EMA/574301/2020
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Procedure No. EMEA/H/C/WS1737

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Forxiga	dapagliflozin	EMEA/H/C/002322/WS1737/0053
Edistride	dapagliflozin	EMEA/H/C/004161/WS1737/0034

Worksharing applicant (WSA): AstraZeneca AB

Table of contents

List of abbreviations

ACE Angiotensin converting enzyme (inhibitor)

AE Adverse event

AF Atrial fibrillation

ALP Alkaline phosphatase

ALT Alanine transaminase

ARB Angiotensin II receptor blockers

AST Aspartate transaminase

BNP B-type natriuretic peptide

BP Blood pressure

BUN Blood urea nitrogen

CABG Coronary artery bypass grafting

CDISC Clinical Data Interchange Standards Consortium

CEA Clinical Event Adjudication (Committee)

CHMP Committee on Human Medicinal Products

CKD Chronic kidney disease

CRF Case report form

CRT Cardiac resynchronisation therapy

CSP Clinical study protocol

CSR Clinical study report

CV Cardiovascular

DAE Adverse event leading to discontinuation of study drug

DKA Diabetic ketoacidosis

DM Diabetes mellitus

DMC Data Monitoring Committee

eCDF Empirical cumulative distribution

ECG Electrocardiogram

eGFR Estimated glomerular filtration rate

EQ-5D-5L EuroQol 5-dimensional 5-level questionnaire

ePRO Electronic patient reported outcome

FAS Full analysis set

GCP Good Clinical Practice

Hb Haemoglobin

HbA1c Glycated haemoglobin

HF Heart failure

HFH hospitalisation for heart failure

HFrEF Heart failure with reduced left ventricular ejection fraction

HR Hazard Ratio

IB Investigator's Brochure

ICF Informed consent form

ICH International Council for Harmonisation

IEC Independent Ethics Committee

IRB Institutional Review Board

IP Investigational products.

ITT Intention-to-treat

IxRS Interactive voice or web response system

KCCQ Kansas City Cardiomyopathy Questionnaire

LV Left ventricular

LVEF Left ventricular ejection fraction

MA Marked abnormality

MedDRA Medical dictionary for regulatory activities (version 22.0)

MI Myocardial infarction

MRA Mineralocorticoid receptor antagonist

NLI National Lead Investigator (Committee)

NT-proBNP N-terminal pro b-type natriuretic peptide

NYHA New York Heart Association

PACD Primary analysis censoring date

PCI Percutaneous coronary intervention

PGIC Patient global impression of change

PGIS Patient global impression of severity

PK Pharmacokinetic

PRO Patient reported outcome

PTDV Premature treatment discontinuation visit

SAE Serious adverse event

SAP Statistical analysis plan

SAS Safety analysis set

SAS® Statistical Analysis System

SCV Study closure visit

SED Study end date

SGLT2 Sodium-glucose co-transporter 2

T1DM Type 1 diabetes mellitus

T2DM Type 2 diabetes mellitus

TSS Total symptom score

WoC Withdrawal of consent

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 11 November 2019 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

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, IIIA and IIIB

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC for Edistride and Forxiga to add a new indication for the treatment of symptomatic heart failure with reduced ejection fraction in adults. The Package Leaflet and Labelling are updated in accordance.
The RMP version 18 has also been submitted.
Furthermore, the PI is brought in line with the latest QRD template version 10.1, as well as editorial change (addition of SI unit for blood glucose).

The worksharing procedure requested amendments to the Summary of Product Characteristics, Labelling 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 of 19 July 2018 on the granting of a (product-specific) waiver for dapagliflozin (Forxiga), (EMEA-000694-PIP03-17) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

Information relating to orphan market exclusivity

N/A

Similarity

N/A

Derogation(s) of market exclusivity

N/A

WSA request for additional market protection

The WSA requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The WSA received Scientific advice from the CHMP on 26 May 2016 (EMA/CHMP/SAWP/336742/2016). The Scientific advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Kristina Dunder

Martina Weise

Timetable	Actual dates
Submission date	11 November 2019
Start of procedure:	30 November 2019
CHMP Co-Rapporteur Assessment Report	27 January 2020
CHMP Rapporteur Assessment Report	24 January 2020
PRAC Rapporteur Assessment Report	24 January 2020
PRAC members comments	5 February 2020
PRAC Outcome	13 February 2020
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 February 2020
Request for supplementary information (RSI)	27 February 2020
CHMP Rapporteur Assessment Report	25 May 2020
PRAC Rapporteur Assessment Report	25 May 2020
PRAC members comments	3 June 2020
Updated PRAC Rapporteur Assessment Report	4 June 2020
PRAC Outcome	11 June 2020
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	18 June 2020
Request for supplementary information (RSI)	25 June 2020
CHMP Rapporteur Assessment Report	21 August 2020

Timetable	Actual dates
PRAC Rapporteur Assessment Report	21 August 2020
PRAC members comments	26 August 2020
PRAC Outcome	4 September 2020
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	10 September 2020
Request for supplementary information (RSI)	17 September 2020
CHMP Rapporteur Assessment Report	30 Sep 2020
PRAC Rapporteur Assessment Report	30 Sep 2020
CHMP members comments	05 Oct 2020
PRAC members comments	05 Oct 2020
Updated PRAC Rapporteur Assessment Report	08 Oct 2020
Updated CHMP Rapporteur Assessment Report	08 Oct 2020
Opinion	15 Oct 2020
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Edistride in comparison with existing therapies (Appendix-1)	15 Oct 2020

2. Scientific discussion

2.1. Introduction

Dapagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor, previously approved for the treatment of patients with T1DM or T2DM. In the current variation, the MAH is applying for a new indication (*X is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fractio*n) based on the results of one pivotal phase III study; D1699C00001, hereafter referred to as DAPA-HF.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule along with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis (Kasichayanula et al 2014). Based on this mechanism, a beneficial effect in patients with heart failure (HF) could be expected. However, the glycosuric effect decreases with decreasing renal function and additional effects have been proposed to be relevant for patients with heart failure.

In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid have been discussed to be relevant for cardio-renal effects of dapagliflozin (e.g. Esterline RL, et al., European journal of endocrinology. 2018;178(4): R113-r25., Ferrannini et al., Diabetes Care. 2016;39(7):1108-14; 2016, Hallow et al 2018, Am J Physiol Renal Physiol. 2018;315(5): F1295-F306. Lytvyn et al 2017; Circulation. 2017;136(17):1643-58.). Lytvyn et al. provided an overview over the multiplicity of proposed mechanisms of cardiorenal protection with SGLT2 inhibition (Figure 3). At present, it is obvious that actions beyond a blood glucose lowering effect are of key relevance for CV protection but the individual contribution of the different effects to cardiovascular protection is unclear.

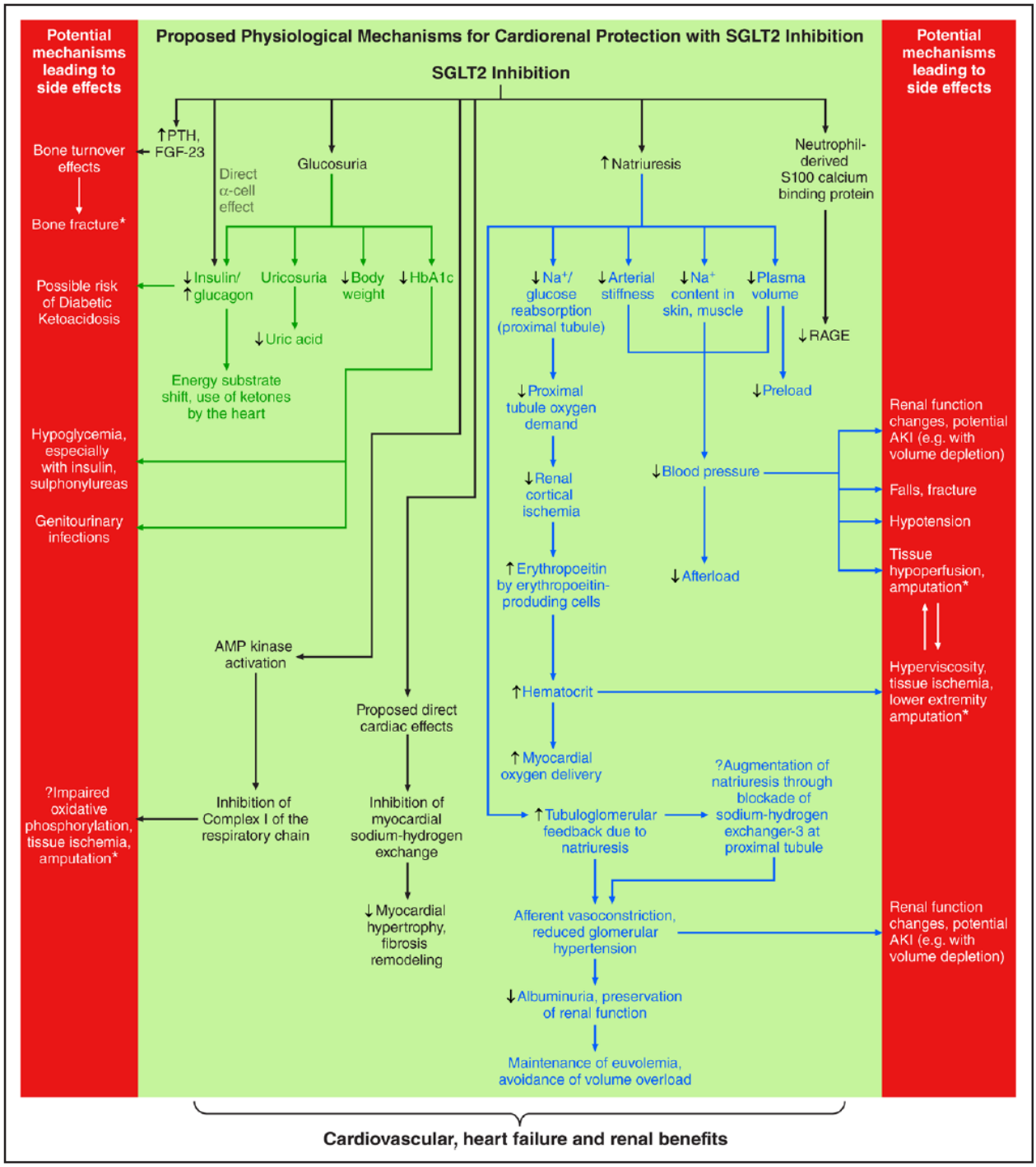


Figure 3. Integrated physiological basis for proposed mechanisms leading to cardiorenal benefits and risks associated with sodium glucose cotransport-2 inhibition.

*Only reported in the CANVAS Program. AKI indicates acute kidney injury; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; and RAGE, receptor for advanced glycation end products.

The prevalence of HF is estimated at 1% to 2% in the Western world (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017) and in a report from US community-based samples, 5-year mortality in HFrEF patients was 66%(Tsao et al 2018). The core symptoms of HF include shortness of breath, fatigue, and peripheral oedema and hospitalisations due to decompensations are frequently occurring. Current standard of care includes renin-angiotensin system (RAS) blockade, Beta blockade,

and mineralocorticoid receptor antagonists (MRAs) (if deemed appropriate). In addition to these therapies, diuretics are used to reduce symptoms from fluid overload. More recently, neprilysin inhibition (in conjunction with RAS blockade) was added as a new treatment option.

CHMP scientific advice

The MAH applied for a scientific advice from the CHMP in May 2016. The main topics covered in the advice letter were; appropriateness of the proposed study design for a heart failure indication, choice of primary endpoints, treatment regimens, background medication, statistical testing strategy and safety data collection.

2.2. Non-clinical aspects

This application is an extension of indication variation for Edistride/Forxiga and the active substance is dapagliflozin. The current therapeutic indications are insufficiently controlled type 1 and type 2 diabetes mellitus as an adjunct for maintaining a sufficient glycaemic control according to the summary of product characteristics. The applied new indication is chronic heart failure with reduced ejection fraction.

The applicant has submitted three non-clinical studies.

2.2.1. Introduction

Dapagliflozin is a selective sodium- glucose cotransporter 2 (SGLT2) inhibitor and prevents the renal reabsorption of glucose and is thus reducing the blood glucose levels in hyperglycaemic patients. The applicant has submitted three non-clinical reports investigating whether treatment of dapagliflozin may attenuate the deterioration of heart function in two different mouse models of diabetes, i.e. BTBR.Cg-Lep^{OB}/WiscJ and C57Bl/6 J-lep^{OB} mice. *In vitro* studies using cardiac fibroblasts was performed to elucidate whether attenuation of inflammasome activation may play a role in the mechanism of action by dapagliflozin.

In addition, since the initial marketing authorization approval, a toxicology study has been performed to date. Applicant has provided an Addendum to Non-clinical Written Summary, a toxicology report where a 6-month cancer study with regard to urinary bladder cancer is presented.

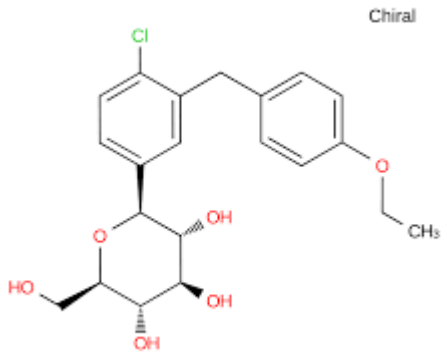
2.2.2. Pharmacology

AZ13219875, dapagliflozin, is a selective SGLT2 inhibitor. Applicant has submitted three non-clinical studies proving target engagement and proof of mechanism for SGLT2 inhibition.

Chemical name	(1S)-1,5-anhydro-1-{4-chloro-3-[(4-

	ethoxyphenyl)methyl]phenyl}-D-glucitol
Compound code	AZ13219875
Synonym Name	Dapagliflozin
Formula	C21 H25 Cl O6
Molecular mass	408.880
Batch No.	AZ13219875-002
Source	Medicinal Chemistry, AstraZeneca R&D Mölndal, Sweden

Structure:



2.2.3. **Primary pharmacodynamic studies**

Three new non-clinical studies with the compound AZ13219875 (dapagliflozin), a selective SGLT2 inhibitor, have been provided by applicant and are summarized below.

2.2.3.1. Study number: Nonclinical HF 001

In one study, (study number: Nonclinical HF 001) insulin resistant homozygous male C57BL/6J-lep^{ob} mice (ob/ob$^{-/-}$ mice) was treated with two dose levels, 1.5 and 4.0 mg/kg/day , delivered in drinking water for 10 weeks. A vehicle control group was also included (n= 18 per group).

Effect of dapagliflozin on urinary glucose excretion

Treatment with AZ13219875, dapagliflozin, resulted in a dose-dependent increase in urinary glucose excretion at weeks 5 and 10 (Table 1). This result indicates that both dapagliflozin dose

groups demonstrated statistically significant target engagement.

Treatment group	Urine glucose (mmol/L) measured at Baseline	Urine glucose (mmol/L) measured at 5 weeks post administration of dapagliflozin	Urine glucose (mmol/L) measured at 10 weeks post administration of dapagliflozin
Vehicle	157.2 ± 36.3	214.1 ± 60.7	92.1 ± 36.3
1.5 mg/kg/day	225.0 ± 53.6	531.6 ± 27.2 **	454.2 ± 14.2 **
4.0 mg/kg/day	176.8 ± 45.7	559.9 ± 29.4 **	447.4 ± 31.9 **

** indicates $p < 0.01$ for statistical difference between Vehicle vs 1.5 mg/kg/day Dapagliflozin treatment and Vehicle vs 4 mg/kg/day Dapagliflozin treatment. Data analysis used one-way ANOVA, and Bonferroni correction for multiple comparisons. Data presented are Mean ± SEM for urinary glucose measurements.

Effect of dapagliflozin on blood HbA1c

Both treatments groups had lower HbA1c than the vehicle group at 5 and 10 weeks post treatment (Table 2) suggesting in an improvement in the glycaemic control due to inhibition of SGLT2.

Treatment group	HbA1c (mmol/mol) measured at Baseline	HbA1c (mmol/mol) measured at 5 weeks post administration of dapagliflozin	HbA1c (mmol/mol) measured at 10 weeks post administration of dapagliflozin
Vehicle	51.3 ± 1.9	60.2 ± 3.6	54.1 ± 5.5
1.5 mg/kg/day	53.0 ± 2.7	43.0 ±1.6 **	41.2 ± 1.5 **
4.0 mg/kg/day	51.4 ± 3.0	41.1 ±1.4 **	39.7 ± 1.9 **

** indicates $p < 0.01$ for statistical difference between Vehicle vs 1.5 mg/kg/day Dapagliflozin treatment and Vehicle vs 4 mg/kg/day Dapagliflozin treatment. Data analysis used one-way ANOVA, and Bonferroni correction for multiple comparisons. Data presented are Mean ± SD for HbA1c measurements.

Dapagliflozin improved coronary function (CFVR) of the left ventricle

The coronary flow velocity reserve (CFVR), as a measure of microvascular function, was investigated. Dapagliflozin improved the CFVR in the 4.0mg/kg/day treated group, at 5 and 10 weeks after intervention, compared with vehicle group. Figure 1 shows a trend toward dose-dependent changes in CFVR at 5 and 10 weeks compared to the vehicle treated group.

Effect of dapagliflozin on coronary flow velocity reserve (CFVR)

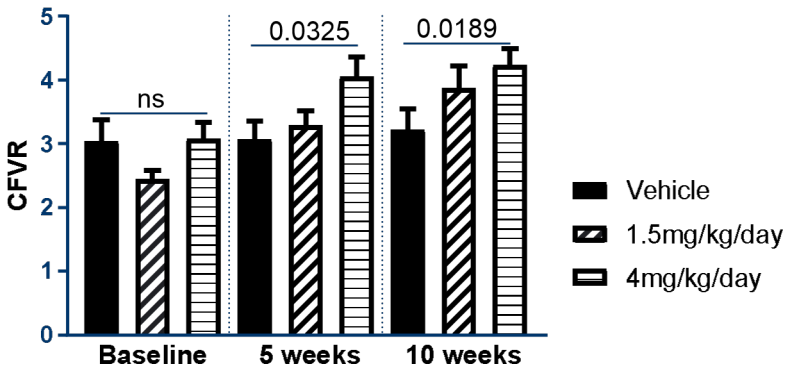


Figure 1. Coronary flow was studied over time in ob/ob$^{-/-}$ mice, treated with either dapagliflozin or vehicle, using noninvasive transthoracic ultrasound (N = 18 mice for each treatment group). Statistical significance for the difference of the mean between groups was assessed using ANOVA, and Bonferroni correction for multiple comparisons. Each bar represents Mean ± SEM.

Dapagliflozin improved left ventricular contractility (FAC)

Left ventricle fractional area change (FAC) is the percent change in left ventricular cross-sectional area between diastole and systole. At 10 weeks both treatment groups showed significantly higher cardiac contractile function compared with the vehicle group (figure 2).

Figure 2 Effect of dapagliflozin on fractional area change (FAC)

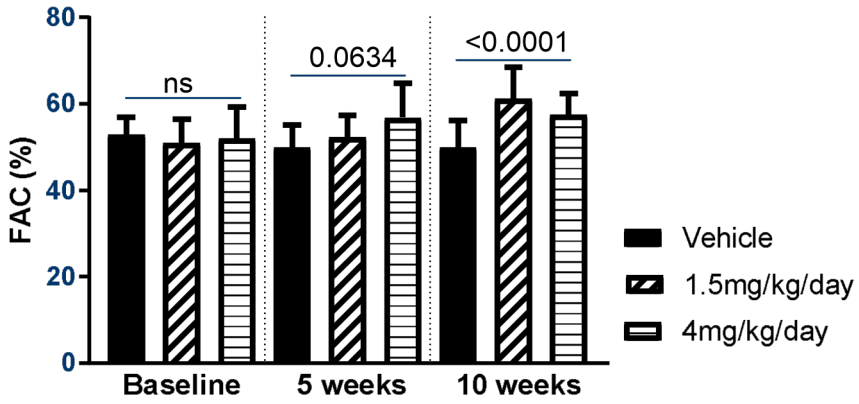


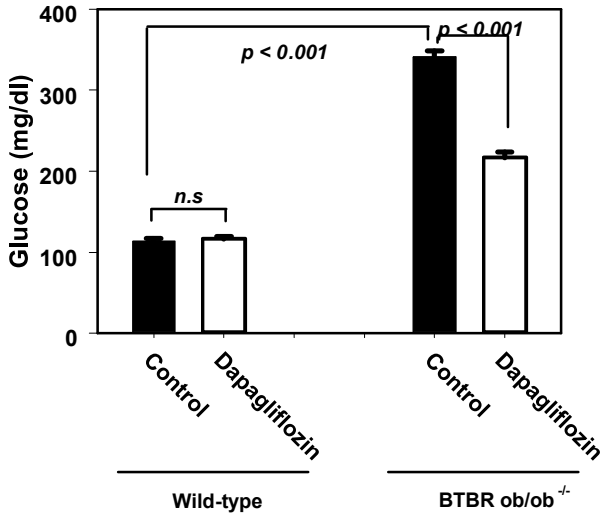
Figure 2. Cardiac contractile function (FAC) was studied over time in ob/ob$^{-/-}$ mice, treated with either dapagliflozin or vehicle, using non-invasive transthoracic ultrasound (N = 18 mice for each treatment group). Statistical significance for the difference of the mean between groups was

assessed using ANOVA, and Bonferroni correction for multiple comparisons. Each bar represents Mean ± SEM.

