10 mg (N=688)	Placebo (N=722)
Any AE with outcome = death	121 (17.6)	125 (17.3)
Any SAE (including events with outcome = death)	366 (53.2)	373 (51.7)
Any AE leading to discontinuation of IP	71 (10.3)	75 (10.4)
Any AE leading to interruption of IP	138 (20.1)	129 (17.9)
Any AE possibly related to IP[b]	79 (11.5)	69 (9.6)
Any amputation[c]	8 (1.2)	9 (1.2)
Any SAE or DAE suggestive of volume depletion[d]	18 (2.6)	10 (1.4)
Any renal SAE or DAE[d]	44 (6.4)	50 (6.9)

Source: Table 14.3.2.1.1, D169CC00001 CSR

Table 32 Number of subjects with AEs in any category - eGFR at baseline ≥45 mL/min/1.73m^2 and < 60 mL/min/1.73m2 - on treatment (SAS)

AE Category	Number (%) of subjects[a] Dapa 10 mg (N=826)	Placebo (N=829)
Any AE with outcome = death	104 (12.6)	108 (13.0)
Any SAE (including events with outcome = death)	338 (40.9)	389 (46.9)
Any AE leading to discontinuation of IP	37 (4.5)	48 (5.8)
Any AE leading to interruption of IP	115 (13.9)	146 (17.6)
Any AE possibly related to IP[b]	80 (9.7)	74 (8.9)
Any amputation[c]	5 (0.6)	7 (0.8)
Any SAE or DAE suggestive of volume depletion[d]	11 (1.3)	15 (1.8)
Any renal SAE or DAE[d]	15 (1.8)	20 (2.4)

Source: Table 14.3.2.1.2, D169CC00001 CSR

Table 33 Number of subjects with AEs in any category - eGFR at baseline ≥60 mL/min/1.73m^2 - on treatment (SAS)

AE Category	Number (%) of subjects[a] Dapa 10 mg (N=1612)	Placebo (N=1575)
Any AE with outcome = death	176 (10.9)	188 (11.9)
Any SAE (including events with outcome = death)	657 (40.8)	661 (42.0)
Any AE leading to discontinuation of IP	74 (4.6)	58 (3.7)
Any AE leading to interruption of IP	183 (11.4)	219 (13.9)
Any AE possibly related to IP[b]	114 (7.1)	92 (5.8)
Any amputation[c]	6 (0.4)	9 (0.6)
Any SAE or DAE suggestive of volume depletion[d]	13 (0.8)	7 (0.4)
Any renal SAE or DAE[d]	14 (0.9)	9 (0.6)

Source: Table 14.3.2.1.3, D169CC00001 CSR

Effect by age

The effect of age at baseline (≤ 65 years, > 65 years) was summarised for SAEs, AEs with outcome of death, DAEs, temporary interruption of IP, AEs possibly related to IP, SAEs and DAEs suggestive of volume depletion, renal SAEs and DAEs, and amputations (**Table 34**, **Table 35**).

Table 34 Number of subjects with AEs in any category - age at baseline ≤ 65 - on treatment (SAS)

AE Category	Number (%) of subjects[a] Dapa 10 mg (N=743)	Placebo (N=759)
Any AE with outcome = death	81 (10.9)	75 (9.9)
Any SAE (including events with outcome = death)	318 (42.8)	332 (43.7)
Any AE leading to discontinuation of IP	39 (5.2)	35 (4.6)
Any AE leading to interruption of IP	90 (12.1)	107 (14.1)
Any AE possibly related to IP[b]	51 (6.9)	55 (7.2)
Any amputation[c]	6 (0.8)	8 (1.1)
Any SAE or DAE suggestive of volume depletion[d]	10 (1.3)	4 (0.5)
Any renal SAE or DAE[d]	20 (2.7)	21 (2.8)

Source: Table 14.3.2.1.4, D169CC00001 CSR

Table 35 Number of subjects with AEs in any category - age at baseline > 65 - on treatment (SAS)

AE Category	Number (%) of subjects[a] Dapa 10 mg (N=2383)	Placebo (N=2368)
Any AE with outcome = death	320 (13.4)	346 (14.6)
Any SAE (including events with outcome = death)	1043 (43.8)	1091 (46.1)
Any AE leading to discontinuation of IP	143 (6.0)	146 (6.2)
Any AE leading to interruption of IP	346 (14.5)	387 (16.3)
Any AE possibly related to IP[b]	222 (9.3)	180 (7.6)
Any amputation[c]	13 (0.5)	17 (0.7)
Any SAE or DAE suggestive of volume depletion[d]	32 (1.3)	28 (1.2)
Any renal SAE or DAE[d]	53 (2.2)	58 (2.4)

Source: Table 14.3.2.1.5, D169CC00001 CSR

The effect of age at baseline ≤75 years and >75 years on-treatment, see **Table 36**.