2.2.3.2. Study number: Nonclinical HF 002

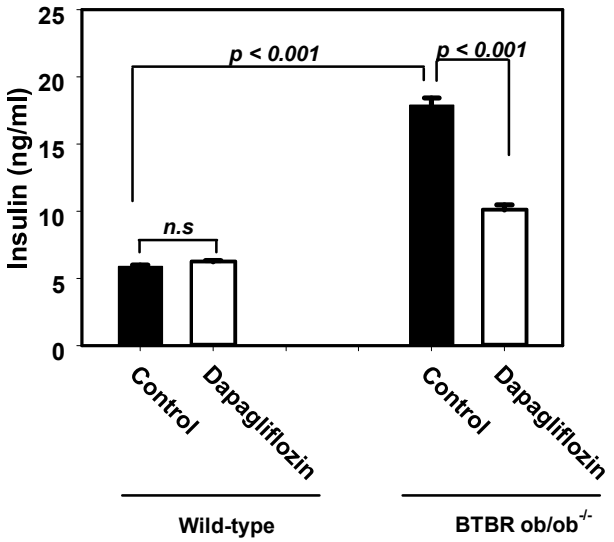
In the second study,BTBR ob/ob$^{-/-}$ mouse model was administrated with 1 mg/kg/day for 8 weeks to determine (1) whether treatment with dapagliflozin may attenuate the deterioration of heart function; (2) whether dapagliflozin treatment affects the cardiac remodelling; and (3) whether inflammasome activation may play a role in the mechanism of action for the observed cardioprotective effect of dapagliflozin.

Effect of dapagliflozin (1mg/kg/day) treatment on the fasting blood glucose in wild-type and in BTBR ob/ob$^{-/-}$ mice



Each treatment group consists of 6 animals. Each bar represents Mean ± SEM values One-way ANOVA was used for statistical data analysis, n.s= no statistical significance.

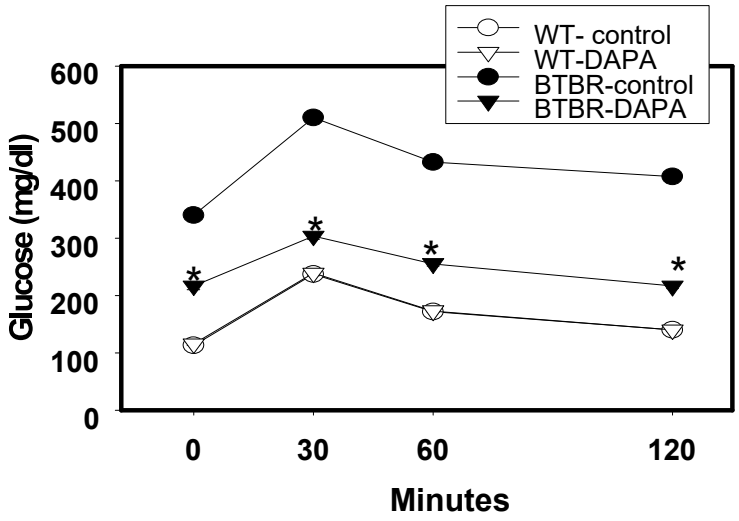
Effect of dapagliflozin treatment on the fasting plasma insulin in wild-type and BTBR ob/ob$^{-/-}$ mice



Each treatment group consists of 6 animals. Each bar represents Mean ± SEM values. One-way ANOVA was used for statistical data analysis, n.s= no statistical significance.

Dapagliflozin treatment improved glucose tolerance and restored β-cell insulin secretory function in BTBR ob/ob-/- mice

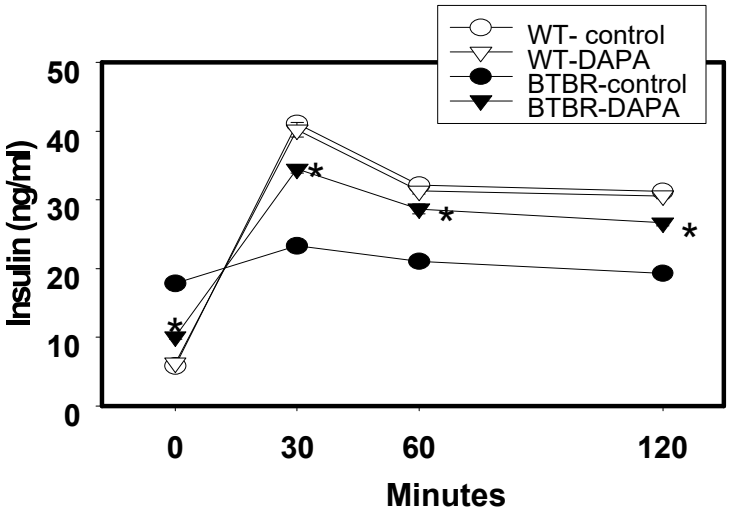
ipGTT in wild-type and BTBR ob/ob$^{-/-}$ mice



ipGTT was performed after 8 weeks of treatment with either vehicle or dapagliflozin in wild-type and BTBR ob/ob-/- mice. Blood glucose was measured at 0, 30, 60 and 120 min after i.p. injection of 1g/kg glucose. Each treatment group consists of 6 animals. Each data point

represents Mean ± SEM values. One-way ANOVA was used for statistical data analysis *p < 0.001 for BTBR-Dapagliflozin vs BTBR-Control.

Effect of dapagliflozin treatment on the insulin profile in the ipGTT experiment in wild-type and BTBR ob/ob-/- mice



ipGTT was performed after 8 weeks of treatment with either vehicle or dapagliflozin in wild-type and BTBR ob/ob$^{-/-}$ mice Plasma was collected at 0, 30, 60 and 120 min after i.p. injection of 1g/kg glucose Plasma insulin concentration was measured using ELISA method Each treatment group consists of 6 animals Each data point represents Mean ± SEM values One-way ANOVA was used for statistical data analysis * $p < 0.001$ for BTBR-Dapagliflozin vs BTBR-Control

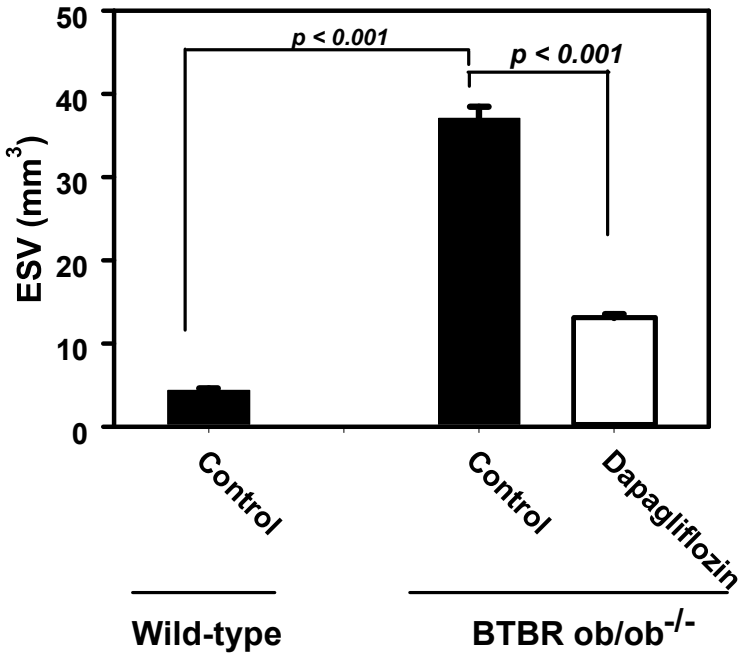
Dapagliflozin treatment reversed cardiac dysfunction in BTBR ob/ob$^{-/-}$ mice, as measured by Echocardiography

After 8 weeks of treatment with either dapagliflozin (1mg/kg/day) or vehicle mice in all treatment and genotype groups were anesthetized. Echocardiogram test was performed on each mouse.

End systolic volume (ESV) is the lowest volume of blood in the ventricle at any point in the cardiac cycle. Left ventricular ESV is a marker of ventricular contractility that is relatively insensitive to loading conditions. It is also an indicator of remodeling after myocardial necrosis, such as resulting from infarction. High left ventricular ESV is associated with the mortality and incident heart failure.

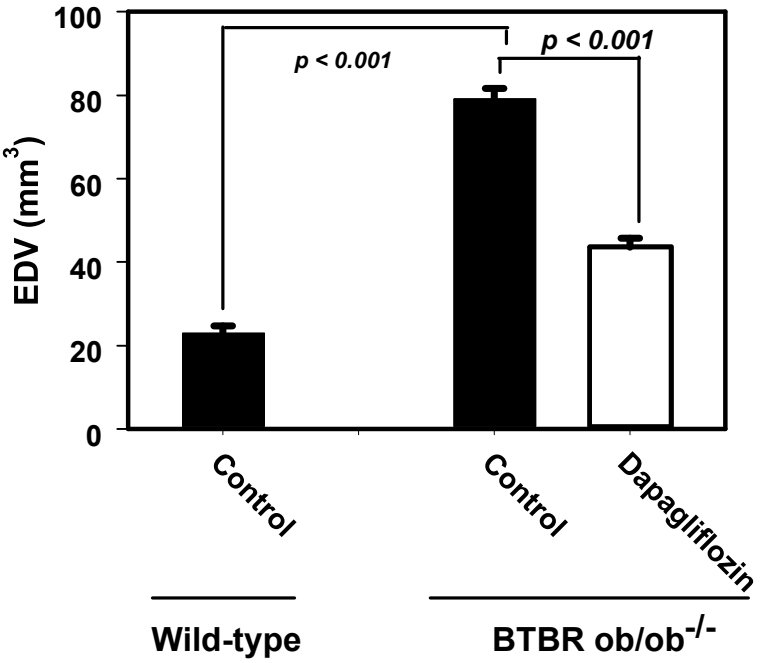
End-diastolic volume (EDV) is the volume of blood in the left or right ventricle at end load or filling in (diastole) or the amount of blood in the ventricles just before systole. Larger ventricular distension results in the increase of the length of the sarcomeres in the cardiac muscle prior to contraction (systole). The more the heart muscle fibers are stretched (enlarged EDV), the harder the heart will squeeze. Squeezing harder may cause the heart muscle to thicken over time, resulting in cardiac remodelling.

Dapagliflozin treatment lowered the left ventricular ESV in BTBR ob/ob$^{-/-}$ mice



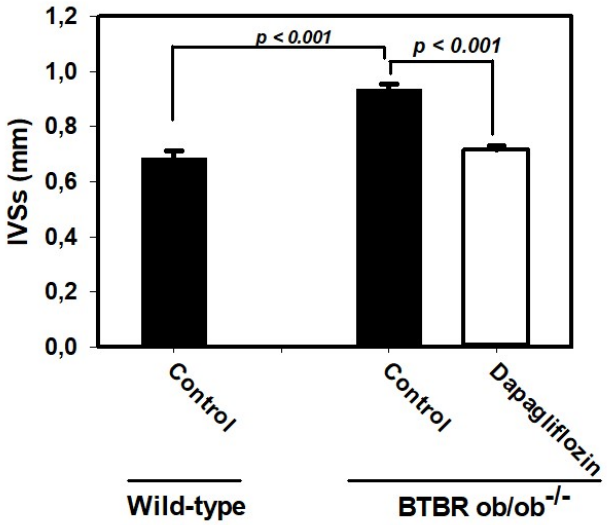
Each treatment group consists of 8 animals Each bar represents Mean ± SEM values One-way ANOVA was used for the statistical data analysis.

Dapagliflozin treatment lowered the left ventricular EDV in BTBR ob/ob$^{-/-}$ mice



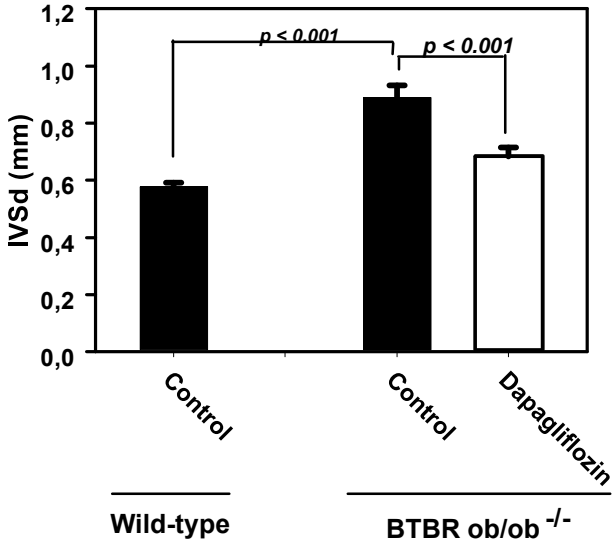
Each treatment group consists of 8 animals. Each bar represents Mean ± SEM values. One-way ANOVA was used for the statistical data analysis.

Dapagliflozin reversed interventricular septum thickening, measured by IVSs and IVSd, in BTBR ob/ob$^{-/-}$ mice



Each treatment group consists of 8 animals. Each bar represents Mean ± SEM values. One-way ANOVA was used for the statistical data analysis.

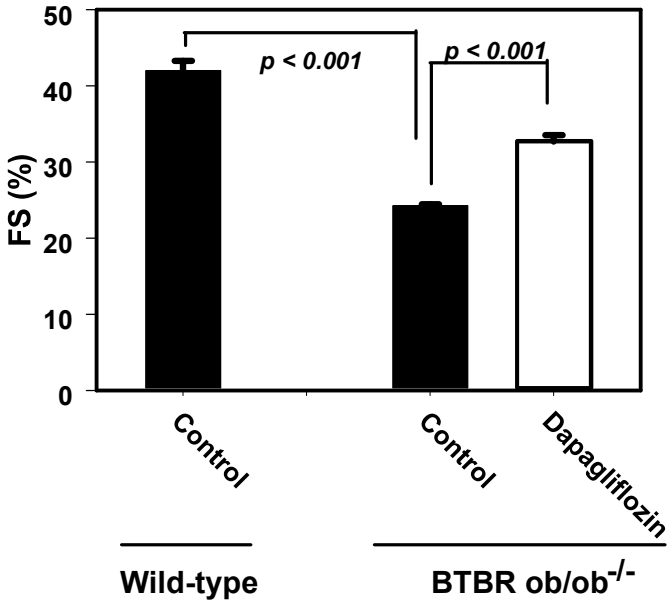
Dapagliflozin treatment lowered the IVSd in BTBR ob/ob$^{-/-}$ mice



Each treatment group consists of 8 animals. Each bar represents Mean ± SEM values. One-way ANOVA was used for the statistical data analysis.

Dapagliflozin treatment improved the FS in BTBR ob/ob$^{-/-}$ mice

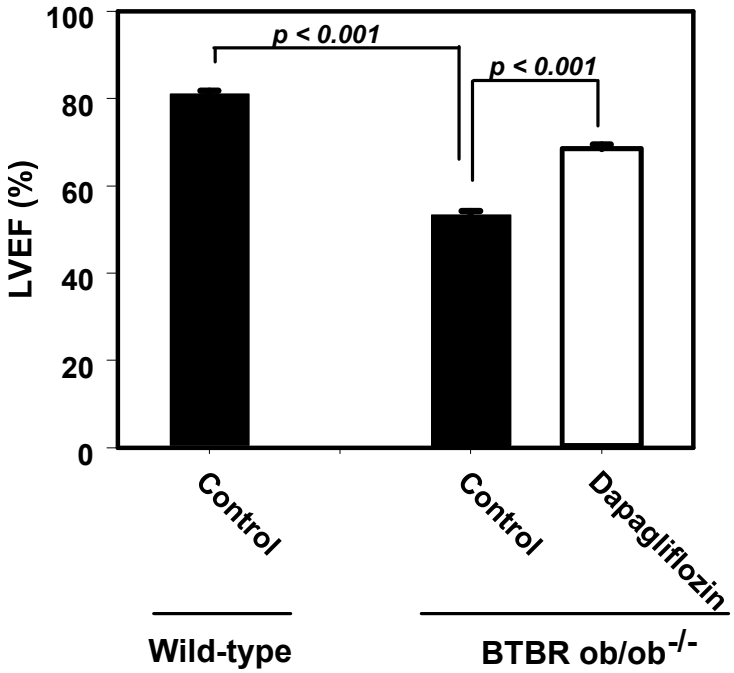
Fractional shortening (FS) estimates the degree of shortening of the left ventricular diameter between end-diastole and end-systole. FS is a measure of the heart's muscular contractility.



Each treatment group consists of 8 animals. Each bar represents Mean ± SEM values. One-way ANOVA was used for the statistical data analysis.

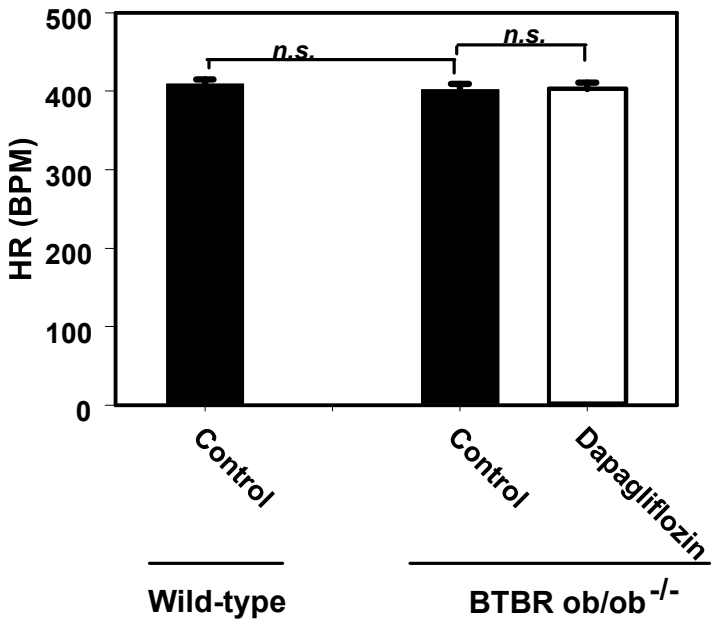
Dapagliflozin treatment improved the LVEF in BTBR ob/ob-/- mice.

Left ventricular ejection fraction (LVEF) estimates the percentage of total amount of blood in the left ventricle pumped out with each heartbeat.



Each treatment group consists of 8 animals. Each represents Mean ± SEM values. One-way ANOVA was used for statistical data analysis.