Table 36 Number of Subjects with AEs in Any Category – age at baseline ⩽ 75 and > 75 – On Treatment (SAS)

AE Category	Age at Baseline ≤ 75		Age at Baseline > 75	
	Number (%) of subjects [a]		Number (%) of subjects [a]	
	Dapa 10 mg (N = 1925)	Placebo (N = 1985)	Dapa 10 mg (N = 1201)	Placebo (N = 1142)
Any AE with outcome = death	214 (11.1)	230 (11.6)	187 (15.6)	191 (16.7)
Any SAE (including events with outcome = death)	812 (42.2)	879 (44.3)	549 (45.7)	544 (47.6)
Any AE leading to discontinuation of IP	91 (4.7)	100 (5.0)	91 (7.6)	81 (7.1)
Any AE leading to interruption of IP	258 (13.4)	296 (14.9)	178 (14.8)	198 (17.3)
Any AE possibly related to IP [b]	141 (7.3)	136 (6.9)	132 (11.0)	99 (8.7)
Any amputation [c]	18 (0.9)	22 (1.1)	1 (0.1)	3 (0.3)
Any SAE or DAE suggestive of volume depletion [d]	26 (1.4)	14 (0.7)	16 (1.3)	18 (1.6)
Any renal SAE or DAE [d]	39 (2.0)	50 (2.5)	34 (2.8)	29 (2.5)

Source: Table IEMT8479.47905a

Extrinsic factors

No extrinsic factors were analysed in the DELIVER study.

Safety related to drug-drug interactions and other interactions

Interactions between dapagliflozin and other drugs or food were addressed in the original dapagliflozin T2DM clinical programme. For a summary, refer to the dapagliflozin product label. No new information is available on the potential impact on safety of such interactions in patients with HF and LVEF > 40%.

Discontinuation due to adverse events

The proportions of patients with DAEs were low and balanced between treatment groups: 182 patients (5.8%) in the dapagliflozin group and 181 patients (5.8%) in the placebo group (**Table 37**). DAEs by PT were distributed among many PTs. The most common AEs by PT, that led to permanent

discontinuation of IP were urinary tract infection, renal impairment, and cardiac failure in the dapagliflozin group and cardiac failure, acute kidney injury, and chronic kidney disease in the placebo group.

Table 37 Number of Subjects with AEs (≥ 0.1%) Leading to Discontinuation of IP by PT – On Treatment (SAS)

Preferred term	Number (%) of subjects [a]	
	Dapa 10 mg (N = 3126)	Placebo (N = 3127)
Subjects with any AE leading to discontinuation of IP [b]	182 (5.8)	181 (5.8)
Urinary tract infection	11 (0.4)	6 (0.2)
Renal impairment	10 (0.3)	7 (0.2)
Cardiac failure	9 (0.3)	20 (0.6)
Acute kidney injury	7 (0.2)	8 (0.3)
Chronic kidney disease	6 (0.2)	8 (0.3)
Hypotension	6 (0.2)	1 (0.0)
COVID-19	5 (0.2)	2 (0.1)
Renal failure	5 (0.2)	3 (0.1)
Asthenia	4 (0.1)	1 (0.0)
Haemorrhagic stroke	4 (0.1)	2 (0.1)
Ischaemic stroke	4 (0.1)	5 (0.2)

Source: Table 14.3.5.2, D169CC00001 CSR

Use in pregnancy and lactation

Pregnant and nursing patients were excluded from participating in the DELIVER study. There were no pregnancies reported during the study.

Overdose

In DELIVER, an overdose was defined as the accidental or intentional suspected single intake of more than 50 tablets of 10 mg dapagliflozin tablets, or repeated intake of more than 10 tablets of 10 mg dapagliflozin tablets. No events of IP overdose were reported during the DELIVER study.

Drug abuse

The potential for drug abuse for dapagliflozin has not been studied. Based on its pharmacological properties, dapagliflozin is not likely to have a potential for drug abuse and no findings during the clinical study programme indicate that dapagliflozin induces drug abuse or dependence.

Withdrawal and rebound

The effect of dapagliflozin withdrawal and rebound has not been studied. There is no evidence that suggests the potential for withdrawal or rebound.

Post marketing experience

Dapagliflozin was first approved for treatment of patients with T2DM in Australia on 05 October 2012 and it is currently approved in over 100 countries. Dapagliflozin is also approved for the treatment of HF with LVEF ≤ 40% in more than 100 countries and chronic kidney disease in more than 90 countries. Furthermore, it is approved for type 1 diabetes mellitus in Japan.

Post-marketing experience in the approved indications is summarised in regular PBRERs that are submitted to regulatory authorities worldwide. The dapagliflozin PBRER with data lock 04 April 2022 (dated 30 May 2022) included more than 24 million patient-years of post-marketing exposure (cumulative until 31 March 2022). At the data lock of the dapagliflozin PBRER, there was no new information to alter the overall positive benefit-risk profile for dapagliflozin in the approved indications.

Impact of Covid 19

About 76% of the follow-up time of the study occurred during the COVID-19 pandemic. In total, 9.4% of all patients had at least one reported AE associated with COVID-19 infection, 10.0% in the dapagliflozin group and 8.8% in the placebo group. The proportion of patients with any SAE associated with COVID-19 (10.0% vs 8.7%) and an COVID-19 infection associated AE with outcome death (2.4% vs 1.9%) was also numerically higher in the dapagliflozin group compared with the placebo group. However, the COVID-19 pandemic did not appear to have an impact on the interpretation of the safety results.

2.5.1. Discussion on clinical safety

In the DELIVER study, 3,126 subjects were treated with dapagliflozin for a total exposure of 6,426 PY regardless of interruptions (i.e., on and off treatment), with 2,682 subjects (86%) for at least 52 weeks, 2,306 subjects (74%) for at least 1,5 years and 1,898 subjects (61%) for at least 2 years. The mean duration of exposure for dapagliflozin was 24.7 months, and the median duration of exposure was 26.9 months. The actual mean/median duration of exposure, excluding interruptions (i.e., on-treatment) was similar to 'on and off treatment' with a total exposure of 6,372 PY for dapagliflozin. The median duration of follow-up was 28 months.

Data collection in this study focused on serious AEs (SAEs), AEs leading to discontinuation (DAEs) and AEs of special interest.

On-treatment, the number of fatal cases (12.8% and 13.5%) and SAEs (43.5% and 45.5%) were balanced between dapagliflozin and placebo. The most frequently reported SAEs for dapagliflozin and placebo were in the SOC Infections and infestations (16.4% and 16.2%) and the SOC Cardiac disorders (18.5% and 21.2%). The most reported SAEs for dapagliflozin vs placebo were cardiac failure (8.4% vs 11.0%), COVID-19 (5.3% vs 4.2%), pneumonia (3.1% vs 3.1%) and COVID-19 pneumonia (2.5% vs 2.6%).

Urinary tract infections

The incidence of SAEs (1.3% vs 1.2%) and DAEs (0.4% vs 0.3%) of UTIs for dapagliflozin vs placebo were balanced.

Genital infections

Two SAEs of genital infection one in each treatment group were reported. Three patients (0.1%), all in the dapagliflozin treatment group, had a DAE of genital infection.

Volume depletion

The incidence of SAEs suggestive of volume depletion was low and balanced for dapagliflozin (1.1%) and placebo (1.0%).

Renal events

The incidence of serious renal adverse events (1.8% and 2.2%) and the discontinuation rate or renal adverse events (0.7% and 0.6%) was balanced for dapagliflozin and placebo. The same pattern was observed for SAEs of acute kidney injury, i.e., the incidences was balanced for dapagliflozin (1.5%) and placebo (1.6%).

Diabetic ketoacidosis

In the dapagliflozin group, 3 events (in 2 subjects) were adjudicated as a definite DKA and 2 events as a possible DKA. In the placebo group no event was adjudicated as a definite DKA and 2 events as a possible DKA.

Major hypoglycaemic events

In the DELIVER study, only major hypoglycaemic events were collected. On treatment, subjects with major hypoglycaemic events were balanced; 0.2% in the dapagliflozin (n=6) and placebo group (n=7), respectively. Four serious cases in the dapagliflozin group and one in the placebo group. No subject discontinued due to any major hypoglycaemic event. All patients with major hypoglycaemic events had T2DM at baseline.

Amputations

On- and off-treatment, the incidence of subjects who underwent at least one amputation was 0.6% (n=19) in the dapagliflozin group and 0.8% (n=26) in the placebo group, corresponding to event rates of 0.3 and 0.4 subjects per 100 patient-years, respectively. All subjects, except 4 patients in each treatment group, had T2DM at baseline. Most subjects with surgical amputations in the dapagliflozin group (63%) and the placebo group (58%) had one amputation; all but one (in the dapagliflozin group) was lower limb amputations. The numbers of patients with major amputations (below knee and above knee) were the same in both treatment groups (8 patients in each treatment group).

The number of patients with any potential risk factor AE related to risk for lower limb amputation was 6.6% for dapagliflozin and 7.0% for placebo. Of these patients, the number of patients who underwent subsequent amputations was 0.6% (n=18) in the dapagliflozin treatment group, and 0.8% (n=25) in the placebo group.

Fournier's gangrene

On- and off-treatment, 4 subjects with SAE indicating genital area infections or necrotising fasciitis were identified: 1 (0.0%) in the dapagliflozin groups (1 anal abscess) and 3 (0.1%) in the placebo group (1 necrotising fasciitis, 1 testicular abscess and 1 vulval cellulitis). None of the events was confirmed by the Applicant as Fournier's gangrene.

Cardiac ischaemic events and stroke

On treatment, the incidence of subjects with unstable angina (1.7% vs 2.2% for dapagliflozin vs placebo) or myocardial infarction AE (2.2% vs 2.3% for dapagliflozin vs placebo) were balanced or slightly higher for placebo compared with dapagliflozin. The incidence of subjects with any stroke AE was balanced for dapagliflozin (3.4%) and placebo (3.2%), respectively.

Laboratory findings/ vital signs

In the DELIVER study, eGFR decreased over time in both the dapagliflozin and the placebo group. The change in eGFR was after 1 month of treatment more pronounced for dapagliflozin compared to placebo (-6.0% vs -0.7%); however, the difference between dapagliflozin and placebo was less noticeable at 24 months (-6.9% vs -5.3%). More patients in the dapagliflozin group (7.8%) than in the placebo group (5.7%) had a serum creatinine ≥1.5 times baseline value. The number of patients with serum creatinine ≥2 times baseline value was balanced between treatment groups (1.1% and 1.2%).

There was a decrease in mean body weight over time in the dapagliflozin group compared to placebo; mean change from baseline up to 36 months of treatment was -2.45 kg (-3.0%) for dapagliflozin and -0.27 kg (-0.3%) for placebo.