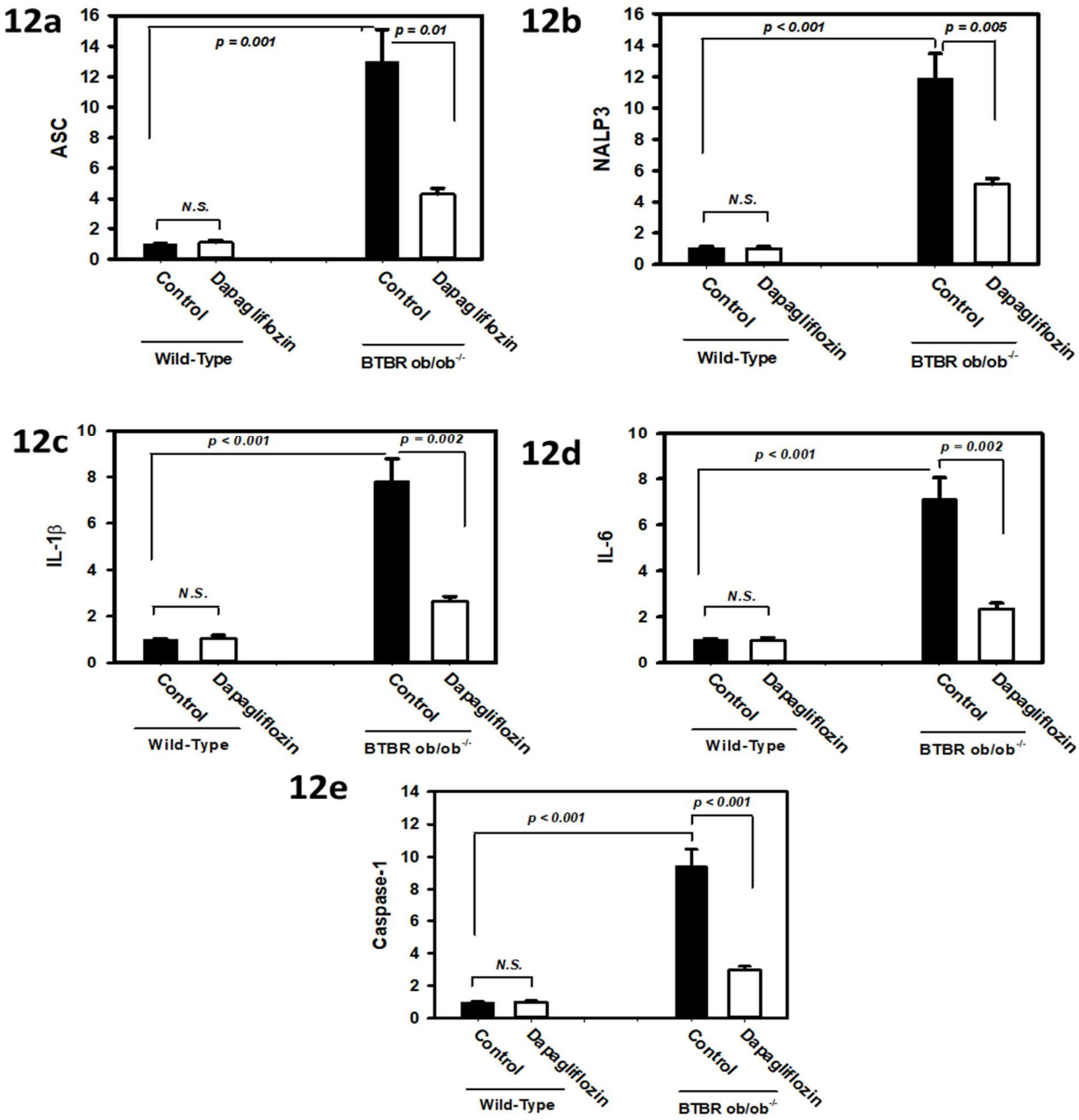
Dapagliflozin treatment did not affect the heart rate in BTBR ob/ob$^{-/-}$ mice



Each treatment group consists of 8 animals. Each bar represents Mean ± SEM values. One-way ANOVA was used for statistical data analysis.

Dapagliflozin treatment attenuates the NLRP3 inflammasome activation in BTBR ob/ob$^{-/-}$ mice

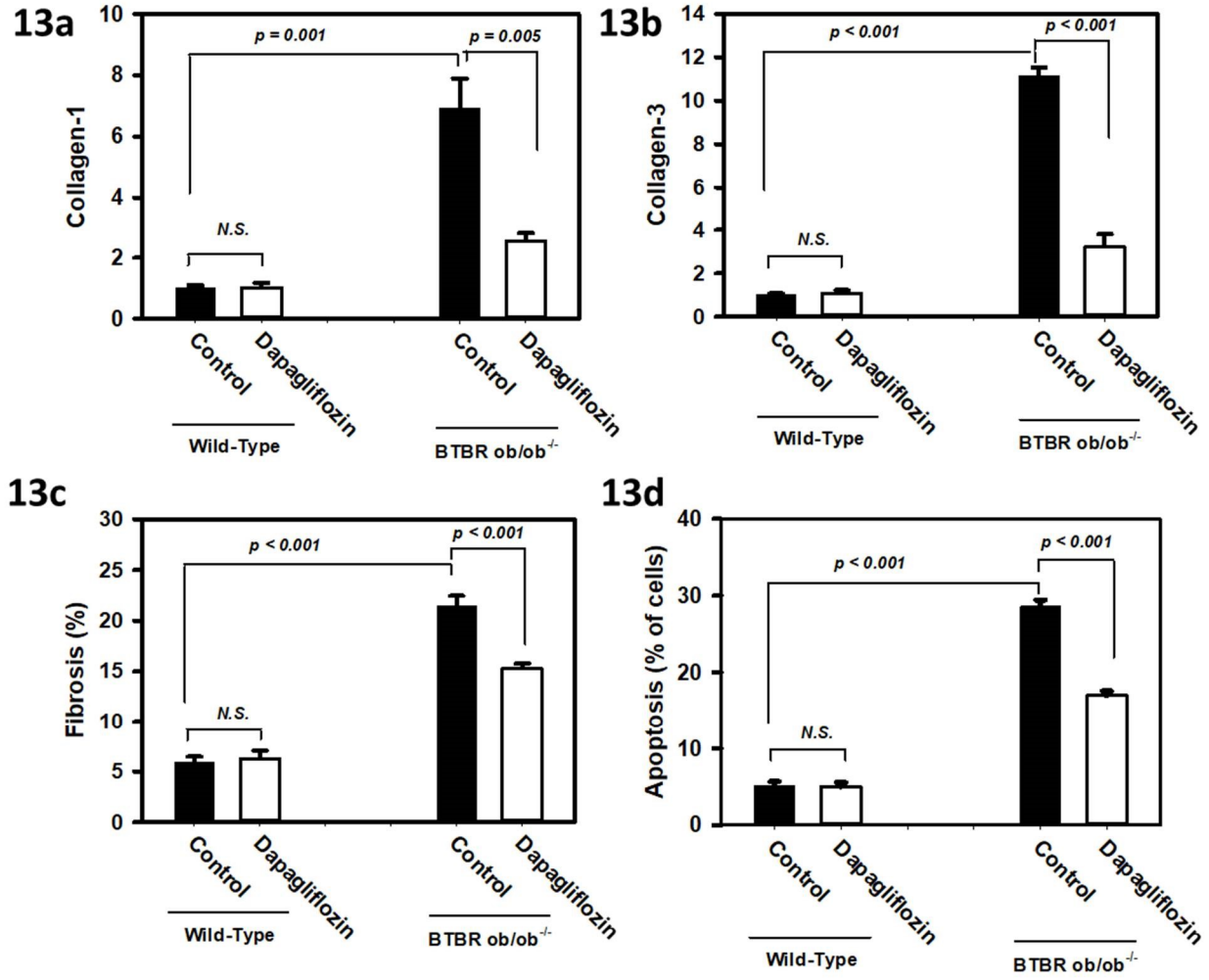
Cardioprotective effect of dapagliflozin was further examined. Heart tissues from wild-type and BTBR ob/ob$^{-/-}$ mice were harvest at the end of 8 weeks treatment with vehicle or dapagliflozin and analysed with Quantitative RT-PCR for mouse genes associated with the NLRP3 inflammasome.



mRNA levels for each inflammasome component were analyzed by RT-PCR. (a) ASC; (b) NALP3; (c) IL-1□; (d) IL-6; (e) Caspase 1. The expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the housekeeping gene for the normalization of data in quantitative RT-PCR experiments estimating the effect. The Y-axis represents the ratio

between normalized mRNA of each gene in the BTBR ob/ob$^{-/-}$ mice and that of the WT-control mice. There were 4 animals in each group. Each bar represents Mean ± SEM values. One-way ANOVA was used for the statistical data analysis.

Dapagliflozin treatment reduced cardiac fibrosis and apoptosis in BTBR ob/ob-/- mice

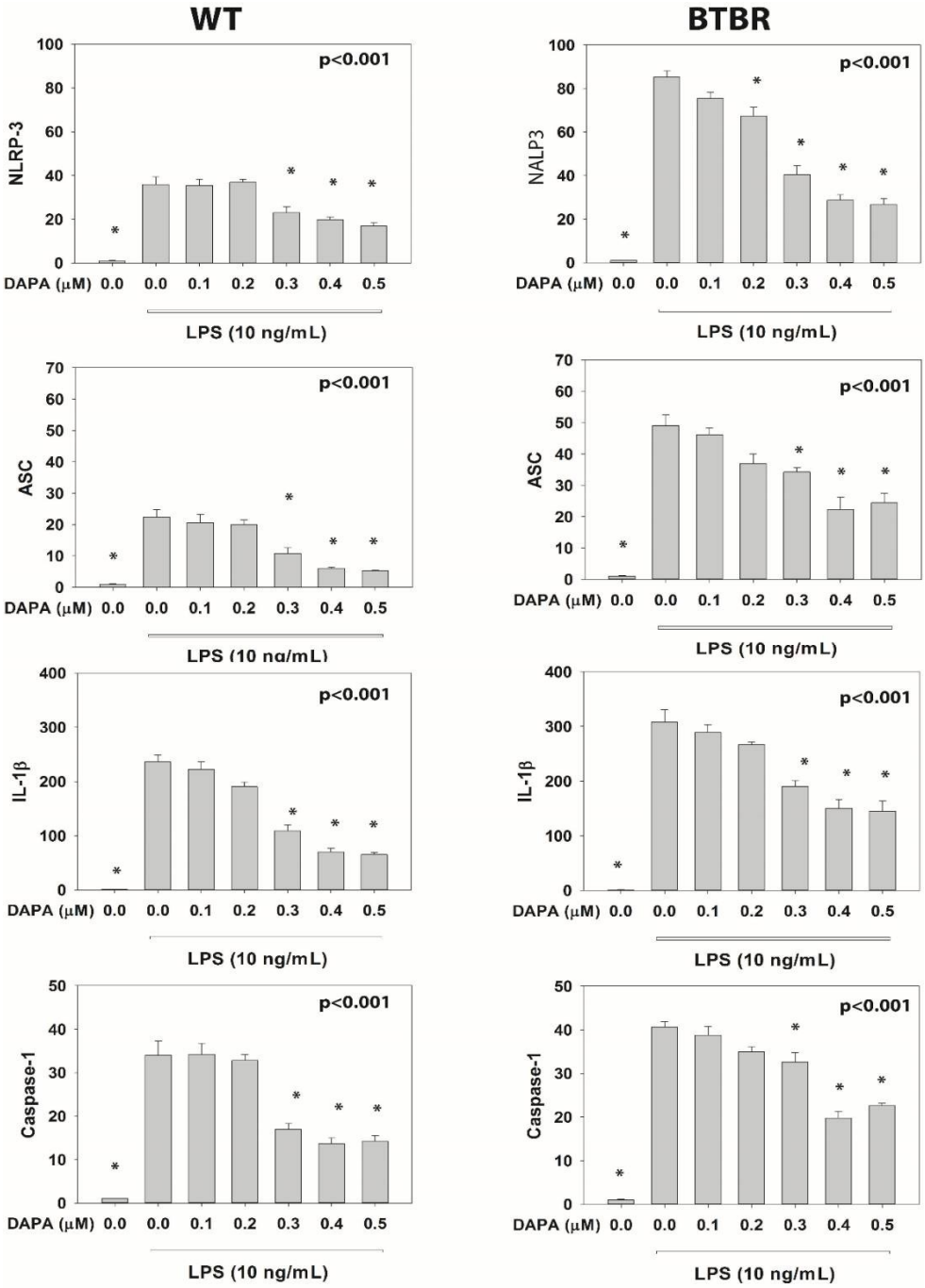


(**a**) Collagen-1 (myocardium mRNA quantitated by RT-PCR); **(b)** Collagen-3 (myocardium mRNA quantitated by RT-PCR); The expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the housekeeping gene for the normalization of data in quantitative RT-PCR experiments estimating the effect. The Y-axis represents the ratio between normalized mRNA of each gene in the BTBR ob/ob$^{-/-}$ mice and that of the WT-control mice. There were 4 animals in each group. Fibrosis; The degree of fibrosis was analysed by Masson's trichrome staining. The Y-axis represents the percentage of myocardium which are occupied by fibrosis. Each treatment group consists of 4 animals. Apoptosis (TUNEL staining); The Y-axis represents the percentage of Tunnel positive cells. Each treatment group consists of 10 animals. Each bar represents Mean ± SEM values. One-way ANOVA was used for the statistical data analysis.

2.2.3.3. Study No. Nonclinical HF 003

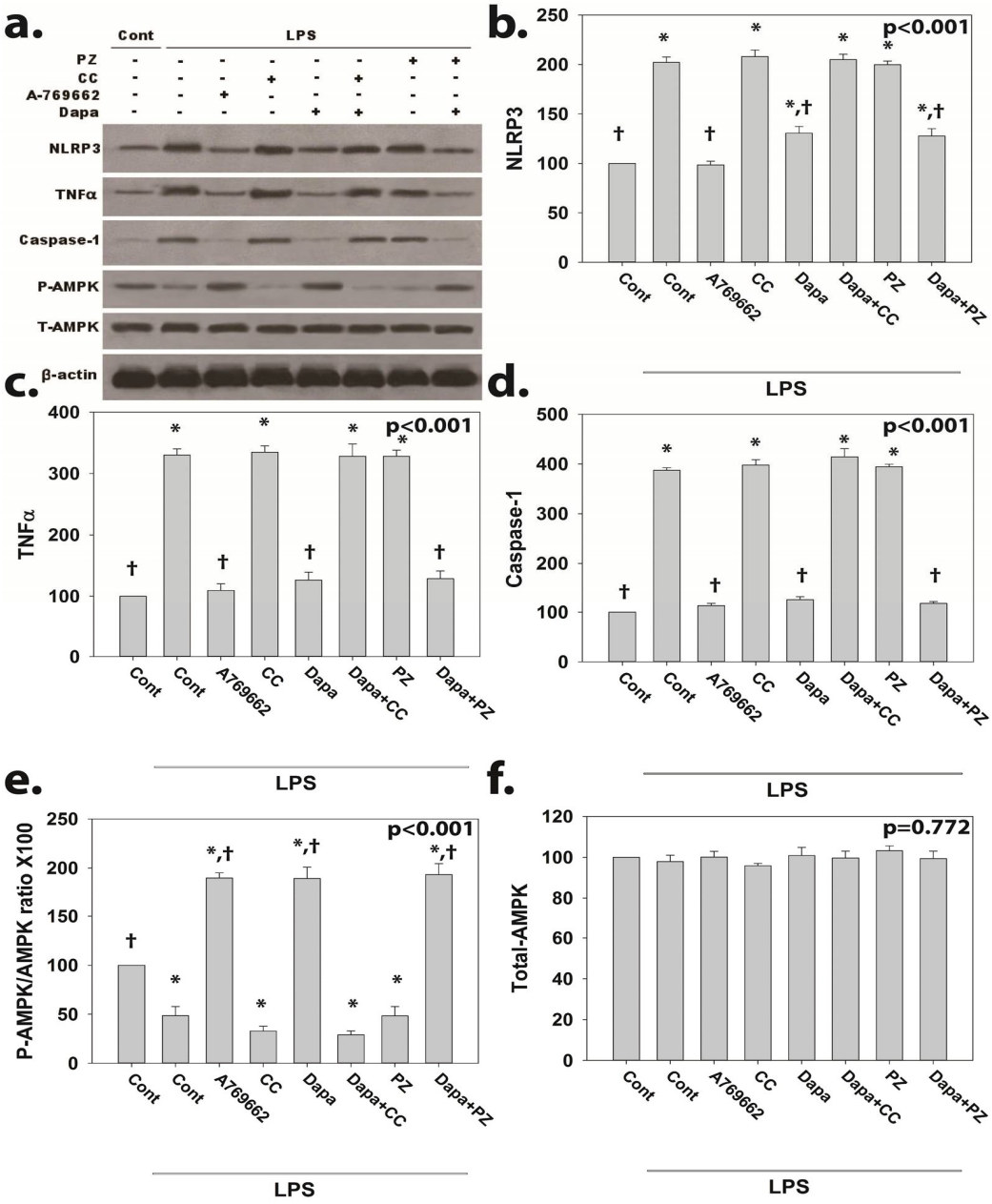
In the third study, it was investigated whether dapagliflozin directly attenuates diabetes-induced activation of the NLRP3 inflammasome in mouse cardio-fibroblasts as well as the molecular pathways involved. This is an *in vitro* study of NLRP3 inflammasome expression in cardiofibroblasts isolated from BTBR ob/ob$^{-/-}$ and WT mice.

Dapagliflozin treatment suppressed the expression of key components of NLRP3 inflammasome



Cardiofibroblasts from WT and BTBR ob/ob$^{-/-}$ mice were incubated with Dapa (from 0 to 0.5 μM) for 16h and then stimulated with 10ng/mL LPS for 3h. Cells were harvested for RT-PCR analysis. mRNA levels of NALP3, ASC, IL-1β, and caspase-1 were quantitated by RT-PCR. The expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the housekeeping gene for the normalization of data in quantitative RTPCR experiments estimating the effect. The Y-axis represents the ratio between normalized mRNA of each gene in each treatment and that in control condition (no dapagliflozin treatment or LPS stimulation).

AMPK phosphorylation and activation played key role in the dapagliflozin-induced attenuation of NLRP3 inflammasome activation



Western blot analysis (a) and digitized densitometric analysis of NLRP3 (b), TNF-α (c), caspase-1 (d), PAMPK/total-AMPK ratio (e) and total AMPK (f) in cell lysates of cardiofibroblasts. Experiments were repeated four times. * denotes p <0.037 when compared with Control without LPS treatment. † denotes p <0.004 when compared with Control with LPS treatment. A769662 – an AMPK activator, CC – Compound C, an AMPK inhibitor, LPS – lipopolysaccharide, PZ – phlorizin, an SGLT1 and SGLT2 inhibitor.

2.2.4. **Toxicology**

Since the initial marketing authorization approval, a toxicology study has been performed to date. Applicant has provided an Addendum to Non-clinical Written Summary, a toxicology report where a 6-month cancer study with regard to urinary bladder cancer is presented. The objective was to determine potential effects of dapagliflozin incidence and degree of invasiveness of urinary bladder carcinomas induced with N-Butyl-N-(4-hydroxybutyl)nitrosamine (BBN) in a rat model for initiation/promotion of tumours in the urinary bladder.

Briefly, animals were treated with BBN (100 or 400 mg/kg/dose) for 6 weeks and following a washout period of 2 weeks, divided in groups receiving either vehicle, dapagliflozin (0.5 mg/kg/day) or uracil (3% via diet as positive control) for additional 26 weeks before necropsy. While a slight increase in urothelial hyperplasia was noted in animals pre-treated with BBN (100 mg/kg/dose) followed by dapagliflozin when compared to corresponding controls, no effects on incidence or invasiveness of transitional cell carcinoma could be associated to dapagliflozin treatment in animals pre-treated with BBN.

2.2.5. **Ecotoxicity/environmental risk assessment**

The environmental risk assessment for dapagliflozin has previously been assessed and no new studies were provided. The applicant has provided an ERA for the indication chronic heart failure with reduced ejection fraction using a default Fpen value and a maximum daily dose of 10 mg.

The resulting PEC/PNEC quotients in Tier A were:

	PEC (μg/L)	PNEC (μg/L)	Trigger value	PEC/PNEC	Risk (Y/N)
	0.05	20000	0.1	2.5×10^{-6}	N
	0.05	100	1.0	5.0×10^{-4}	N
	0.0125	1000	1.0	1.3×10^{-5}	N

The resulting PEC/PNEC quotients in Tier A were:

	PEC (μg/L)	PNEC (μg/L)	Trigger value	PEC/PNEC	Risk (Y/N)
	0.19	6250	1.0	3.0×10^{-5}	N

2.2.6. **Discussion on non-clinical aspects**

In Vivo studies

Applicant has shown convincing results with regard to mechanism of action (MoA) in inhibition of SGLT2 by an increased urinary glucose excretion followed by an improvement in the glycaemic control with reduced HbA1c, fasting blood glucose and insulin levels as well as improved glucose tolerance with restored β-secretory function. In addition, an improved cardiac function was observed in a number of tests. The degree of cardiac fibrosis was reduced with dapagliflozin treatment as well as the number of apoptotic cells. However, whether these improved effects on cardiac function are dependent on stabilisation of the glycaemic control or if dapagliflozin has an independent beneficial effect, can not be evaluated from these *in vivo* studies.