A decrease in mean blood pressure was observed with dapagliflozin vs placebo at month 1 (mean changes of -2.3 mm Hg vs -0.4 mm Hg in SBP) and month 24 (mean changes of -1.1 mm Hg vs 0.3 mm Hg in SBP). This is consistent with the known osmotic diuretic effect of dapagliflozin.

Subgroups

Effect by age

In the DELIVER study, 24% (n=1,502) were ≤65 years of age and 76% (n=4,751) were >65 years of age. About 38% (n=2,343) of the subjects were >75 years of age. A slightly higher reporting rate of SAEs, DAEs and AEs leading to interruptions were noted in the older age group, although the incidences between treatment groups were overall balanced or higher in the placebo groups. However, the incidence of any AE possibly related to IP was increased for dapagliflozin compared to placebo in subjects >65 years (9.3% vs 7.6%) and in subjects >75 years (11.0% vs 8.7%) but was balanced in subjects ≤65 years (6.9% vs 7.2%) and in subjects ≤75 years (7.3% vs 6.9%).

Effect by renal function

The incidence of subjects with any SAE and the incidence of subjects with an AE with fatal outcome was higher in the subgroup eGFR <45 mL/min/1.73 m^2 compared with the eGFR 60–45 mL/min/1.73 m^2 and eGFR ≥60 mL/min/1.73 m^2 subgroups; although, the incidences between treatment groups were balanced or higher in the placebo group.

Overall, subjects with eGFR <45 mL/min/1.73 m^2 had a higher incidence of volume depletion, renal events and events of lower limb amputation compared to subjects with eGFR 60–45 mL/min/1.73 m^2 and eGFR ≥60 mL/min/1.73 m. There was no indication of a worsening of the safety profile with declining renal function; however, subjects with AEs leading to interruptions were more common in subjects with eGFR <45 mL/min/1.73 m^2 treated with dapagliflozin (20.1%) than in those on placebo (17.9%).

2.5.2. Conclusions on clinical safety

The DELIVER study provides information on subjects with heart failure and LVEF >40%. No new safety concerns arise from the provided data.

The safety profile of dapagliflozin in patients with HF and LVEF >40% appears to be in general similar to the one previously documented in patients with HF and LVEF <40% (HFrEF), with and without T2DM. No subgroup analysis regarding the effect of T2DM has been provided in the DELIVER study; however, this was performed in the HF-DAPA study. In subjects with HFrEF, the safety profile with regards to SAEs did not differ between patients with and without diabetes and HbA1c was not reduced in non-diabetic subjects. Based on the mechanism of action, it is not expected that dapagliflozin poses an unwarranted risk of hypoglycaemia in subjects without diabetes.

In the overall population and in the additional subgroup analyses on renal function, the number of SAEs was balanced or lower in the dapagliflozin group than in the placebo group.

The incidence of volume depletion, renal events and events of lower limb amputation increased with decreasing baseline eGFR. In the subgroup eGFR <45 mL/min/1.73 m^2, more subjects interrupted treatment due to an AE in the dapagliflozin group than in the placebo group. However, there was no indication of a worsening of the safety profile with declining renal function.

A slightly higher reporting rate of SAEs, DAEs and AEs leading to interruptions were noted in the older age groups, although the incidences between treatment groups were overall balanced or higher in the placebo groups. However, the incidence of any AE possibly related to IP was increased for dapagliflozin compared to placebo in older subjects (>65 years and >75 years) but was balanced in subjects ≤65 years and ≤75 years. Elderly patients may be at a greater risk for volume depletion and are more likely to have impaired renal function, and/or more likely to be treated with diuretics and with anti-hypertensive products. The present warning in section 4.4 regarding elderly is considered sufficient.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The WSA submitted an updated RMP (version 27.1) with this application. The (main) proposed RMP changes were the following:

- **Part I. Product overview**
  Updated information on the proposed extended HF indication.
- **Part II. Safety specification**
  - Module SI (Epidemiology of the indication): Updated information on epidemiology of HF
  - Module SIII (Clinical trial exposure): Added clinical trial exposure data from the finalised DELIVER study
  - Module SIV (Populations not studied in clinical trials): Congestive HF updated to clarify that use in NYHA class IV is included as missing information
  - Module SV (Post-authorisation experience): Updated with marketing exposure data for dapagliflozin

- Module SVII (Identified and potential risks): Updated with outcome data from the DELIVER study. Added text describing "lower limb amputation" data in the DELIVER study.

- **Part III. Pharmacovigilance plan**
  Updated to remove the DELIVER study
- **Part V. Risk minimisation measures**
  Updated to remove additional PhV activities for "lower limb amputation"
- **Part VI. Summary of the RMP**
  Updated to include information on the proposed extended HF indication. Additional PhV activities for "lower limb amputation" are removed. The DELIVER study is removed from the PhV Plan.