In Vitro studies

Mechanistic explanation, at least in part, is due to the attenuation of the NLRP3-mediated inflammasome activity. In addition, the *in vitro* studies suggest that AMPK phosphorylation and activation play a key role in the dapagliflozin induced attenuation of NLRP3 inflammasome activation. However, the pharmacological effects seen by dapagliflozin in the *in vitro* studies were reached at rather high concentrations. The clinical importance of this mechanism is yet unknown and other mechanisms of action can therefore not be excluded. However, this would not prevent MA in the presence of convincing clinical data.

In conclusion, the non-clinical studies provided by Applicant have shown that dapagliflozin treatment in obese diabetic mouse models improves the structural defects in the cardiac fibroblasts associated with these mouse models. In addition, an increase in the function of left cardiac ventricle was shown.

Overall, the non-clinical pharmacology studies appear to support the rationale to use dapagliflozin in the intended disease indication and no further non-clinical testing is considered necessary.

2.2.7. **Conclusion on the non-clinical aspects (ERA)**

The PEC/PNEC ratio for microorganisms was <0.1. The PEC/PNEC ratios for groundwater and surface water were <1. These risk quotients indicate that dapagliflozin is unlikely to present a risk to microorganisms or the aquatic and groundwater environments.

The effect of dapagliflozin on the sediment dwelling organism Chironomus riparius is investigated in Tier B. The PEC/PNEC ratio for sediment was <1, indicating that dapagliflozin is unlikely to present a risk to sediment dwelling organisms.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of dapagliflozin.

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

2.3. Clinical aspects

GCP

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

2.3.1. Pharmacokinetics

NA

2.3.2. Pharmacodynamics

Mechanism of action

Dapagliflozin is a reversible inhibitor of SGLT2. Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule along with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure (Thomson et al 2012). Secondary effects observed following SGLT2 inhibition with dapagliflozin include a reduction in blood pressure (Sjostrom et al 2015), reduction in body weight (Bolinder et al 2014), and an increase in haematocrit (Lambers Heerspink et al 2013, List et al 2009). In addition to the osmotic diuretic and related haemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid have been discussed (Esterline et al 2018, Ferrannini et al 2016, Hallow et al 2018, Lytvyn et al 2017).

Primary and secondary pharmacology

No specific discussion is submitted, but this is acceptable. By its mechanism of action, dapagliflozin lowers blood glucose and is approved for treatment of patients with diabetes mellitus. The osmotic diuresis is known to increase the risk of hypotension. There is also an increased risk of genital infections and diabetic ketoacidosis in patients with diabetes. See further the safety section of this report.

2.3.1. PK/PD modelling

NA

2.3.2. Discussion /Conclusions on clinical pharmacology

No new data has been submitted.

2.4. Clinical efficacy

2.4.1. **Dose response study(ies)**

Justification of the doses selected in the pivotal trial

No results of dose response studies for the administration in patients with heart failure were submitted. The marketed 10 mg dose of dapagliflozin has demonstrated a favourable benefit/risk balance for the treatment of T2DM in the clinical development programme. 10 mg once daily is the recommended dose in patients with T2DM. A dose of 10 mg once daily was also investigated in the cardiovascular outcome study (DECLARE) showing non-inferiority vs. placebo for the composite of cardiovascular death, myocardial infarction or ischaemic stroke. In this study all patients had type 2 diabetes mellitus and additional cardiovascular risk factors. At baseline, 10.0% of patients in the study had a history of heart failure. dapagliflozin 10 mg demonstrated superiority versus placebo in preventing the composite of hospitalisation for heart failure or cardiovascular death. The difference in treatment effect was driven by hospitalisation for heart failure, with no difference in cardiovascular death. The treatment benefit of dapagliflozin over placebo was observed both in patients with and without established cardiovascular disease, with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR) and region. Based on these data the choice of the same 10 mg once daily dose appears to be reasonable.

Pharmacokinetic and pharmacodynamics data previously showed that 10 mg dapagliflozin near maximally inhibits SGLT2 in the kidney. Whether this is relevant for the heart failure indication is unclear. As discussed below efficacy in the treatment of heart failure is likely not due to its glucose lowering effect.

Every attempt was made to maintain patients on a 10 mg dose of dapagliflozin or matching placebo in the pivotal trial. In specific cases that could not be resolved by reducing the dose of, or stopping concomitant, non-essential medications, reduction of dapagliflozin to 5 mg or matching placebo was allowed per protocol. All patients received the current available standard of care treatment for HFrEF. Therefore, placebo was an appropriate comparator.

In the pivotal study (DAPA HF) few patients received dapagliflozin 5 mg or matching placebo at any time during the study; 1.9% and 1.6% in the dapagliflozin and placebo group, respectively and 1.8% and 1.2%, respectively, had AEs leading to a dose reduction to the 5 mg dose, of which only 4 dose reductions were caused by an SAE. The main AE leading to dose reduction was hypotension. The small number of patients exposed to dapagliflozin 5 mg prevents conclusions about the efficacy of this dose in patients with HFrEF.

2.4.2. **Main study**

Title of Study

Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure with Reduced Ejection Fraction

Short title: Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure **(DAPA- HF)**

Methods

Study Design

The study's primary objective was to determine superiority of dapagliflozin versus placebo in reducing the first occurrence of the primary composite endpoint of CV death, hospitalisation for HF, or an urgent HF visit (hospitalisation for HF and urgent HF visit are hereafter jointly referred to as HF event).

DAPA-HF was a Phase III, international, multi-centre, parallel group, event driven, randomised, double-blind, placebo-controlled study in patients with chronic heart failure with reduced ejection fraction (HFrEF) evaluating the effect of dapagliflozin compared to placebo, given once daily in addition to background regional standard of care therapy for reduction of cardiovascular death or heart failure (HF) events (hospitalisation for HF or an urgent HF visit).

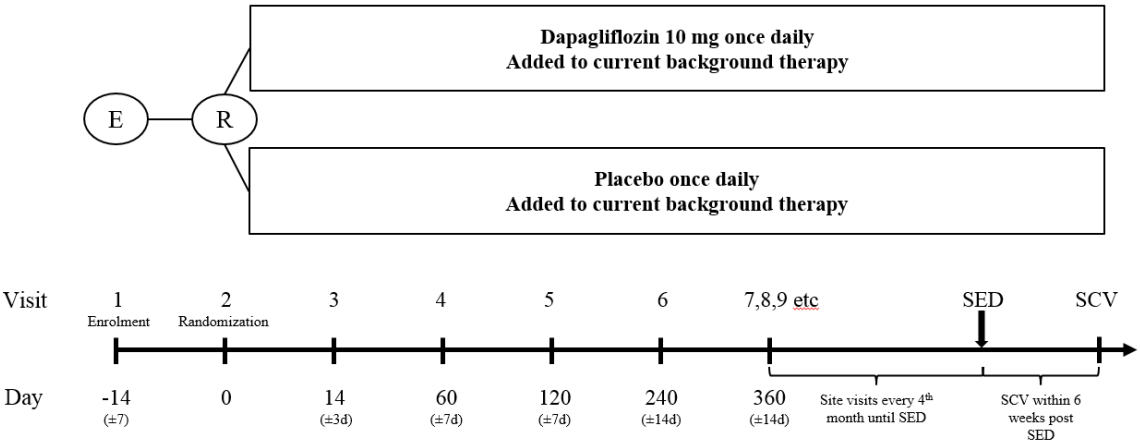
First patient enrolled: 08 February 2017

Last patient last visit: 17 July 2019

Database locked: 11 August 2019

The analyses presented are based on a database lock date of 11 August 2019

Figure 1. Study Design



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

Table 1 provides a breakdown of the number of study sites per country for each geographic region (410 sites in total, 409 after transfer of patients from one closed center to another center).

Table 1 Number of study sites that enrolled patients per country in each geographic region

Asia	Europe		North America	South America
China: 28 sites	Bulgaria: 19 sites	Poland: 14 sites	Canada: 26 sites	Argentina: 28 sites
India: 16 sites	Czech Republic: 13 sites	Russia: 20 sites	United States: 73 sites[a]	Brazil: 18 sites
Japan: 65 sites	Denmark: 6 sites	Slovakia: 13 sites	**Total: 99**	**Total: 46**
Taiwan: 13 sites	Germany: 14 sites	Sweden: 5 sites	-	-
Vietnam: 8 sites	Hungary: 10 sites	United Kingdom: 10 sites	-	-
Total: 130	Netherlands: 10 sites	**Total: 134**	-	-

[a] Subjects were randomised at 410 sites; however, 1 site in the United States closed and the patients were transferred to another, existing, site.

Study participants

Key inclusion criteria:

- Adults with a documented diagnosis of Heart Failure with reduced Ejection Fraction (HFrEF) in NYHA functional class II-IV with and without T2DMwhich had been present for at least 2 months
- Treated with standard of care according to locally recognised HFrEF treatment guidelines. Therapy should have been individually optimised and stable for ≥4 weeks before visit 1 andinclude (unless contraindicated or not tolerated):

(a) an angiotensin converting enzyme (ACE) inhibitor, or angiotensin II receptor blockers (ARB) or sacubitril/valsartan
and
(b) a beta-blocker
and
(c) if considered appropriate by the patient's treating physician; a mineralocorticoid receptor antagonist (MRA)

In addition, each patient should, be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual.

- Diagnosis supported by left ventricular ejection fraction (LVEF) ≤40% and N-terminal pro b-type natriuretic peptide (NT-proBNP) ≥600 pg/mL if not hospitalised for HF within the previous 12 months or ≥400 pg/ml if hospitalised for HF within the previous 12 months. Patients with atrial fibrillation or atrial flutter must have a level ≥900 pg/ml, irrespective of history of HF hospitalisation.
- eGFR ≥30 mL/min/1.73 m^2.

Key exclusion criteria:

- Symptomatic hypotension or systolic BP <95 mmHg
- Recent worsening of HF, significant CV events, or CV procedure (including planned procedure)
- Any condition outside the CV and renal disease area, such as but not limited to malignancy, with a life expectancy of less than 2 years based on investigator´s clinical judgement
- Severe (eGFR <30 mL/min/1.73 m^2), unstable or rapidly progressing renal disease
- Type 1 diabetes mellitus

Treatments

Dapagliflozin 5m and 10 mg film-coated tablets and its matching placebo were packaged in bottles. Each bottle contained 155 tablets.

One tablet daily at approximately the same time was administered (oral). If a dose was missed, the next regularly scheduled dose was to be taken and was not to be doubled by way of compensation. Patients were randomised to the preferred 10 mg dose of dapagliflozin or matching placebo. Every attempt was made to maintain patients on a 10-mg dose , but in specific cases, where a relevant event of volume depletion, hypotension or unexpected worsening of kidney function was seen, and when these could not be resolved by reducing the dose of, or stopping concomitant non-essential medications, as assessed on an individual basis by the investigator, reduction of dapagliflozin to 5mg or matching placebo was allowed.

Patients in the study were treated with background standard of care for HFrEF according to treatment guidelines. Treatment included angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB) or sacubitril/valsartan and beta-blockers, as well as a mineralocorticoid receptor

antagonist (MRA), where appropriate, unless contraindicated or not tolerated. Most patients required a diuretic, generally a loop diuretic, to control symptoms.

Concomitant treatment with any SGLT2 inhibitor, together with study drug, was prohibited during the study. Also in cases when study drug was interrupted or discontinued, open-label SGLT2 inhibitors were only to be administered when all other possibilities to treat the patient had been considered, as they could interfere with the interpretation of study results.

Objectives and Outcome measures

Table 2 Primary and secondary objectives

Primary objective:	Outcome measure:
To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the incidence of CV death or a HF event (hospitalisation for HF or equivalent HF event, ie, an urgent HF visit)**.**	Time to the first occurrence of any of the components of this composite: 1 CV death 2 Hospitalisation for HF 3 An urgent HF visit

Secondary objective:	Outcome measure:
To compare the effect of dapagliflozin versus placebo on CV death or hospitalisation for HF.	Time to the first occurrence of either of the components of this composite: 1 CV death 2 Hospitalisation for HF
To compare the effect of dapagliflozin versus placebo on total number of recurrent HF hospitalisations and CV death.	Total number of (first and recurrent) HF hospitalisations and CV death.
To compare the effect of treatment with dapagliflozin versus placebo on the KCCQ total symptom score for HF symptoms and physical limitations.	Change from baseline measured at 8 months in the total symptom score of the KCCQ, a specific HF patient reported outcome questionnaire.
To determine if dapagliflozin compared with placebo reduces the incidence of a composite endpoint of worsening renal function.	Time to the first occurrence of any of the components of this composite: 1 ≥50% sustained* decline in eGFR 2 Reaching End Stage Renal Disease (ESRD) ☐ Sustained* eGFR <15 ml/min/1.73m^2 or, ☐ Chronic* dialysis treatment or, ☐ Receiving a renal transplant 3 Renal death **As defined in the Clinical Event Adjudication (CEA) charter*

To determine whether dapagliflozin, compared with placebo, reduces the incidence of all-cause mortality.	Time to death from any cause.

The KCCQ (a self-administered 23-item disease-specific instrument for patients with heart failure) was first developed in 1996 and assessments were performed in the DAPA-HF study at randomisation, month 4 (day120), month 8 (day 240), month 12 (Day 360) and every 12 months thereafter at Premature Treatment Discontinuation Visit (PTDV) and at Study Closure Visit (SCV).

The KCCQ TSS subscale quantifies the frequency of four cardinal HF-symptoms (fatigue, peripheral oedema, dyspnoea, and orthopnoea) and how bothersome three of the cardinal HF symptoms (fatigue, peripheral oedema, and dyspnoea) are to patients.

A 5-point threshold was selected as the primary threshold for meaningful within-patient change on the KCCQ TSS at month 8. This threshold was recommended by the KCCQ author based on unpublished analysis of the KCCQ development and validation studies. The 5-point threshold consistent with the threshold for the KCCQ Clinical Summary Score (CSS), which includes the TSS, has been established in the published literature. The Sponsor's independent derivation of thresholds for within-patient meaningful change using anchor-based approaches in two NIH datasets (HF-ACTION and TOPCAT) and in blinded DAPA-HF data, informed additional thresholds used for supportive responder analyses. Responder analyses were conducted on final DAPA-HF data using a 5-point improvement (vs. no improvement or death) and 5-point deterioration or death (vs. no deterioration) from baseline at 8 months in TSS for the main responder analysis. Sensitivity analyses were conducted with thresholds of a 10-point deterioration to account for moderate or large deterioration, a 10-point improvement to account for moderate or large improvement and a 15-point improvement to account for large improvement.

The KCCQ is a well-defined PRO instrument for measuring the experience of HF patients. It has been validated in patients with HF since its initial development in the mid-1990s. The MAH has submitted justifications for the clinical relevance of a 5 point improvement as being clinically relevant.

Table 3 **Overview of the KCCQ Instrument**

KCCQ Domain	Question	#Items	Brief description
Physical limitations	q1a-q1f	6	Measures impact of symptoms on dressing, showering/bathing, walking, housework, climbing stairs, and jogging
Symptoms	q2 – q9	8	Measures three symptoms: dyspnoea, fatigue and peripheral oedema. Patients are asked about the change in symptoms over time (symptom stability); how frequently symptoms are experienced (symptom frequency); and how bothersome symptoms are (symptom burden)
Self-efficacy	q10 - q11	2	Measures degree to which patients believe that they know what to do to keep symptoms from getting worse and whom to call if the disease gets worse
Quality of life	q12 – q14	3	Measures patients' assessment of their quality of life, given the current status of their heart failure, enjoyment of life and number of times patients feel discouraged
Social limitation	q15a-q15d	4	Measures the extent to which heart failure symptoms impair patients' abilities to interact in a number of gender-neutral social activities (i.e. hobbies, household, visiting family or friends, intimate relationships)

Sample size

The primary objective of the study was to determine the superiority of dapagliflozin versus placebo in reducing the incidence of the primary composite endpoint. Assuming a true hazard ratio (HR) of 0.80 between dapagliflozin and placebo, using a one-sided alpha of 2.5%, 844 primary endpoint events would provide a statistical power of 90% for the test of the primary composite endpoint. This was based on an overall 1:1 allocation between dapagliflozin and placebo.

With an annual event rate of 11% in the placebo group, 4500 patients were estimated to provide the required number of primary events, based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 24 months.

4744 patients were actually randomised in this trial and the primary analysis was performed on 888 primary endpoint events. The event rate in the placebo group was slightly higher than expected in the sample size calculation, 15.6 per 100 patient years. The assumptions to support the sample size are considered as adequate and clinically relevant.

Randomisation

Randomisation of patients was performed using an IxRS to balanced blocks to ensure an approximate balance between treatment groups (1:1). Patients were stratified by T2DM status at randomisation to ensure balance between treatment groups T2D at the time of randomization was based on established diagnosis of T2D or HbA1c more or equal to 6.5% (48 mmol/mol) shown at central laboratory test at

enrolment (visit 1). Randomisation was also monitored for geographic region, LVEF value, NYHA class and AF status, the results of which could have led to capping in the IxRS to avoid over- or under-representation in patient sub-groups.

Blinding (masking)

The study was conducted as a double blind trial. An SAP outlining all planned analyses was prepared before un-blinding of the data. The DMC had access to the individual treatment codes and could merge these with the collected study data while the study was ongoing. A DMC charter was prepared detailing the precise roles, responsibilities and procedures that ensured maintenance of the blinding and integrity of the study for the review of accumulating data and interactions with the Executive Committee.

Statistical methods

An SAP outlining all planned analyses was prepared before un-blinding of the data. All analyses were performed with Statistical Analysis System® (SAS®), version 9.4.

No multiplicity adjustment was made to confidence intervals as they were interpreted descriptively and used as a measure of precision. All p-values were unadjusted. P-values for variables not included in the confirmatory testing sequence or following a non-significant test in the sequence were regarded as nominal.

The event-based efficacy analyses included events which occurred on or prior to the Primary analysis censoring date (PACD). Only CV death, HF hospitalisations and urgent HF visits, confirmed by the CEA, were used in the analysis of the primary and secondary endpoints and their components. Deaths adjudicated as 'cause undetermined' were considered CV deaths in these analyses.

Stratification of analyses for T2DM status was performed using the stratification values as entered in the IxRS to determine the randomisation assignment.

Analysis sets

All patients who were randomised to study treatment were included in the FAS irrespective of their protocol adherence and continued participation in the study. Patients were analysed according to their randomised study drug assignment, irrespective of the treatment received.

Interim analysis

One interim analysis was planned to be performed when approximately 75% of the primary events had been adjudicated, using the Haybittle-Peto rule. The significance level for the final analysis was determined by the Haybittle-Peto function based on the actual number and timing of interim analyses. The Sponsor and Investigators remained blinded to the results.

The interim analysis included 74.8% (664 events) of the final number of 888 events. Superiority of dapagliflozin to placebo was tested at a one-sided alpha level of 0.001. If superiority was achieved for the primary endpoint, then superiority of dapagliflozin to placebo on CV death was to be tested at a one-sided level of 0.001. Following the interim analysis, the recommendation for the study was for it to continue as planned.

Type I error control

To control the overall type I error rate at 0.025 one-sided, the significance level was adjusted for one interim analysis of efficacy. The final analysis was performed at the 0.02496 one-sided significance level. For clarity 2-sided p-values are presented and the threshold for statistical significance in the confirmatory testing was 0.04992 (corresponding to the one-sided 0.02496 level). The primary and secondary endpoints included in confirmatory statistical testing used a hierarchical test sequence at the 0.04992 significance level in the following order.

Primary:

- The composite of CV death, hospitalisation for HF, or urgent HF visit

Secondary:

- The composite of CV death and hospitalisation for HF
- Total number for (first and recurrent) hospitalisations for HF and CV death
- Change from baseline at 8 months in the KCCQ-TSS
- The composite of ≥50% sustained decline in eGFR, end stage renal disease and renal death
- Time to death from any cause.

Primary analysis

In the analysis of the primary composite endpoint, treatments (dapagliflozin versus placebo) were compared using a Cox proportional hazards model with a factor for treatment group, stratified by T2DM status at randomisation, and adjusting for history of hospitalisation for heart failure. The analysis used withdrawal of consent (WoC), non-CV death, date of last clinical event assessment and PACD for censoring of patients without any primary event. The Efron method for ties and p-value based on the score statistic was used. Event rates (number of patients with event per 100 patient-years), p-value, HR, and 95% confidence interval were reported.

The contribution of each component of the primary composite endpoint to the overall treatment effect was examined. In the analysis of the components, all first event of the given type were included irrespective of any preceding non-fatal composite event of a different type. Consequently, the sum of the number of patients with events in the component analysis was larger than the number of patients with composite events. Methods similar to those described for the primary analysis were used to separately analyse the time from randomisation to the first occurrence of each component of the primary composite endpoint as well as for secondary time to event endpoints.