Safety concerns

Important identified risks	Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	Bladder cancer Breast cancer Prostate cancer Lower limb amputation
Missing information	Use in patients with NYHA class IV Long-term safety in the paediatric population (aged 10 years and above)

Pharmacovigilance plan

Study (study short name, and title) **Status (planned/ongoing)**	**Summary of objectives**	**Safety concerns addressed**	**Milestones** **(required by regulators)**	**Due dates**
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
MB102118 (D1690R00007) - Observational study: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment Ongoing	To assess the incidence of breast and bladder cancer among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Risk of cancer	Submission of Interim data Submission of final data	2016, 2019, 2021, 2023 2025
Nonclinical mechanistic model studies - Postdoc project	Studies aimed to elucidate the metabolic adaptations in term of glucose flux, lipolysis, and ketogenesis	Diabetic Ketoacidosis including events with	Submission of final data	When available

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
Ongoing	following insulin withdrawal in subjects with diabetes mellitus and absolute or relative endogenous insulin deficiency, when treated with dapagliflozin.	atypical presentation		
~~D169CC00001 Deliver~~ ~~An International, Double-blind, Randomised, Placebo-Controlled Phase III Study to Evaluate the Effect of Dapagliflozin on Reducing CV Death or Worsening Heart Failure in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)~~	~~To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function~~	~~Lower limb amputation~~	~~Submission of final data~~	~~Q3 2022~~
D1680C00019 (CV181375) T2NOW A 26-Week, Multicenter, Randomised, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26-Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin and Saxagliptin in Paediatric Patients with T2DM Who Are Between 10 and < 18 Years of Age	To assess the safety and tolerability of dapagliflozin and saxagliptin in paediatric T2DM subjects aged from 10 to < 18 years, when administered for up to 52 weeks of total treatment. Long term safety data including measures of growth and maturity and Tanner staging and markers of bone health will be collected for up to 104 weeks.	Long-term safety in the paediatric population (aged 10 years and above).	Submission of final data	2024

Risk minimisation measures

Safety concern	Risk minimisation measures
Important identified risks	

Safety concern	Risk minimisation measures	
Diabetic Ketoacidosis including events with atypical presentation	Routine risk minimisations measures: SmPC sections 4.4, 4.8 PL section 4 Information includes that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected (SmPC section 4.4, PL section 2). Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered (SmPC section 4.4). Information that FORXIGA should not be used for patients with T1DM (SmPC section 4.4).	
Important potential risks		
Bladder cancer	No risk minimisation measures.	
Breast cancer	No risk minimisation measures.	
Prostate cancer	No risk minimisation measures.	
Lower limb amputation	Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance provided on potential class effect (SmPC section 4.4) and counsel on routine preventative foot care (SmPC section 4.4 and PL section 2).	
Missing information		
Use in patients with NYHA class IV	Routine risk minimisation measures: SmPC section 4.4	
Long-term safety in the paediatric population (aged 10 years and above)	No risk minimisation measures.	Additional PV: Long term safety data including measures of growth and maturity and Tanner staging and markers of bone health will be collected for up to 104 weeks. D1680C00019 (CV181375) T2NOW

2.7. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

2.8. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated to include information on the use of dapagliflozin in the treatment of symptomatic chronic heart failure.

The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The scope of this application is to extend the current indication "treatment of symptomatic chronic heart failure with reduced ejection fraction" to include heart failure (HF) with mildly reduced or preserved left ventricular ejection fraction (LVEF > 40%).

The claimed indication is:

"Forxiga is indicated in adults for the treatment of symptomatic chronic heart failure ~~with reduced ejection fraction~~."

The prevalence of known HF is approximately 1% to 2% of the general adult population. HF with LVEF > 40% accounts for approximately half of all HF cases. Heart failure is a clinical syndrome consisting of cardinal symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart.

Patients with signs and symptoms of HF are categorized, based on measurement of left-ventricular ejection fraction (LVEF), as having HF with reduced LVEF (HFrEF) (typically <40%) or HF with preserved LVEF (HFpEF). HFpEF is typically defined as LVEF ≥50%; HF with LVEF in the 40% to 49% may be characterized as HF with mid-range ejection fraction (HFmrEF).

3.1.2. Available therapies and unmet medical need

Pharmacotherapy is the cornerstone of treatment for heart failure with reduced ejection fraction (HFrEF). Diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, or angiotensin II receptor blocker-neprilysin inhibitor, mineralocorticoid receptor antagonists, and beta-

blockers can improve symptoms and haemodynamics as well as reduce hospitalizations and mortality (Iwaz et al 2016).

With regards to heart failure with mildly reduced ejection fraction (HFmrEF), the ESC Guideline (McDonagh et al 2021) states that diuretics should be used to control congestion. Although the guideline does not make any strong recommendations, treatment with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, or angiotensin II receptor blockers-neprilysin inhibitor may be considered based on subgroup analysis of trials in HFpEF.

Dapagliflozin is an inhibitor of SGLT2, currently approved for the treatment of T2DM (since 2012), HFrEF, and CKD. The indication for the treatment of HFrEF (LVEF ≤ 40%), approved in Nov 2020, was based on positive results from the DAPA-HF study (D1699C00001).

There is a lack of approved pharmacotherapy indicated for heart failure with preserved ejection fraction (HFpEF) as reflected in the current HF treatment guidelines. However, recently (March 2022), another SGLT2 inhibitor, empagliflozin, was approved for the use in patients with HF and LVEF > 40%.

Considering that HF is a common and serious medical condition with a high risk of repeat hospitalisation for HF and a high mortality, there remains an unmet medical need for new treatment options that reduce morbidity and mortality in patients with HF and LVEF > 40%.

3.1.3. Main clinical studies

DELIVER was a Phase III international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled study in 6263 patients (44% female) with HF and LVEF > 40%. The primary objective was to evaluate the effect of dapagliflozin 10 mg tablets versus placebo, given once daily, in reducing the composite of CV death or an HF event (hospitalisation for HF or urgent HF visit). Two hypotheses were tested for this primary objective simultaneously: in the full study population and in a subpopulation with LVEF < 60%. The secondary endpoints included the composite of CV death and HF events (first and recurrent), change from baseline in the TSS of the KCCQ at 8 months, time to CV death and time to all-cause mortality.

The median time in study until PACD was 28.0 months and median time until last visit was 28.5 months. The mean age of the study population was 71.7 years and 43.9% of patients were female. 48% of patients were recruited in Europe/Saudi Arabia. Almost 45% of patients had a medical history of T2DM. About 75% of patients were in NYHA class II and about 24% were in NYHA class III. 30% of patients had a LVEF ≥ 60%. Most patients were diagnosed with HF < 5 years before enrolment and 40.5% of patients had been hospitalised for HF prior to study enrolment. The median LVEF was 54.0% and the median NT-proBNP was 1011.0 pg/mL.

DELIVER and DAPA-HF, the latter being a study in patients with HF and reduced LVEF, were powered for the primary composite endpoint and not for individual components of the composite. A pooled analysis of patient-level data from DELIVER and DAPA-HF has been provided 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 treatment effect of dapagliflozin on CV death.

3.2. Favourable effects

Dapagliflozin was superior to placebo in reducing the incidence of primary composite endpoint of CV death or an HF event (HR 0.82 [95% CI 0.73, 0.92], p = 0.0008). The event rates per 100 patient

years of 7.8 for dapagliflozin and 9.6 for placebo. All components of the composite endpoint contributed to the outcome, although CI overlapped for CV-death and urgent HF visits.

The composite secondary endpoint of recurrent HF events and CV death was also met (RR 0.77 [95% CI 0.67, 0.89], p = 0.0003), again the outcome was mainly driven by the recurrent HF events.

The outcome in the subgroup with LVEF < 60% was in line with that if the overall population for the primary endpoint and the composite secondary endpoint.

The change from baseline in KCCQ Scores was significantly greater in the dapagliflozin treated group (WR1.11 [95% CI 1.03, 1.21], p = 0.0086). The responder analysis showed that the proportion of patients who experienced a moderate (≥ 5 points) or large (≥ 14 points) deterioration in KCCQ Scores was significantly lower in the dapagliflozin treated group (moderate: 24% vs 29% and large: 13.5% vs 18.4%), whereas no differences were observed for patients reporting an improvement.

CV deaths were numerically fewer in the dapagliflozin treated group (231 vs 261), but the difference was not statistically significant. The events of all-cause death were also numerically fewer in the dapagliflozin treated group (497 vs 526), but again the difference was not statistically significant.

Subgroup analysis of the primary composite endpoint showed that the outcome was consistent across all prespecified subgroups by LVEF as well as across all prespecified demographic subgroups. The only divergent findings were observed in one very small subgroup, i.e., Black or African. The subgroup analysis performed on the subpopulation with LVEF <60% was consistent with the overall population. An additional subgroup analysis by age (<65, 65-74, 75-84 and ≥ 85 years) showed consistent findings across age groups.

Analysis of the data to evaluate the impact of the COVID-19 pandemic did not reveal any inconsistencies compared to the main analysis.

The pooled analysis of patient level data from the two studies DELIVER and DAPA HF showed a HR of 0.78 (95% CI 0.72, 0.85) for the primary composite endpoint. The analysis further showed a consistent effect over the entire range of LVEF observed at baseline, with a stable HR of about 0.8.

In the pooled analysis, a significant effect on CV death (HR 0.85 [95% CI 0.75, 0.96]) and all-cause mortality (HR 0.90 [95% CI 0.82, 0.99]) is observed. The effect on CV death was consistent across the range of observed LVEF at baseline.

3.3. Uncertainties and limitations about favourable effects

In the CHMP scientific advice in 2017, the MAH was requested to provide data in support of the mechanism of action for SGLT2 inhibitors when used in the treatment of heart failure. No new data has been provided, instead the MAH refers to the literature. The MAH's interpretation of these data is that the primary effect of dapagliflozin—inhibition of SGLT2 in the proximal kidney tubules—leads to changes in sodium, glucose, and fluid handling, which leads to a decrease in volume overload. This off-loading of the heart has beneficial effects on cardiac remodelling, which leads to improved diastolic parameters. The decongestive effect and reversal of some of the structural changes in the heart are the likely drivers of the benefit on HF events and mortality.

There is uncertainty with respect to patients with chronic heart failure and T1DM. These patients were not included in the study and no data on efficacy in the heart failure indication are available. B/R cannot be considered positive in this population due to the increased risk of DKA in this population. Therefore, treatment of these patients is not recommended, as reflected in the SmPC.

3.4. Unfavourable effects

In DELIVER, 3,126 subjects were treated with dapagliflozin for a total exposure of 6,426 PY (on- and off-treatment) with 86% exposed for at least 52 weeks and 61% for at least 2 years. The mean and median duration of exposure was 24.7 months and 26.9 months, respectively.

Data collection in this study focused on serious AEs (SAEs), AEs leading to discontinuation (DAEs) and AEs of special interest.