Kaplan-Meier estimates of the cumulative proportion of patients with event were calculated and plotted for the composite endpoint and for the individual components.

Sensitivity analyses

Undetermined cause of death: A sensitivity analysis of the primary analysis was performed, where deaths adjudicated as 'undetermined' were not included as endpoint events but were treated as censoring events.

Missing data and informative censoring: The time-to-event analysis using the Cox regression depended on the assumption of non-informative or ignorable censoring, corresponding to the missing-at-

random assumption. The missing data in this context were patients who were prematurely censored due to withdrawal of consent, were lost to follow-up, or had otherwise incomplete follow-up of endpoints.

A tipping point analysis was pre-specified to assess the robustness of the statistical significance of the primary analysis with respect to prematurely censored subjects. Due to the size 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". Patients in the dapagliflozin group, censored before PACD, including those censored due to non-CV death, were considered having experienced the composite endpoint, using their censoring time as the time of the imputed event. Patients in the placebo group, censored before PACD, were considered censored and event free.

Analysis of recurrent HF events and CV death

The composite outcome of recurrent HF hospitalisations or CV death was analysed by the semi-parametric proportional rates model (Lin et al 2000) to test the treatment effect and to quantify the treatment difference in terms of the rate ratio with 95% confidence interval and p-value.

In addition, the 2 components in the composite endpoint (total HF hospitalisations and CV death) were analysed separately to quantify the respective treatment effects and check the consistency between the composite and the components. To account for the correlation between the 2 components, the joint modelling (frailty model) approach (Rogers et al 2016) was used for the component analyses. Non-parametric estimates of HF hospitalisation rates over time allowing for death as terminal event were also provided (Ghosh and Lin 2000).

Analysis of change from baseline at 8 months in the KCCQ total symptom score

Change from baseline at 8 months in KCCQ TSS at baseline was transformed to a composite endpoint with fractional ranks, using the mean method for ties and stratified by T2DM status at randomisation. Deaths prior to the 8-month assessment were assigned the worst ranks within each stratum. Of the patients who died the relative ranking was based on their last value of change from baseline in TSS while alive before deriving fractional ranks. This composite endpoint was analysed using the rank ANCOVA method (Stokes et al 2012), adjusted for ranked baseline TSS value, to test the null hypothesis of no differences in the distributions of ranked outcomes between the 2 treatment groups. The Cochran Mantel Haenszel (CMH) test, stratified for the T2DM status at randomisation, was used to compare treatment groups. The p value from the CMH test of treatment effect at 8 months was used for the confirmatory statistical testing of this secondary endpoint.

The win ratio and the corresponding 95% confidence interval (Wang and Pocock 2016) adjusted for baseline KCCQ-TSS and stratified by T2DM were reported as a summary statistic using the same ranking approach as in the KCCQ TSS hypothesis test. The win ratio represents the odds of having a more favourable outcome versus a less favourable outcome when assigned to the dapagliflozin 10 mg treatment group as opposed to placebo. This was accomplished by creating all possible pairs of patients across arms and labelling patients ondapagliflozin 10 mg in each pair as "winner", "loser" or "tied", based on their ranks. The crude win ratio is defined as the ratio of the number of "winner" pairs divided by the number of "loser" pairs and an estimated win ratio greater than 1 favours dapagliflozin.

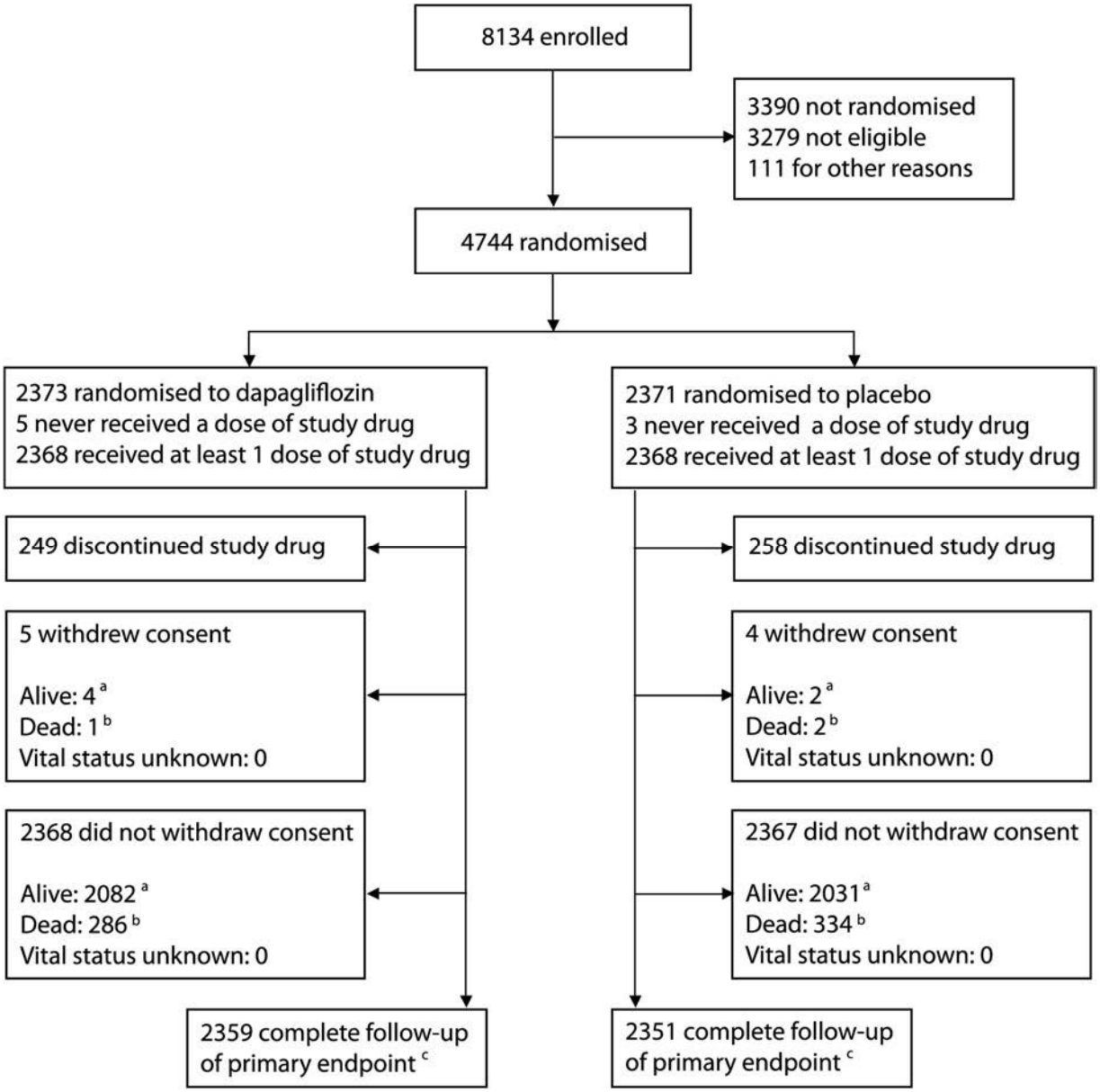
Number and percentage of patients in each treatment group were summarized across the following categories: 5-point improvement from baseline to 8 months in KCCQ-TSS and 5-point deterioration from baseline to 8 months in KCCQ-TSS. If a patient had a baseline value of TSS $\geq$ 95 points, i.e. near the "ceiling", they were defined as having a 5-point improvement only if they had TSS $\geq$ 95 points at 8 months. Similarly, for deterioration. The proportion of TSS responder categories were compared between

treatment groups using a logistic regression model including treatment group, stratification variable (T2D at randomisation) and baseline TSS value. Additional responder analyses were performed in the same way as for 5 points improvement and deterioration described above, using the thresholds of clinically meaningful within-patient change from baseline TSS derived from anchor-based analyses (10 point improvement, 10 point deterioration, 15 point improvement.

Patients with missing data in KCCQ-TSS for other reasons than death will have their missing TSS imputed using the multiple imputation (MI) methodology under the Missing at Random (MAR) assumption.

Results

Figure 2 Participant flow



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

[c] Dead at any time during study

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

Table 4 Numbers analysed

Numbers analysed	**Number of subjects**	
	Dapa 10mg	**Placebo**
Subjects randomised	2373	2371
Subjects included in full analysis set	2373	2371
Subjects included in safety analysis set[a,b]	2368	2368
Subjects excluded from safety analysis set[a] (Patients who did not receive at least one dose of IP)	5	3

Table 5 Reasons for discontinuation of treatment

Table 14.1.1 Subject Disposition (All subjects)

	Number (%) of subjects		
	Dapa 10mg	**Placebo**	**Total**
Subjects randomised	2373	2371	4744
Stratified as T2DM	1034 (43.6)	1032 (43.5)	2066 (43.5)
Stratified as not T2DM	1339 (56.4)	1339 (56.5)	2678 (56.5)
Subjects who did not receive IP	5 (0.2)	3 (0.1)	8 (0.2)
Subjects who discontinued IP	249 (10.5)	258 (10.9)	507 (10.7)
Subject decision	115 (4.8)	123 (5.2)	238 (5.0)
Adverse event	109 (4.6)	112 (4.7)	221 (4.7)
Severe non-compliance to protocol	6 (0.3)	3 (0.1)	9 (0.2)
Development of study specific discontinuation criteria	2 (0.1)	0	2 (0.0)
Confirmed DKA	2 (0.1)	0	2 (0.0)
Positive Pregnancy Test	0	0	0
Other	17 (0.7)	20 (0.8)	37 (0.8)
Subjects who withdrew consent	5 (0.2)	4 (0.2)	9 (0.2)
Dead [d]	1 (0.0)	2 (0.1)	3 (0.1)
Alive [e]	4 (0.2)	2 (0.1)	6 (0.1)
Vital status unknown	0	0	0

[a] Informed consent received.
[b] The denominator for reasons not randomized is the number of enrolled subjects not randomized.
[c] Failed inclusion/exclusion criteria are presented by descending frequency.
[d] Dead at any time during study.
[e] Confirmed alive on or after PACD.
[f] Subjects with a primary event or censored due to death or at PACD in the analysis of the primary endpoint.
ALT Alanine transaminase. AST Aspartate transaminase. BP Blood Pressure. CABG Coronary artery bypass grafting. CKD-EPI Chronic kidney disease epidemiology collaboration equation. CRT Cardiac resynchronization therapy. Dapa Dapagliflozin. DKA Diabetic ketoacidosis. eGFR Estimated glomerular filtration rate. HF Heart failure. HFrEF Heart failure with reduced left ventricular ejection fraction. LVEF Left ventricular ejection fraction. MI Myocardial infarction. NT-proBNP N-terminal pro b-type natriuretic peptide. NYHA New York Heart Association. IP Investigational product. PACD Primary analysis censoring date. PCI Percutaneous coronary intervention. T2DM Type 2 diabetes mellitus. TIA Transient ischemic attack. ULN Upper limit of normal.

Approximately 11 % discontinued treatment, with similar reasons in both groups.

Conduct of the study

One amendment to the study protocol was made after start of recruitment; it had no negative impact on the robustness of the study.

Protocol deviations

The number of subjects with important protocol deviations in each treatment group are summarised in Table 9. Important protocol deviations were balanced between treatment groups with respect to frequency and type.

While only 1 patient with LVEF >40% was randomised, a total of 92 (1.9%) patients were randomised despite failing the inclusion criterion of LVEF ≤40% within the last 12 months prior to enrolment, 54 (2.3%) in the dapagliflozin treatment group and 38 (1.6%) in the placebo group. Most of these patients had an intervention (eg surgical, device, or pharmacological), with the potential to improve LVEF, within that 12-month period without the mandated repeat LVEF assessment ≥3 months post intervention.

14 (0.6%) and 18 (0.8%) patients (Dapa10 mg/placebo) were randomized despite of failing the NT-proBNP inclusion criterion. Symptomatic hypotension or systolic BP <95 mmHg at 2 out of 3 measurements at visit 1 or visit 2 as an exclusion criterion was present in 13 (0.5%) and 15 (0.6%) of patients respectively. Other reasons for not meeting inclusion/exclusion criteria were less frequent. A total of 26 (0.5%) patients took open-label SGLT2 inhibitors (other than the study drug) during the study (see Table 14.1.5.5); 13 (0.3%) were considered prohibited medication (ie, concomitant treatment in combination with study drug.

Table 6 Important protocol deviations (FAS)

	Number (%) of subjects		
	Dapa 10mg (N=2373)	**Placebo (N=2371)**	**Total (N=4744)**
Number of patients with at least 1 important deviation	120 (5.1)	107 (4.5)	227 (4.8)
Randomised but did not fulfil all inclusion and exclusion criteria	112 (4.7)	104 (4.4)	216 (4.6)
Received IP not allocated by IxRS	0	0	0
Patient received prohibited medications during IP period i.e. SGLT2 Inhibitor[a]	8 (0.3)	5 (0.2)	13 (0.3)

Source: Table 14.1.2

[e] SGLT2 inhibitors taken concomitantly with study drug.

Note that the same subject may have had more than 1 important protocol deviation.

Dapa Dapagliflozin. FAS Full analysis set. IP investigational product.

Treatment Compliance

The calculation of treatment compliance included only patients with a complete record of the number of tablets returned. Treatment compliance was high and similar between treatment groups. In the dapagliflozin and placebo groups, 81.2% and 79.5% of patients, respectively, had a compliance of >80%, and 75.1% and 74.2%, respectively, had a compliance of >90%. Median (IQR) compliance was 98.8% (95.6%to 100%) and 98.7% (95.5% to 100%) in the dapagliflozin and placebo groups, respectively.

Baseline data

Table 7 Demographics

		Dapa 10mg (N=2373)	Placebo (N=2371)	Total (N=4744)
Demographic characteristic				
Age (years)	n	2373	2371	4744
	Mean	66.2	66.5	66.3
	SD	11.0	10.8	10.9
Sex n (%)	Male	1809 (76.2)	1826 (77.0)	3635 (76.6)
	Female	564 (23.8)	545 (23.0)	1109 (23.4)
Region n (%)	Asia/Pacific	543 (22.9)	553 (23.3)	1096 (23.1)
	Europe	1094 (46.1)	1060 (44.7)	2154 (45.4)
	North America	335 (14.1)	342 (14.4)	677 (14.3)
	South America	401 (16.9)	416 (17.5)	817 (17.2)

Table 8 Body mass index

Subject characteristic		Dapa 10mg (N=2373)	Placebo (N=2371)	Total (N=4744)
Body Mass Index (kg/m²)	n	2371	2371	4742
	Mean	28.2	28.1	28.2
	SD	6.0	5.9	6.0
	Median	27.0	27.0	27.0
	Min	14	14	14
	Max	77	60	77
Body Mass Index group (kg/m²) n (%)	n	2371	2371	4742
	<30	1537 (64.8)	1533 (64.7)	3070 (64.7)
	≥30	834 (35.2)	838 (35.3)	1672 (35.3)

Table 9 Renal function

		Dapa 10mg (N=2373)	Placebo (N=2371)	Total (N=4744)
Subject characteristic				
Serum Creatinine (µmol/L)[a]	n	2372	2370	4742
	Q1	83	84	83
	Median	99.0	100.0	99.0
	Q3	120	119	120
eGFR (ml/min/1.73 m^2)[b]	n	2372	2370	4742
	Q1	51	51	51
	Median	64.0	64.0	64.0
	Q3	80	79	80
	Mean	66.0	65.5	65.8
	SD	19.6	19.3	19.4
eGFR category (ml/min/1.73 m^2)[b]	n	2372	2370	4742
	< 30	13 (0.5)	11 (0.5)	24 (0.5)
	30- < 45	349 (14.7)	346 (14.6)	695 (14.7)
	45- < 60	600 (25.3)	607 (25.6)	1207 (25.5)

Table 10 Time from diagnosis and hospitalisation for heart failure

		Dapa 10mg (N=2373)	Placebo (N=2371)	Total (N=4744)
Time from diagnosis of HF to enrolment	n	2373	2371	4744
	0 - 3 Months	80 (3.4)	70 (3.0)	150 (3.2)
	>3 - 6 Months	179 (7.5)	214 (9.0)	393 (8.3)
	>6 - 12 Months	272 (11.5)	283 (11.9)	555 (11.7)
	>1 - 2 Years	320 (13.5)	366 (15.4)	686 (14.5)
	>2 - 5 Years	578 (24.4)	527 (22.2)	1105 (23.3)
	>5 Years	944 (39.8)	911 (38.4)	1855 (39.1)
Prior HF hospitalisation	n	2373	2371	4744
	Yes	1124 (47.4)	1127 (47.5)	2251 (47.4)

Table 11 Heart failure characteristics

		Dapa 10mg (N=2373)	Placebo (N=2371)	Total (N=4744)
Subject characteristic				
NYHA class at enrolment n (%)	N	2373	2371	4744
	II	1606 (67.7)	1597 (67.4)	3203 (67.5)
	III	747 (31.5)	751 (31.7)	1498 (31.6)
	IV	20 (0.8)	23 (1.0)	43 (0.9)
LVEF (%)	N	2373	2371	4744
	Q1	26	25	26
	Median	32	32	32
	Q3	37	36	37
Main aetiology of HF n (%)	N	2373	2371	4744
	Ischaemic	1316 (55.5)	1358 (57.3)	2674 (56.4)
	Non-Ischaemic	857 (36.1)	830 (35.0)	1687 (35.6)
	Unknown	200 (8.4)	183 (7.7)	383 (8.1)
Atrial Fibrillation or Flutter at enrolment ECG	N	2373	2371	4744
	Yes	569 (24.0)	559 (23.6)	1128 (23.8)
QRS duration	N	2358	2358	4716
	QRS duration ≥150 msec	546 (23.2)	499 (21.2)	1045 (22.2)
	QRS duration ≥130 msec	839 (35.6)	798 (33.8)	1637 (34.7)
NT-proBNP (pg/mL)[a]	N	2372	2370	4742
	Q1	857	857	857
	Median	1428	1446	1437
	Q3	2655	2641	2650

Table 12 Medical history

Characteristic	Number (%) of subjects Dapa 10mg (N=2373)	 Placebo (N=2371)	 Total (N=4744)
Cardiac disorders			
Angina pectoris	505 (21.3)	478 (20.2)	983 (20.7)
Angina unstable	69 (2.9)	57 (2.4)	126 (2.7)
Atrial fibrillation	916 (38.6)	902 (38.0)	1818 (38.3)
Atrial flutter	107 (4.5)	118 (5.0)	225 (4.7)
Cardiac valve disease	511 (21.5)	510 (21.5)	1021 (21.5)
Coronary artery stenosis	931 (39.2)	949 (40.0)	1880 (39.6)
Myocardial infarction	1027 (43.3)	1065 (44.9)	2092 (44.1)
Ventricular arrhythmia	402 (16.9)	360 (15.2)	762 (16.1)
Metabolism and nutrition disorders			
Dyslipidaemia	1444 (60.9)	1426 (60.1)	2870 (60.5)
Gout	231 (9.7)	257 (10.8)	488 (10.3)
Type 2 diabetes mellitus	993 (41.8)	990 (41.8)	1983 (41.8)

Table 13 Heart failure/CV medication

	Number (%) of subjects		
	Dapa 10mg (N=2373)	**Placebo (N=2371)**	**Total (N=4744)**
Treatments			
ACE inhibitor (ACEi)	1332 (56.1)	1329 (56.1)	2661 (56.1)
Angiotensin receptor blocker (ARB)	675 (28.4)	632 (26.7)	1307 (27.6)
Neprilysin inhibitor/ARB (ARNI)	250 (10.5)	258 (10.9)	508 (10.7)
Beta Blocker	2278 (96.0)	2280 (96.2)	4558 (96.1)
Mineralocorticoid receptor antagonist (MRA)	1696 (71.5)	1674 (70.6)	3370 (71.0)
ACEi or ARB	1999 (84.2)	1953 (82.4)	3952 (83.3)
ACEi, ARB or ARNI	2235 (94.2)	2207 (93.1)	4442 (93.6)
(ACEi, ARB or ARNI) and Beta Blocker	2151 (90.6)	2125 (89.6)	4276 (90.1)
(ACEi, ARB or ARNI) and Beta Blocker and MRA	1558 (65.7)	1533 (64.7)	3091 (65.2)
Diuretics	2216 (93.4)	2217 (93.5)	4433 (93.4)
Loop diuretics	1907 (80.4)	1918 (80.9)	3825 (80.6)
Other diuretics[a]	1798 (75.8)	1757 (74.1)	3555 (74.9)
Vasodilators	404 (17.0)	362 (15.3)	766 (16.1)
Digitalis glycosides	445 (18.8)	442 (18.6)	887 (18.7)
Ivabradine	119 (5.0)	109 (4.6)	228 (4.8)

a Other diuretics include Mineralocorticoid receptor antagonist (MRA)

Outcomes and estimation

Primary efficacy variable – CV death or HF event

Dapagliflozin was superior to placebo in reducing the incidence of any event in the composite of CV death or an HF event, with a 26% relative risk reduction (95% CI 15% to 35 %).

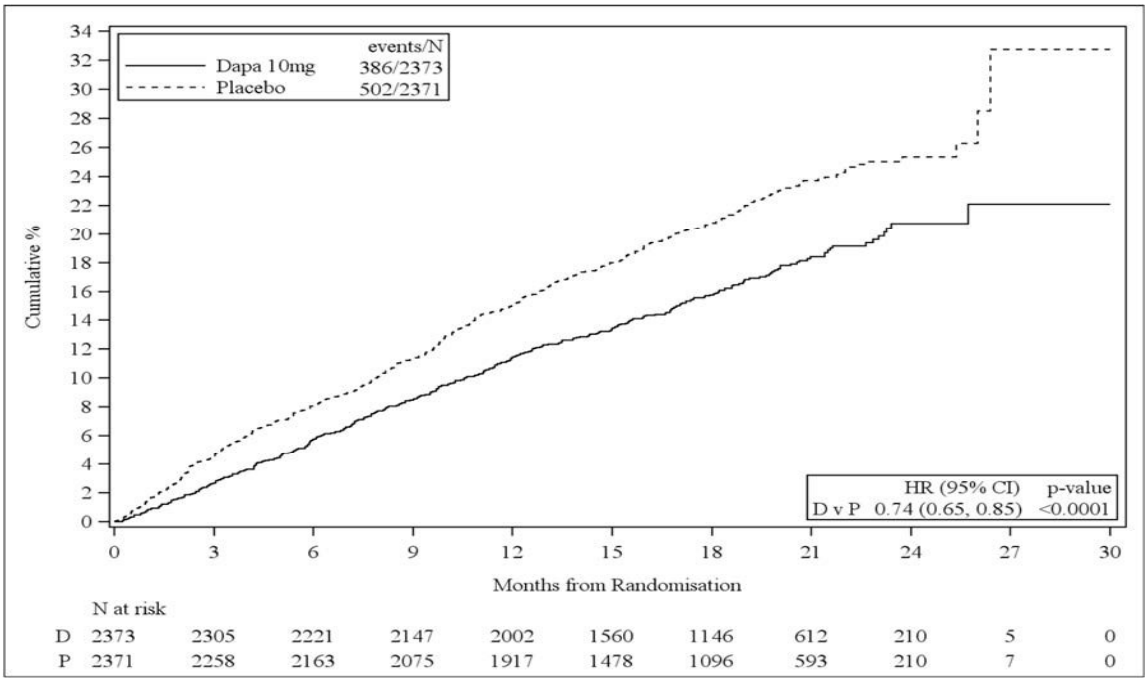


Figure 3 Kaplan-Meier plot of the primary composite endpoint time to first CV death or HF event (FAS)

All 3 components of the primary composite endpoint individually contributed to the overall treatment effect observed, as evidenced by the lower incidence of CV deaths, hospitalizations for HF, and urgent HF visits in the dapagliflozin treatment group compared to placebo. Although not formally tested for significance, treatment with dapagliflozin was associated with an 18% (95% CI 2% to 31%) relative risk reduction in CV death, a 30% (95% 17% to 41%) relative risk reduction in hospitalization for HF, and a 57% (95% CI 10% to 80%) relative risk reduction in urgent HF visits, compared with placebo. (Figure 4).

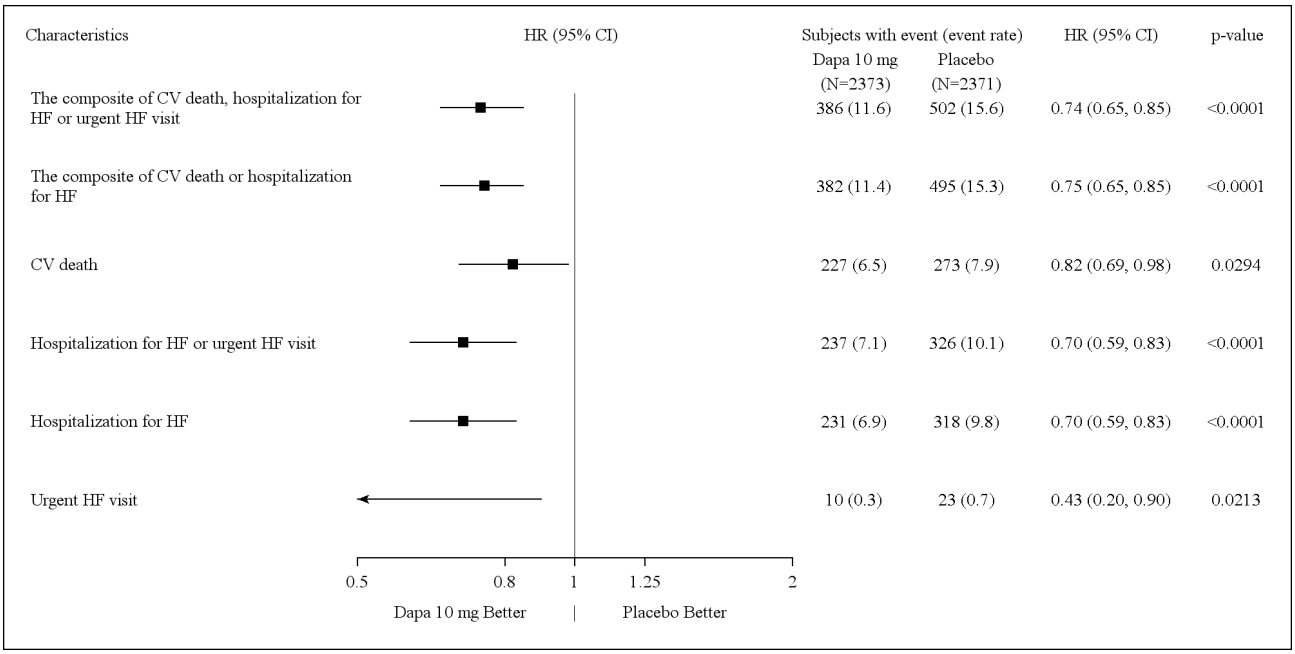


Figure 4 Forest plot of the primary composite endpoint and individual components (FAS)

Sensitivity analyses

A sensitivity analysis, in which deaths adjudicated as 'undetermined' were not included as endpoint events but were treated as censoring events, was conducted, and the result was consistent with that of the primary analysis.

A tipping point analysis, to assess the robustness of the observed result for the primary endpoint with regard to censoring prior to PACD (Primary analysis censoring date) due to incomplete follow-up and due to non-CV death was pre-specified. In light of the magnitude of the observed treatment effect and the low frequency of incomplete follow-up, with <3% of patients in each treatment group censored before PACD the tipping-point analysis was not performed. Instead, a "worst case scenario" analysis was performed; patients in the dapagliflozin treatment group, censored before PACD, including those censored due to non-CV death, were considered having experienced the composite endpoint, using their censoring time as the time of the imputed event. This rendered in total 54 new events in the dapagliflozin treatment group. Patients in the placebo group, censored before PACD, were considered censored and event free. In this analysis, the resulting treatment effect estimate remained statistically significant (HR 0.85 [95% CI 0.74, 0.96], p=0.0103).

Secondary efficacy variables

Table 14 Total number of (first and recurrent) HF hospitalisations and CV death.

	Dapa 10 mg (N=2373)	**Placebo (N=2371)**	

Variable	Number of events	Event rate	Number of events	Event rate	Rate/ Hazard Ratio[a]	95% CI	p-value
The composite of CV death or recurrent HF hospitalisations	567	16.3	742	21.6	0.75	(0.65, 0.88)	0.0002
Recurrent HF hospitalisations	340	9.8	469	13.6	0.72	(0.59, 0.86)	0.0005
CV Death[a]	227	6.5	273	7.9	0.82	(0.69, 0.98)	0.0294

Hazard ratio for CV death as an individual component is derived from Cox proportional hazards regression. Event rates are presented as the average number of events per 100 patient-years of follow-up

Rate ratio for dapa 10mg versus placebo, confidence interval and 2-sided p-value are calculated from the LWYY proportional rates model stratified by T2DM status at randomisation, with factors for treatment group and history of HF hospitalisation.If HF hospitalisation and CV death occurred at the same day, then only the CV death is counted in this table.

Fewer patients in the dapagliflozin group, compared with placebo, had ≥1 and ≥2 events of hospitalisation for HF or CV death (Table 21). Results of a supportive analysis, using a joint frailty model, were consistent with the main analysis of the endpoint.

Table 21 Summary of HF hospitalisations and CV Death - number of events per patient (FAS)

	Number of subjects (%)			
	HF Hospitalisation		HF Hospitalisation or CV Death	
Events per patient	Dapa 10mg (N=2373)	Placebo (N=2371)	Dapa 10mg (N=2373)	Placebo (N=2371)
0	2143 (90.3)	2053 (86.6)	1991 (83.9)	1876 (79.1)
≥1	230 (9.7)	318 (13.4)	382 (16.1)	495 (20.9)
≥2	72 (3.0)	96 (4.0)	120 (5.1)	157 (6.6)
Total events	340	469	567	742

Source: Table 14.2.3.3

If HF hospitalisation and CV death occurred at the same day, then only the CV death is counted in this table.

CV Cardiovascular. Dapa Dapagliflozin. FAS Full analysis set. HF Heart failure. N Number of subjects in treatment group.

Patient reported outcome questionnaires

At 8 months, the KCCQ compliance was 88.7% and 87.6% in the dapagliflozin and placebo treatment group, respectively. Treatment with dapagliflozin resulted in a statistically significant benefit over placebo

in heart failure symptoms, as measured by change from baseline to Month 8 in the KCCQ-TSS, (Win Ratio 1.18 [95% CI 1.11, 1.26]; p < 0.0001).
In addition, responder analyses based on different magnitudes of improvement/deterioration was performed;

Table 15 Percent of patients with clinically meaningful improvement and deterioration on the KCCQ-TSS at 8 months

Change from baseline at 8 months:	**Dapagliflozin 10 mg n=2086[a]**	**Placebo n=2062[a]**		
Improvement	**n (%) improved[b]**	**n (%) improved[b]**	**Odds ratio[c] (95% CI)**	**p-value**
≥5 points (small improvement)	1198 (57.4)	1030 (50.0)	1.15 (1.08, 1.23)	<0.0001
≥10 points (moderate to large improvement)	1124 (53.9)	968 (46.9)	1.15 (1.08, 1.22)	<0.0001
≥15 points (large improvement)	1120 (53.7)	984 (47.7)	1.14 (1.07, 1.22)	<0.0001
Deterioration	**n (%) deteriorated[d]**	**n (%) deteriorated[d]**	**Odds ratio[e] (95% CI)**	**p-value**
≥5 points (small deterioration)	524 (25.1)	682 (33.1)	0.84 (0.78, 0.90)	<0.0001
≥10 points (moderate to large deterioration)	385 (18.5)	495 (24.0)	0.85 (0.79, 0.92)	<0.0001

Source: see DAPA-HF CSR Tables 14.2.4.3, 14.2.4.4, 14.2.4.6, 14.2.4.7 in Module 5.3.5.1 and PRO evidence dossier in Module 5.3.5.3. [a] Number of subjects with an observed KCCQ-TSS or who died prior to 8 months.

[b] Number of subjects who had an observed improvement of at least 5, 10, or 15 points from baseline. Patients who died prior to the given timepoint are counted as not improved.

[c] For improvement, an odds ratio >1 favours dapagliflozin 10mg.

[d] Number of subjects who had an observed deterioration of at least 5 or 10 points from baseline. Patients who died prior to the given timepoint are counted as deteriorated.

[e] For deterioration, an odds ratio <1 favours dapagliflozin 10mg.

Patients with a KCCQ-TSS at baseline which was too high for them to experience an improvement were defined as improved if they remained there at 8 months. Similarly, patients with a KCCQ-TSS at baseline which was too low for them to experience a deterioration were defined as deteriorated if they remained there at 8 months. Odds ratios are obtained from logistic regression with baseline KCCQ score as a covariate and T2DM stratum.

Dapa Dapagliflozin. FAS Full analysis set. CI Confidence interval. KCCQ Kansas City Cardiomyopathy Questionnaire. N Number of subjects in treatment group. T2DM Type 2 diabetes mellitus.

Renal endpoints

No statistically significant difference was observed for the predefined renal composite endpoint between Dapa 10 mg and placebo. There were 28 endpoint events in the dapagliflozin treatment group and 39 endpoint events in the placebo group (Figure 5 and Table 15).

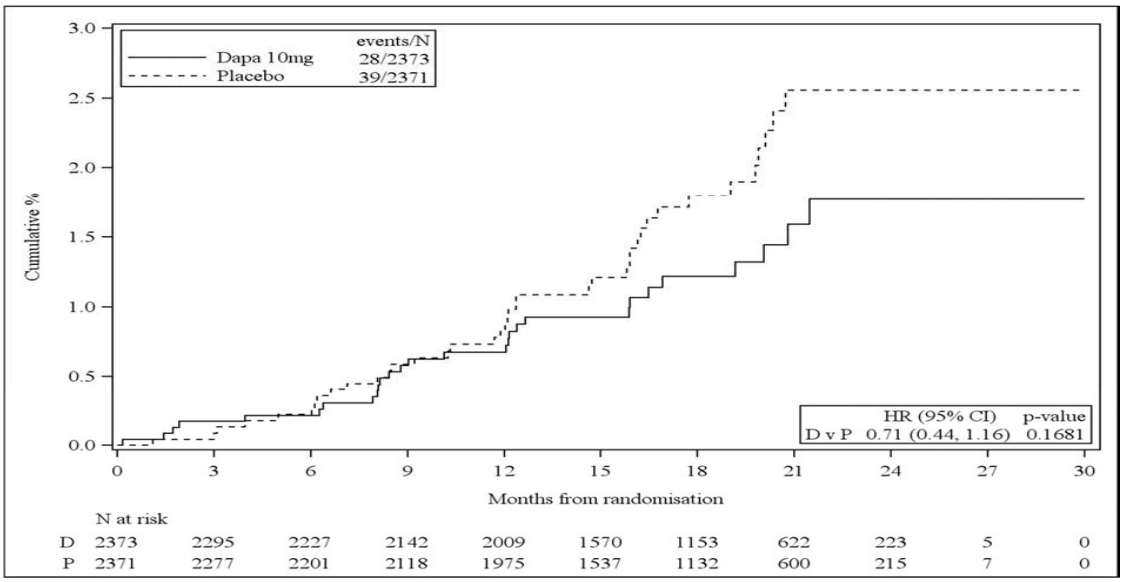


Figure 5 Time to the first occurrence of any of the components of the composite of ≥50% sustained decline in eGFR, end stage renal disease or renal death

Table 16 Analysis of the composite endpoint of worsening renal function and components (FAS)

	Dapa 10 mg (N=2373)		Placebo (N=2371)				
Variable	Subjects with events n (%)	Event rate	Subjects with events n (%)	Event rate	Hazard ratio	95% CI	p-value
The composite of ≥50% sustained decline in eGFR, ESRD or Renal death	28 (1.2)	0.8	39 (1.6)	1.2	0.71	(0.44, 1.16)	0.1681
≥50% sustained decline in eGFR	14 (0.6)	0.4	23 (1.0)	0.7	0.60	(0.31, 1.16)	0.1260
ESRD	16 (0.7)	0.5	16 (0.7)	0.5	1.00	(0.50, 1.99)	0.9947
Sustained eGFR <15 ml/min/1.73 m^2	1 (<0.1)	0.0	0	0			
Chronic dialysis treatment	16 (0.7)	0.5	16 (0.7)	0.5	1.00	(0.50, 1.99)	0.9932
Renal transplant	0	0	0	0			
Renal Death	0	0	1 (<0.1)	0.0			

Source: Table 14.2.5.1
The number of events for the individual components are the actual number of first events for each component and their sum exceeds the number 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, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model (score test) stratified by T2DM status at randomisation, with factors for treatment group and baseline eGFR.
CI Confidence interval. Dapa Dapagliflozin. eGFR Estimated glomerular filtration rate. ESRD End stage renal disease. FAS Full analysis set. N Number of subjects in treatment group. T2DM Type 2 diabetes mellitus.

There were no significant differences in the incidence of renal events. In particular there was even no numerical difference in patients reaching end stage renal disease or requiring dialysis. The cases were few. No conclusions can be drawn and no data should be included in section 5.1 of the SmPC.

All cause mortality

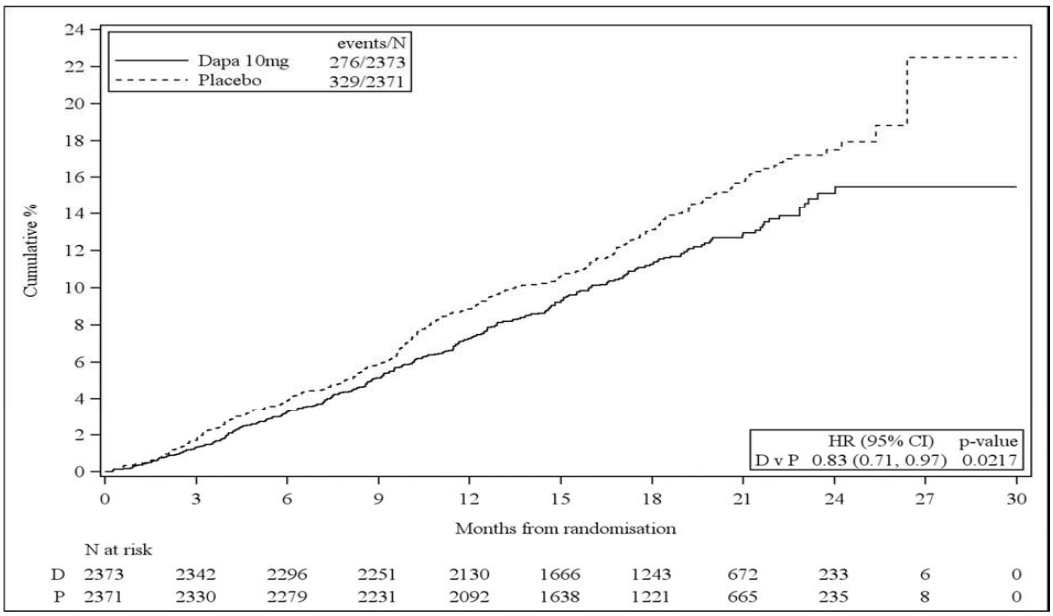


Figure 6 Time to death from any cause

The hierarchical testing sequence stopped before the endpoint of time to death from any cause could be assessed. Hence, the analysis of all-cause mortality was not conducted as part of the confirmatory testing sequence. All-cause mortality was driven by CV death. There were 173 and 207 deaths in the dapagliflozin and placebo groups, respectively, adjudicated as CV death, and 48 and 54 death adjudicated as non-CV deaths in the dapagliflozin and placebo groups, respectively. Undetermined cause of death was counted as CV death; there were 54 and 66 deaths in the dapagliflozin and placebo group, respectively, adjudicated as undetermined cause of death. Death occurring after withdrawal of consent were not adjudicated; there was 1 death in the dapagliflozin treatment group and 2 deaths in the placebo group after withdrawal of consent.