The number of fatal cases (12.8% and 13.5%) and SAEs (43.5% and 45.5%) were balanced between dapagliflozin and placebo. The most frequently reported SAEs for dapagliflozin and placebo were in the SOC Infections and infestations (16.4% and 16.2%) and the SOC Cardiac disorders (18.5% and 21.2%). The most reported SAEs for dapagliflozin vs placebo were cardiac failure (8.4% vs 11.0%), COVID-19 (5.3% vs 4.2%), pneumonia (3.1% vs 3.1%) and COVID-19 pneumonia (2.5% vs 2.6%).

The incidence of SAEs (1.3% vs 1.2%) and DAEs (0.4% vs 0.3%) of *urinary tract infections* for dapagliflozin vs placebo were balanced.

Two SAEs of *genital infections* one in each treatment group were reported. Three patients (0.1%), all in the dapagliflozin treatment group, had a DAE of genital infection.

Frequencies of SAEs suggestive of *volume depletion* was low and balanced for dapagliflozin (1.1%) and placebo (1.0%).

SAEs of *renal adverse events* (1.8% and 2.2%) and the discontinuation rate or renal adverse events (0.7% and 0.6%) was balanced for dapagliflozin and placebo. The same pattern was observed for SAEs of acute kidney injury, i.e., the incidences for dapagliflozin (1.5%) and placebo (1.6%) was balanced.

In the dapagliflozin group, 3 events (in 2 subjects) were adjudicated as a definite *diabetic ketoacidosis (DKA)* and 2 events as a possible DKA. In the placebo group no event was adjudicated as a definite DKA and 2 events as a possible DKA.

In the DELIVER study, only *major hypoglycaemic events* were collected. On treatment, subjects with major hypoglycaemic events were balanced; 0.2% in the dapagliflozin (n=6) and placebo group (n=7), respectively. Four serious cases in the dapagliflozin group and one in the placebo group. No subject discontinued due to any major hypoglycaemic event. All patients with major hypoglycaemic events had T2DM at baseline.

On- and off-treatment, the incidence of subjects who *underwent at least one amputation* was 0.6% (n=19) in the dapagliflozin group and 0.8% (n=26) in the placebo group, corresponding to event rates of 0.3 and 0.4 subjects per 100 patient-years, respectively. All subjects, except 4 patients in each treatment group, had T2DM at baseline. Most subjects with surgical amputations in the dapagliflozin group (63%) and the placebo group (58%) had one amputation; all but one (in the dapagliflozin group) was lower limb amputations.

Cardiac ischaemic events and stroke

The incidence of subjects with unstable angina (1.7% vs 2.2% for dapagliflozin vs placebo) or myocardial infarction AE (2.2% vs 2.3% for dapagliflozin vs placebo) were balanced or slightly higher for placebo compared with dapagliflozin. The incidence of subjects with any stroke AE was balanced for dapagliflozin (3.4%) and placebo (3.2%), respectively.

Laboratory findings/ vital signs

In the DELIVER study, eGFR decreased over time in both the dapagliflozin and the placebo group. The change in eGFR was after 1 month of treatment more pronounced for dapagliflozin compared to

placebo (-6.0% vs -0.7%); however, the difference between dapagliflozin and placebo was less noticeable at 24 months (-6.9% vs -5.3%).

There was a decrease in mean body weight over time in the dapagliflozin group compared to placebo; -1.3% vs 0.01% at 12months, -1.7% vs 0.1% at 24 months and -3.0% vs -0.3% at 36 months.

A decrease in mean blood pressure was observed with dapagliflozin vs placebo at month 1 (mean changes of -2.3 mm Hg vs -0.4 mm Hg in SBP) and month 24 (mean changes of -1.1 mm Hg vs 0.3 mm Hg in SBP). This is consistent with the known osmotic diuretic effect of dapagliflozin.

Subgroups

In the DELIVER study, 24% (n=1,502) were ≤65 years of age and 76% (n=4,751) were >65 years of age. About 38% (n=2,343) of the subjects were >75 years of age. A slightly higher reporting rate of SAEs, DAEs and AEs leading to interruptions were noted in the older age group, although the incidences between treatment groups were overall balanced or higher in the placebo groups. However, the incidence of any AE possibly related to IP was increased for dapagliflozin compared to placebo in subjects >65 years (9.3% vs 7.6%) and in subjects >75 years (11.0% vs 8.7%) but was balanced in subjects ≤65 years (6.9% vs 7.2%) and in subjects ≤75 years (7.3% vs 6.9%).

The incidence of subjects with any SAE and with an AE with fatal outcome was higher in the subgroup eGFR <45 mL/min/1.73 m^2 compared with the eGFR 60–45 mL/min/1.73 m^2 and eGFR ≥60 mL/min/1.73 m^2 subgroups; although, the incidences between treatment groups were balanced or higher in the placebo group. Overall, subjects with eGFR <45 mL/min/1.73 m^2 had a higher incidence of volume depletion, renal events and events of lower limb amputation compared to subjects with eGFR 60–45 mL/min/1.73 m^2 and eGFR ≥60 mL/min/1.73 m. Subjects with AEs leading to interruptions were more common in subjects with eGFR <45 mL/min/1.73 m^2 treated with dapagliflozin (20.1%) than in those on placebo (17.9%).