Ancillary analyses

Exploratory variables

Treatment with dapagliflozin numerically reduced the incidence of time to the first occurrence of any of the components of the expanded composite endpoint of worsening HF (Table 14.2.7.1)

Table 14.2.7.1 Analysis of the expanded composite of worsening HF (FAS)

	Dapa 10mg (N=2373)		Placebo (N=2371)				
Variable	Subjects with events n (%)	Event rate	Subjects with events n (%)	Event rate	Hazard ratio	95% CI	p-value
The composite of CV death, hospitalization for HF, urgent HF visit or documented evidence of worsening HF[a]	527 (22.2)	16.5	684 (28.8)	22.6	0.73	(0.65, 0.82)	<0.0001
CV Death	227 (9.6)	6.5	273 (11.5)	7.9	0.82	(0.69, 0.98)	0.0294
Hospitalization for HF	231 (9.7)	6.9	318 (13.4)	9.8	0.70	(0.59, 0.83)	<0.0001
Urgent HF visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43	(0.20, 0.90)	0.0213
Documented evidence of worsening HF	264 (11.1)	8.0	340 (14.3)	10.8	0.74	(0.63, 0.87)	0.0003

[a] Evidence of worsening HF documented by the investigator on a specific CRF page, including symptoms/signs leading to initiation of a new treatment for HF sustained for at least 4 weeks or augmentation of existing oral therapy for HF (e.g., increase in dose of diuretic) sustained for at least 4 weeks. CV death, hospitalization for HF and HF urgent visit are defined by adjudicated events as for the primary endpoint.
Event rates are presented as the number of subjects with event per 100 patient years of follow-up.
Hazard ratio for Dapa 10mg vs placebo, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model (score test) stratified by T2DM status at randomization, with factors for treatment group and history of HF hospitalization.
Dapa Dapagliflozin. FAS Full analysis set. HF Heart failure. CI Confidence interval. N Number of subjects in treatment group. T2DM Type 2 diabetes mellitus.

In addition, 3 adjudicated exploratory endpoints are reported: time to first fatal or non-fatal MI; time to first fatal or non-fatal stroke of any cause; and number of events with doubling of serum creatinine. There was no difference between dapagliflozin and placebo groups in time to first fatal or non-fatal MI and time to first fatal or non-fatal stroke of any cause (Tables 14.2.7.10 and 11)

Table 14.2.7.10 Analysis of time to first myocardial infarction (FAS)

	Dapa 10mg (N=2373)		Placebo (N=2371)				
Variable	Subjects with events n (%)	Event rate	Subjects with events n (%)	Event rate	Hazard ratio	95% CI	p-value
Myocardial infarction	46 (1.9)	1.3	41 (1.7)	1.2	1.11	(0.73, 1.69)	0.6252

Table 14.2.7.11 Analysis of time to first stroke of any cause (FAS)

	Dapa 10mg (N=2373)		Placebo (N=2371)				
Variable	Subjects with events n (%)	Event rate	Subjects with events n (%)	Event rate	Hazard ratio	95% CI	p-value
Stroke	42 (1.8)	1.2	46 (1.9)	1.3	0.90	(0.59, 1.37)	0.6285

Event rates are presented as the number of subjects with event per 100 patient years of follow-up.
Hazard ratio for Dapa 10mg vs placebo, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model (score test) stratified by T2DM status at randomization, with a factor for treatment group.
Dapa Dapagliflozin. FAS Full analysis set. CI Confidence interval. N Number of subjects in treatment group. T2DM Type 2 diabetes mellitus.

There were fewer patients with events of doubling of serum creatinine in the dapagliflozin treatment group (43 [1.8%]) compared with placebo (77 [3.2%]). The total number of events was 44 and 83 respectively in the two groups.

The exploratory composite endpoint including the weaker and less clearly defined component of documented evidence of worsening HF was in line with the primary endpoint. This endpoint is influenced by the antidiuretic effect leading to reduction of oedemas. The clinical benefit per se is less clear and the results less robust compared with the primary analysis.

The Analysis of change from baseline of EQ-5D-5L mobility score, care score (washing and dressing), usual activity score, pain/discomfort score, anxiety/depression score, VAS score and utility scores did not show significant or clinically relevant differences between Dapa 10 mg and Placebo over 24 months. The measure is not specifically designed to investigate patients with chronic heart failure and does not contradict the results of the Kansas City Cardiomyopathy Questionnaire that indicated a significant improvement in symptom frequency and symptom burden.

The results for the effect of Dapagliflozin vs. Placebo on HbA1c, weight and systolic blood pressure are summarized below (Table 12 – 14) analyses

Table 12: Analysis of change from baseline in HbA1c - Subjects with T2DM at baseline (FAS)

						Repeated measures analysis						
	Absolute values			Change from baseline		Change from baseline			Difference between Dapa 10mg and Placebo			
Treatment group Time point	n	Mean	SD	Mean	SD	LS Mean	SE	95% CI	LS Mean difference	SE	95% CI	p-value
Dapa 10mg												
Baseline	1074	7.41	1.51									
14 days	1044	7.32	1.42	-0.08	0.40	-0.08	0.0113	(-0.10, -0.06)	-0.08	0.0160	(-0.11, -0.05)	<.0001
2 Months	1004	7.08	1.30	-0.32	0.85	-0.32	0.0255	(-0.37, -0.27)	-0.30	0.0361	(-0.37, -0.22)	<.0001
4 Months	1007	7.12	1.31	-0.29	1.05	-0.28	0.0332	(-0.35, -0.22)	-0.26	0.0472	(-0.35, -0.17)	<.0001
8 Months	971	7.19	1.42	-0.21	1.14	-0.20	0.0374	(-0.28, -0.13)	-0.24	0.0533	(-0.34, -0.13)	<.0001
12 Months	918	7.20	1.36	-0.19	1.16	-0.19	0.0394	(-0.27, -0.11)	-0.32	0.0563	(-0.43, -0.21)	<.0001
16 Months	758	7.19	1.39	-0.17	1.23	-0.17	0.0435	(-0.25, -0.08)	-0.30	0.0621	(-0.42, -0.18)	<.0001
20 Months	519	7.24	1.45	-0.08	1.23	-0.09	0.0548	(-0.20, 0.02)	-0.26	0.0786	(-0.41, -0.11)	0.0010
24 Months	226	7.30	1.54	-0.09	1.39	-0.06	0.0721	(-0.20, 0.08)	-0.22	0.1025	(-0.42, -0.02)	0.0341

This table includes subjects with T2DM at baseline defined as history of T2DM or HbA1c ≥6.5% at both visit 1 and visit 2.
n= the number of subjects with non-missing value at baseline and at the given time point, included in the repeated measures analysis.
The repeated measures model includes terms for randomised treatment group, baseline measurement, visit and visit by treatment group interaction.
Dapa Dapagliflozin. FAS Full analysis set. CI Confidence interval. N Number of subjects in treatment group. LS Least squares. SD Standard deviation. SE Standard error. T2DM Type 2 diabetes mellitus.

Table 13: Analysis of change from baseline in weight (FAS)

						Repeated measures analysis						
	Absolute values			Change from baseline		Change from baseline			Difference between Dapa 10mg and Placebo			
Treatment group Time point	n	Mean	SD	Mean	SD	LS Mean	SE	95% CI	LS Mean difference	SE	95% CI	p-value
Dapa 10mg												
Baseline	2373	80.65	20.01									
14 days	2326	80.30	19.91	-0.48	1.65	-0.48	0.0796	(-0.64, -0.33)	-0.47	0.1125	(-0.69, -0.25)	<.0001
2 Months	2260	80.02	19.96	-0.69	2.34	-0.70	0.0799	(-0.86, -0.55)	-0.70	0.1130	(-0.92, -0.48)	<.0001
4 Months	2241	80.03	19.94	-0.74	3.58	-0.73	0.0803	(-0.89, -0.58)	-0.72	0.1137	(-0.94, -0.50)	<.0001
8 Months	2158	79.98	19.72	-0.88	3.86	-0.85	0.0813	(-1.01, -0.69)	-0.88	0.1151	(-1.11, -0.65)	<.0001
12 Months	2069	79.81	19.76	-1.09	4.44	-1.09	0.0825	(-1.25, -0.93)	-1.00	0.1171	(-1.23, -0.77)	<.0001
16 Months	1728	79.69	19.68	-1.11	4.93	-1.19	0.0867	(-1.36, -1.02)	-1.13	0.1231	(-1.37, -0.89)	<.0001
20 Months	1177	80.71	19.36	-1.39	5.27	-1.48	0.0978	(-1.67, -1.29)	-1.27	0.1389	(-1.55, -1.00)	<.0001
24 Months	516	81.42	19.41	-1.59	5.55	-1.60	0.1321	(-1.86, -1.34)	-1.45	0.1868	(-1.81, -1.08)	<.0001

n = The number of subjects with non-missing value at baseline and at the given time point, included in the repeated measures analysis.
The repeated measures model includes terms for randomised treatment group, baseline measurement, visit and visit by treatment group interaction.
Dapa Dapagliflozin. FAS Full analysis set. CI Confidence interval. N Number of subjects in treatment group. LS Least squares. SD Standard deviation. SE Standard error. T2DM Type 2 diabetes mellitus.

Table 14: Analysis of change from baseline in systolic blood pressure (FAS)

						Repeated measures analysis						
	Absolute values			Change from baseline		Change from baseline			Difference between Dapa 10mg and Placebo			
Treatment group Time point	n	Mean	SD	Mean	SD	LS Mean	SE	95% CI	LS Mean difference	SE	95% CI	p-value
Dapa 10mg												
Baseline	2373	122.03	16.30									
14 days	2328	119.08	16.34	-3.10	12.33	-3.11	0.2383	(-3.58, -2.65)	-2.39	0.3370	(-3.05, -1.73)	<.0001
2 Months	2261	119.79	16.61	-2.44	13.66	-2.49	0.2647	(-3.01, -1.97)	-1.92	0.3740	(-2.65, -1.18)	<.0001
4 Months	2243	119.73	16.80	-2.57	14.44	-2.57	0.2762	(-3.11, -2.03)	-1.70	0.3913	(-2.47, -0.94)	<.0001
8 Months	2160	120.54	16.77	-1.92	14.92	-1.97	0.2957	(-2.55, -1.39)	-1.27	0.4191	(-2.09, -0.45)	0.0024
12 Months	2071	120.24	16.83	-2.25	15.19	-2.20	0.3033	(-2.79, -1.60)	-1.14	0.4309	(-1.99, -0.30)	0.0081
16 Months	1728	120.70	17.35	-2.47	15.82	-2.31	0.3344	(-2.96, -1.65)	-1.56	0.4747	(-2.49, -0.63)	0.0010
20 Months	1180	120.83	17.22	-2.80	15.83	-2.70	0.3859	(-3.46, -1.94)	-1.58	0.5481	(-2.65, -0.50)	0.0040
24 Months	516	121.76	17.58	-3.20	16.08	-3.48	0.5253	(-4.51, -2.45)	-0.76	0.7420	(-2.22, 0.69)	0.3045

n = The number of subjects with non-missing value at baseline and at the given time point, included in the repeated measures analysis.
The repeated measures model includes terms for randomised treatment group, baseline measurement, visit and visit by treatment group interaction.
Dapa Dapagliflozin. FAS Full analysis set. CI Confidence interval. N Number of subjects in treatment group. LS Least squares. SD Standard deviation. SE Standard error. T2DM Type 2 diabetes mellitus.

The observed reductions induced by dapagliflozin on HbA1c, body weight and systolic blood pressure are consistent with previous results and are reflected in the current Dapagliflozin SPC labelling.
However, the magnitude of the effect size of dapagliflozin on HbA1c (placebo-adjusted LS mean difference of -0.2% to -0.3% during the DAPA-HF trial) was modest, which might be explained by the low baseline HbA1c (7.41%) and a higher use of additional antidiabetic agents in the placebo group over the study duration. An LS Mean difference in SBP in the range of 1 – 2 mmHg is of clinical relevance for cardiovascular events in patients with arterial hypertension but cannot explain the magnitude of the clinical effect as observed in DAPA HF (risk reduction by 26% for the primary endpoint). E.g. Fuchs and Welton (Hypertension 2020; 75: 285–292 discussed data from cohort studies indicating a doubling of the risk for CVD for a 20 mm Hg higher level of SBP and 10 mm Hg higher level of DBP. Similarly, the moderate weight loss and of the moderate reduction in HbA1c in patients with T2DM may only contribute to a minor degree if at all.

Table 17 Heart failure medication during study

Overall/ Treatments		Number (%) of subjects				
		Baseline (N=4744)	4 months (N=4632)	8 months (N=4515)	12 months (N=4244)	24 months (N=579)
n	Dapa 10mg	2373	2325	2265	2141	291
	Placebo	2371	2307	2250	2103	288
ACE inhibitor (ACEi)	Dapa 10mg	1332 (56.1)	1270 (54.6)	1213 (53.6)	1136 (53.1)	164 (56.4)
	Placebo	1329 (56.1)	1255 (54.4)	1203 (53.5)	1102 (52.4)	167 (58.0)
Angiotensin receptor blocker (ARB)	Dapa 10mg	675 (28.4)	650 (28.0)	636 (28.1)	602 (28.1)	77 (26.5)
	Placebo	632 (26.7)	612 (26.5)	587 (26.1)	557 (26.5)	54 (18.8)
Neprilysin inhibitor/ARB (ARNI)	Dapa 10mg	250 (10.5)	262 (11.3)	275 (12.1)	265 (12.4)	34 (11.7)
	Placebo	258 (10.9)	277 (12.0)	307 (13.6)	288 (13.7)	52 (18.1)
Beta Blocker	Dapa 10mg	2278 (96.0)	2233 (96.0)	2158 (95.3)	2040 (95.3)	279 (95.9)
	Placebo	2280 (96.2)	2202 (95.4)	2140 (95.1)	1997 (95.0)	270 (93.8)
Mineralocorticoids/Aldoserone antagonists (MRA)	Dapa 10mg	1696 (71.5)	1633 (70.2)	1591 (70.2)	1513 (70.7)	212 (72.9)
	Placebo	1674 (70.6)	1636 (70.9)	1580 (70.2)	1495 (71.1)	188 (65.3)

Overall/ Treatments		Number (%) of subjects				
		Baseline (N=4744)	4 months (N=4632)	8 months (N=4515)	12 months (N=4244)	24 months (N=579)
Diuretics	Dapa 10mg	2216 (93.4)	2147 (92.3)	2087 (92.1)	1977 (92.3)	268 (92.1)
	Placebo	2217 (93.5)	2167 (93.9)	2103 (93.5)	1980 (94.2)	270 (93.8)
Loop diuretics	Dapa 10mg	1907 (80.4)	1821 (78.3)	1761 (77.7)	1668 (77.9)	235 (80.8)
	Placebo	1918 (80.9)	1879 (81.4)	1818 (80.8)	1710 (81.3)	247 (85.8)
Other diuretics[a]	Dapa 10mg	1798 (75.8)	1731 (74.5)	1680 (74.2)	1593 (74.4)	227 (78.0)
	Placebo	1757 (74.1)	1724 (74.7)	1669 (74.2)	1588 (75.5)	200 (69.4)

[a] Other diuretics include Mineralocorticoid receptor antagonist (MRA).
n is the number of subjects alive in study at the target time point. n is the denominator for percentage.
The table shows the number(%) of subjects taking the medication at the target time point.
Dapa Dapagliflozin. FAS Full analysis set. N Number of subjects in treatment group.

HF medication did not change much during the study and it seems as if patients in the placebo group had a relevant treatment with 94 % being treated with diuretics.

Summary of main study(ies)

The following tables summarise 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 18. Summary of Efficacy

Title: Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure **(DAPA- HF)**		
Design	DAPA-HF was a global, event-driven, randomised, double-blind, placebo-controlled Phase III study conducted at 410 sites across 20 countries, and included 4744 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 HF events, when added to background standard of care, in patients with HFrEF in NYHA class II-IV, with T2DM or without diabetes.	
	Duration of main phase:	Mean duration of study 18.2 months (range 0 to 27.8 months, event driven study)

Hypothesis	Superiority		
Treatments groups	Dapagliflozin 10 mg		2373
	Placebo		2371
Endpoints and definitions	Primary endpoint		composite endpoint of CV death or HF events
	Secondary endpoint		Time to the first occurrence of either of the components of the composite: CV death Hospitalisation for HF
	Secondary endpoint		Total number of (first and recurrent) HF hospitalisations and CV death
Database lock			

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analyses set		
Descriptive statistics and estimate variability	Treatment group	dapagliflozin	placebo
	Number of subject	2373	2371
	Primary %	11.6	15.6
	CV death%	6.5	7.9
	HF event%	7.1	10.1

Effect estimate per comparison	Primary endpoint	Comparison groups	
		HR	0.74
		variability statistic	95% CI 0.65-0.85
		P-value	<0.0001
	CV death	Comparison groups	
		HR	0.82
		variability statistic	95% CI 0.69-0.98
		P-value	0.03
	HF event	Comparison groups	
		HR	0.70
		variability statistic	95% CI 0.59-0.83
		P-value	<0.0001
Notes			

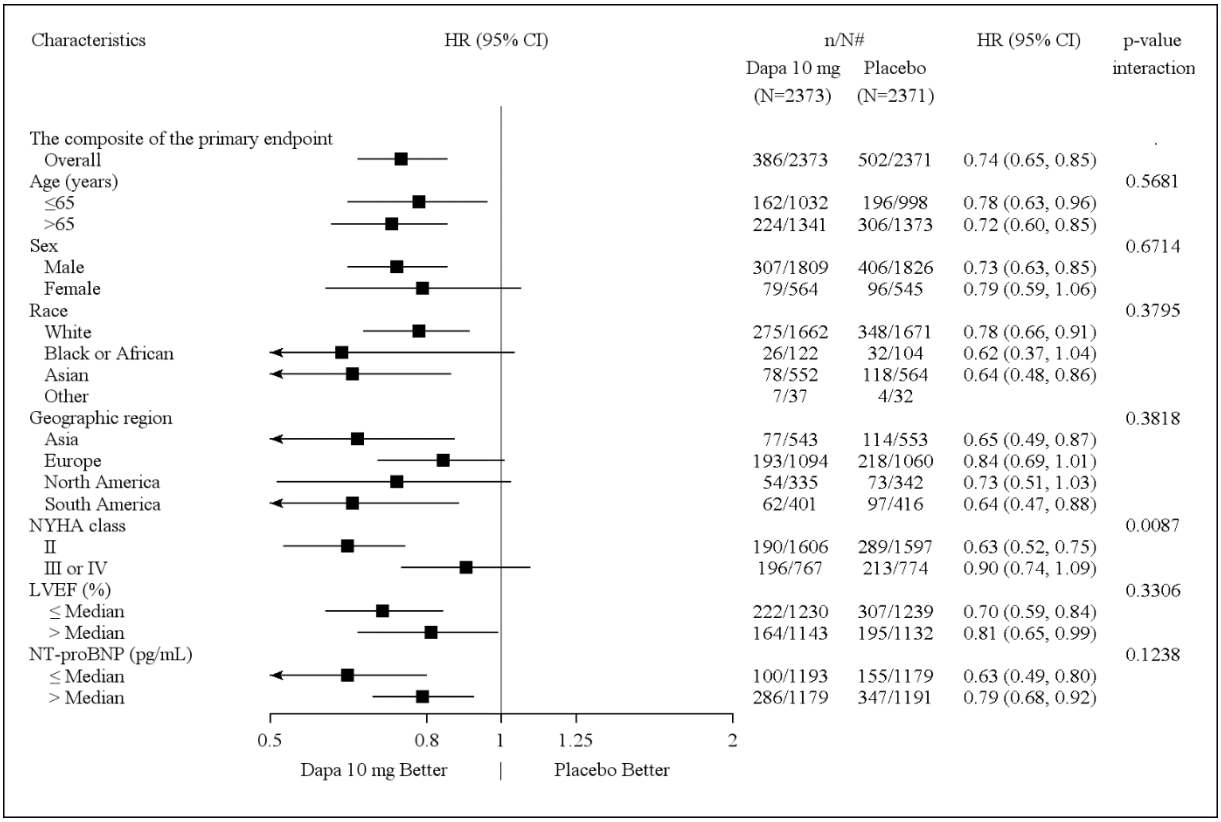
Analysis performed across trials (pooled analyses and meta-analysis)

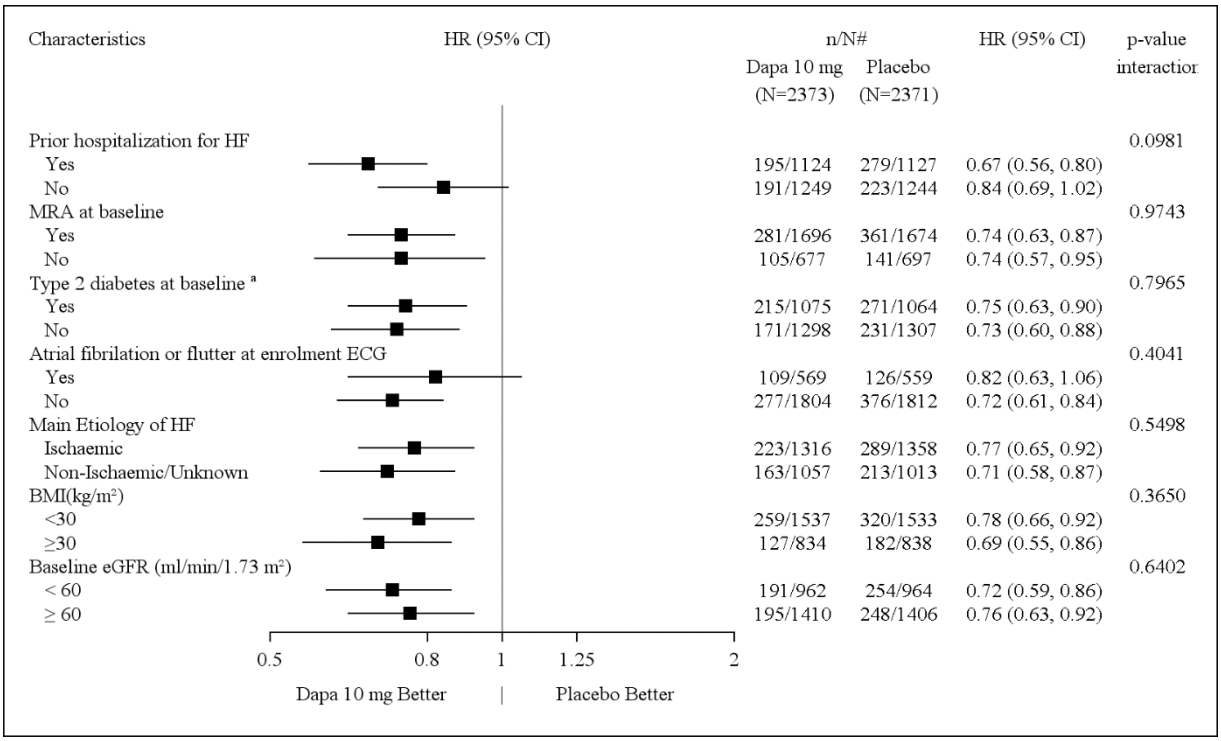
NA

Results in sub-populations (prespecified)

The results of pre-specified sub-group analyses for the primary outcome are summarized in Figure 7. There was some heterogeneity but for most entities the p value for interaction was > 0.05 with the exception of NYHA class (p = 0.0087).