3.5. Uncertainties and limitations about unfavourable effects

The safety profile of dapagliflozin in patients with HF and LVEF >40% appears to be in general similar to the one previously documented in patients with HF and LVEF ≤40% (HFrEF), with and without T2DM. In subjects with HFrEF, the safety profile with regards to SAEs did not differ in any substantial way between patients with and without diabetes and HbA1c was not reduced in non-diabetic subjects. Based on the mechanism of action, dapagliflozin is not expected to pose poses an unwarranted risk of hypoglycaemia in subjects without diabetes.

In the subgroup eGFR <45 mL/min/1.73 m^2, more subjects interrupted treatment due to an AE in the dapagliflozin group than in the placebo group. However, there was no indication of a worsening of the safety profile with declining renal function.

3.6. Effects Table

Table 38 Effects Table for Edistride/Forxiga in the treatment of HF (data cut-off: 22 April 2022)

Effect	Short description	Unit	Dapa	Placebo	Uncertainties / Strength of evidence	Refe-rences
Favourable Effects						
CV death or a HF event	CV death, hospitalisation for HF or	event rates per	7.8	9.6	**HR 0.82** (95% CI 0.73 to 0.92)	DELIVER study

Effect	Short description	Unit	Dapa	Placebo	Uncertainties / Strength of evidence	Refe-rences
	urgent HF visit	100 PY				
CV death or rHF	CV death and recurrent HF events	event rates per 100 PY	11.8	15.3	**RR 0.77** (95% CI 0.67 to 0.89)	DELIVER study
KCCQ	Change from baseline at 8 months in the KCCQ TSS		8.3	5.2	**WR 1.11** (95% CI 1.03 to 1.21)	DELIVER study
Unfavourable Effects						
Any SAE (including outcome death)	On-treatment	n (%)	1,361 (43.5)	1,423 (45.5)		DELIVER study
Any SAE or DAE suggestive of volume depletion		n (%)	42 (1.3)	32 (1.0)		
Any renal SAE or DAE		n (%)	73 (2.3)	79 (2.5)		
Any definite or probable DKA		n (%)	2 (0.1)	0		
Any amputation		n (%)	19 (0.6)	25 (0.8)		

Abbreviations: TSS – total symptom score.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

HF with LVEF > 40%, i.e., HFmrEF and HFpEF, is a common, serious, progressive condition characterised by frequent periods of hospitalisation and a high mortality. Currently, only one medicinal product (another SGLT2i) is approved for the treatment of HF patients with LVEF > 40%. Thus, new treatment options are needed. Dapagliflozin reduced the incidence of CV death and HF worsening with 18% compared to placebo in a population with HF and LVEF >40%. The pivotal study is considered to be of adequate design and conduct and the results with respect to reduced risk of CV death and worsening of HF are considered as robust and of clinical relevance. Subgroup analysis of the primary composite endpoint showed that the outcome was consistent across all prespecified subgroups by LVEF, including patients with LVEF >60% at baseline, as well as across all prespecified demographic subgroups. This includes a subgroup analysis by age (<65, 65-74, 75-84 and ≥ 85 years). The outcome across LVEF subgroups is further supported by data from a pooled analysis of the two studies DELIVER and DAPA HF, which showed a consistent effect over the entire range of LVEF observed at baseline. The pooled analysis also showed a significant effect on CV death (HR 0.85 [95% CI 0.75, 0.96]) and all-cause mortality (HR 0.90 [95% CI 0.82, 0.99]).

No new safety concerns arise from the provided data in patients with HF and LVEF >40%. The number of SAEs was balanced or lower in the dapagliflozin group compared with the placebo group. There was no indication of a worsening of the safety profile with impaired renal function. A slightly higher reporting rate of SAEs, DAEs and AEs leading to interruptions were noted in the older age groups, although the incidences between treatment groups were overall balanced or higher in the placebo

groups. The incidence of any AE possibly related to IP was increased for dapagliflozin compared to placebo in older subjects (>65 years) but was balanced in subjects ≤65 years. The safety profile appears to be in general similar to that previously documented for dapagliflozin, including in patients with HF and LVEF <40% (HFrEF). No subgroup analysis regarding the effect of T2DM has been provided in the DELIVER study; however, this was performed in the HFrEF population (DAPA-HF study). In subjects with HFrEF, the safety profile with regards to SAEs did not differ in any substantial way between patients with and without diabetes and HbA1c was not reduced in non-diabetic subjects. Also, based on the mechanism of action, dapagliflozin is not expected to pose an unwarranted risk of hypoglycaemia in subjects without diabetes.

3.7.2. Balance of benefits and risks

The documented benefits in the study population included in the DELIVER trial are considered to be of clinical relevance and to outweigh risks. No new safety concerns arise from the provided data in patients with HF and LVEF >40%.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Edistride/Forxiga is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include population with Heart Failure and LVEF > 40% for Forxiga and its duplicate Edistride, based on final results from study D169CC00001 (DELIVER); The DELIVER study is a category 3, Post-Authorisation Safety Study (PASS) listed in the dapagliflozin RMP to evaluate the potential risk of lower limb amputation; This was an international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled Phase III study in patients with HF and LVEF > 40%, evaluating the effect of dapagliflozin 10 mg compared with placebo, given once daily in addition to background therapy, including treatments to control co-morbidities, in reducing the composite of CV death or an HF event (hospitalisation for HF or urgent HF visit). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet are updated in accordance. Version 27 of the RMP has also been submitted.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.