Figure 7 Forest plot of the primary composite of CV death or HF event by pre specified subgroups (FAS)





[a] Defined as history of T2DM or HbA1c ≥6.5% at both enrolment and randomisation visits. This analysis does not include T2DM as a stratification factor.

n/N# Number of subjects with event / number of subjects in the sub-group.

Hazard ratio for Dapa 10mg versus placebo, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model (score test) stratified by T2DM status at randomisation, with factors for history of HF hospitalisation, the relevant sub-group variable, treatment group and the interaction between treatment group and the sub-group variable.

Hazard ratio estimates are not presented for sub-groups with less than 15 events in total, both arms combined.

When analysing the results in the subgroups for the individual components of the primary endpoint, there was not much variability for heart failure events (hospitalization for HF or urgent HF visit) with point estimates of the HRs between 0.61 and 0.83 for all of the above mentioned subgroups (Table 14.2.2.5 of the study report, not shown). More heterogeneity was observed in the analysis of CV deaths by subgroups with a p-value for an interaction < 0.05 for NYHA class and NT-proBNP and a p value of 0.06 for atrial fibrillation.

Table 14.2.2.5 Analysis of CV death by subgroups (FAS)

Subject characteristic Category	Dapa 10mg (N=2373) Number of subjects	Subjects with event n(%)	Event rate	Placebo (N=2371) Number of subjects	Subjects with event n(%)	Event rate	Hazard ratio	95% CI	p-value	Interaction p-value
Age (years)										0.7660
≤ 65	1032	95 (9.2)	6.4	998	107 (10.7)	7.5	0.85	(0.65, 1.12)	0.2517	
> 65	1341	132 (9.8)	6.6	1373	166 (12.1)	8.2	0.81	(0.64, 1.01)	0.0630	
Sex										0.6830
Male	1809	189 (10.4)	7.2	1826	224 (12.3)	8.5	0.84	(0.69, 1.02)	0.0709	
Female	564	38 (6.7)	4.5	545	49 (9.0)	6.0	0.76	(0.49, 1.16)	0.1948	
Race										0.9974
White	1662	166 (10.0)	6.6	1671	201 (12.0)	8.0	0.82	(0.67, 1.01)	0.0653	
Black or African	122	13 (10.7)	7.2	104	12 (11.5)	8.1	0.86	(0.39, 1.89)	0.7072	
Asian	552	45 (8.2)	6.1	564	57 (10.1)	7.7	0.80	(0.54, 1.19)	0.2744	
Other	37	3 (8.1)	5.1	32	3 (9.4)	5.9				
Geographic region										0.1698
Asia	543	44 (8.1)	6.1	553	54 (9.8)	7.4	0.83	(0.56, 1.23)	0.3534	
Europe	1094	126 (11.5)	7.4	1060	125 (11.8)	7.6	0.97	(0.76, 1.25)	0.8389	
North America	335	19 (5.7)	4.2	342	32 (9.4)	7.1	0.59	(0.33, 1.04)	0.0649	
South America	401	38 (9.5)	6.3	416	62 (14.9)	10.1	0.62	(0.42, 0.93)	0.0200	
NYHA class										0.0023
II	1606	100 (6.2)	4.2	1597	155 (9.7)	6.7	0.63	(0.49, 0.81)	0.0003	
III or IV	767	127 (16.6)	11.6	774	118 (15.2)	10.5	1.09	(0.85, 1.41)	0.4848	
LVEF (%)										0.9236
≤ median	1230	137 (11.1)	7.7	1239	166 (13.4)	9.3	0.83	(0.66, 1.04)	0.1111	
> median	1143	90 (7.9)	5.2	1132	107 (9.5)	6.4	0.82	(0.62, 1.08)	0.1569	
NT-proBNP (pg/mL)										0.0247
≤ median	1193	53 (4.4)	3.0	1179	87 (7.4)	5.0	0.60	(0.42, 0.84)	0.0027	
> median	1179	174 (14.8)	10.3	1191	186 (15.6)	11.0	0.94	(0.76, 1.15)	0.5411	
Prior hospitalization for HF										0.2642
Yes	1124	106 (9.4)	6.4	1127	141 (12.5)	8.6	0.74	(0.58, 0.96)	0.0204	
No	1249	121 (9.7)	6.6	1244	132 (10.6)	7.3	0.91	(0.71, 1.16)	0.4431	
MRA at baseline										0.6860
Yes	1696	171 (10.1)	6.9	1674	207 (12.4)	8.5	0.80	(0.66, 0.98)	0.0342	
No	677	56 (8.3)	5.6	697	66 (9.5)	6.4	0.87	(0.61, 1.24)	0.4444	
Type 2 diabetes at baseline[a]										0.6997
Yes	1075	121 (11.3)	7.7	1064	148 (13.9)	9.7	0.79	(0.63, 1.01)	0.0603	
No	1298	106 (8.2)	5.5	1307	125 (9.6)	6.5	0.85	(0.66, 1.10)	0.2257	
Atrial fibrillation or flutter at enrolment ECG										0.0630
Yes	569	66 (11.6)	7.6	559	58 (10.4)	6.9	1.10	(0.77, 1.57)	0.5862	
No	1804	161 (8.9)	6.1	1812	215 (11.9)	8.2	0.75	(0.61, 0.92)	0.0051	
Main etiology of HF										0.1272
Ischaemic	1316	152 (11.6)	7.8	1358	170 (12.5)	8.6	0.92	(0.74, 1.14)	0.4327	
Non-ischaemic/Unknown	1057	75 (7.1)	4.8	1013	103 (10.2)	7.0	0.69	(0.51, 0.93)	0.0136	
BMI (kg/m^2)										0.1787
< 30	1537	164 (10.7)	7.3	1533	181 (11.8)	8.2	0.89	(0.72, 1.10)	0.2891	
≥ 30	834	63 (7.6)	5.0	838	92 (11.0)	7.4	0.69	(0.50, 0.95)	0.0216	
Baseline eGFR (ml/min/1.73 m^2)										0.4084
< 60	962	119 (12.4)	8.5	964	134 (13.9)	9.6	0.88	(0.69, 1.13)	0.3293	
≥ 60	1410	108 (7.7)	5.2	1406	139 (9.9)	6.8	0.76	(0.59, 0.98)	0.0344	

[a] Defined as history of T2DM or HbA1c ≥6.5% at both visit 1 and visit 2. This analysis does not include T2DM as a stratification factor.
Event rates are presented as the number of subjects with event per 100 patient years of follow-up.
Hazard ratio for Dapa 10mg vs placebo, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model (score test) stratified by T2DM status at randomization, with factors for history of HF hospitalization, the relevant subgroup variable, treatment group and the interaction between treatment group and the subgroup variable.
Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.
BMI Body mass index. CI Confidence interval. Dapa Dapagliflozin. eGFR Estimated glomerular filtration rate. ECG electrocardiogram. FAS Full analysis set. HF Heart failure.
MRA Mineralocorticoid receptor antagonist. NT-proBNP N-terminal pro b-type natriuretic peptide. N Number of subjects in treatment group. NYHA New York Heart Association. LVEF Left Ventricular Ejection Fraction.

The results for all-cause mortality by subgroup were overall consistent with the results for CV mortality.

Results in sub-populations (post hoc)

By HFrEF severity

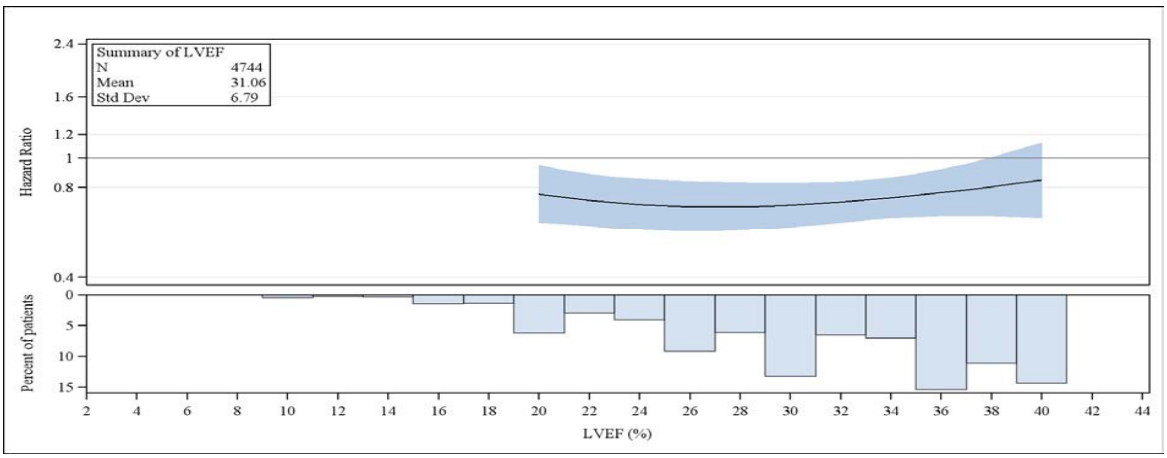
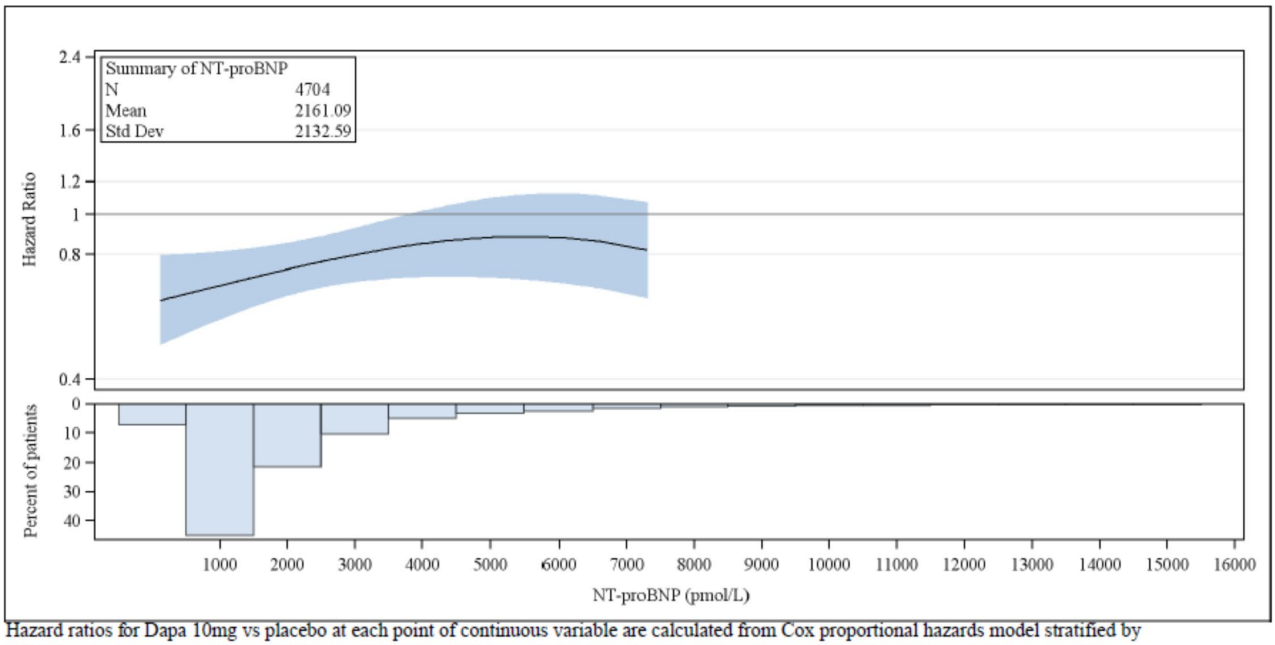


Figure 8 Hazard ratio of the primary endpoint by baseline LVEF (FAS)

Hazard ratios for Dapa 10mg versus placebo at each point of continuous variable are calculated from Cox proportional hazards model stratified by T2DM status at randomisation, with factors for history of HF hospitalisation, the relevant continuous variable, the treatment group and the interaction between treatment group and the continuous variable. The continuous variable was transformed using a restricted cubic spline with 3 knots at 5th, 50th and 95th percentiles of the range before including in the model. Band on the plot shows 95% confidence interval calculated using the same model.

As a post hoc analysis the applicant has provided results for the Hazard ratio of the primary endpoint by different continuous factors. Baseline ejection fraction had little influence on the HR in this analysis, whereas for NT-pro-BNP HRs tended to be higher at higher NT-pr-BNP levels.(Figure 8).



Hazard ratios for Dapa 10mg vs placebo at each point of continuous variable are calculated from Cox proportional hazards model stratified by T2DM status at randomization, with factors for history of HF hospitalization, the relevant continuous variable, the treatment group and the interaction between treatment group and the continuous variable. The continuous variable was transformed using a restricted cubic spline with three knots at 5th, 50th and 95th percentiles of the range before including in the model. Band on the plot shows 95% confidence interval calculated using the same model. Values greater than 16000 pmol/L were not used in the model.
Dapa Dapagliflozin. FAS Full analysis set. HF Heart failure. T2DM Type 2 diabetes mellitus. NT-proBNP N terminal pro b-type natriuretic peptide.

Figure 9b Hazard ratio of the primary endpoint by baseline NT-proBNP (FAS)

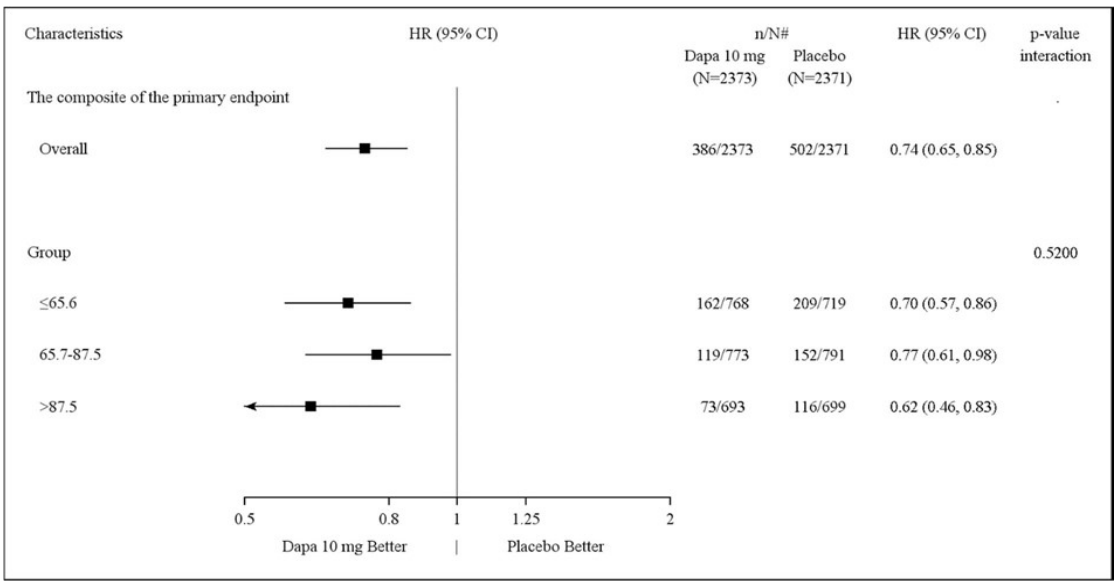
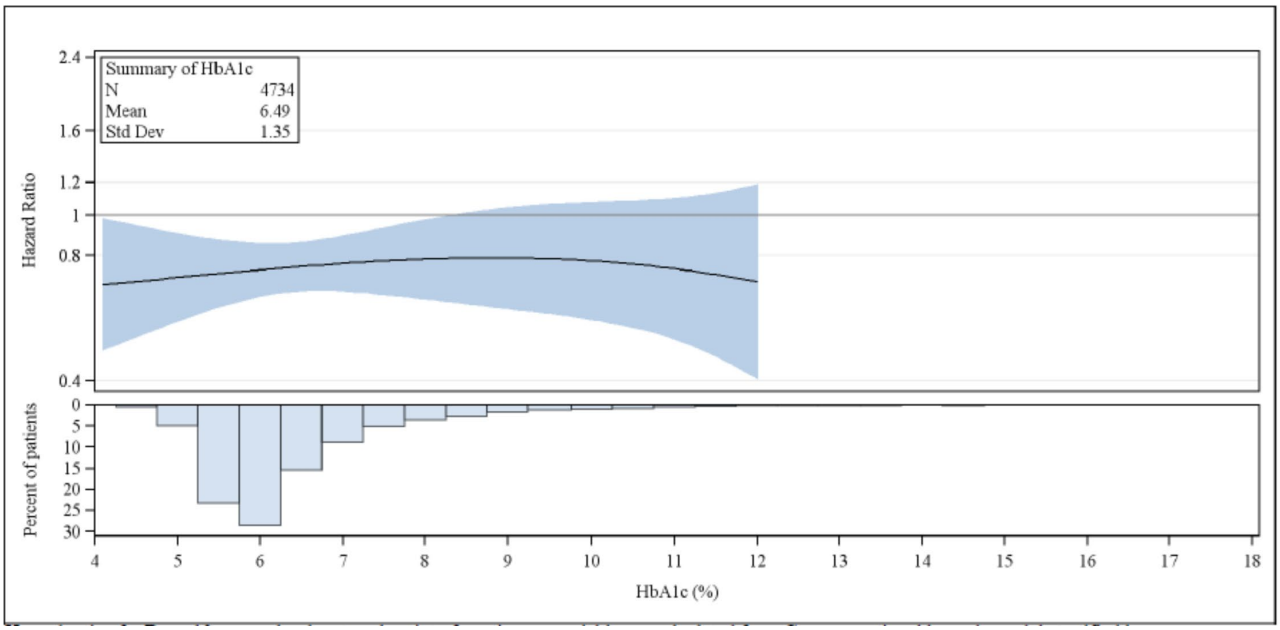


Figure 10 Forest plot of the primary composite endpoint by tertiles of KCCQ-TSS at baseline (FAS)

Source: see DAPA-HF CSR Figure 14.2.2.17.1 in CTD Module 5.3.5.1 n/N# Number of subjects with event / number of subjects in the sub-group. Hazard ratio for dapa 10mg versus placebo, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model (score test) stratified by T2DM status at randomisation, with factors for history of HF hospitalisation, the relevant subgroup variable, treatment group and the interaction between treatment group and the sub-group variable.

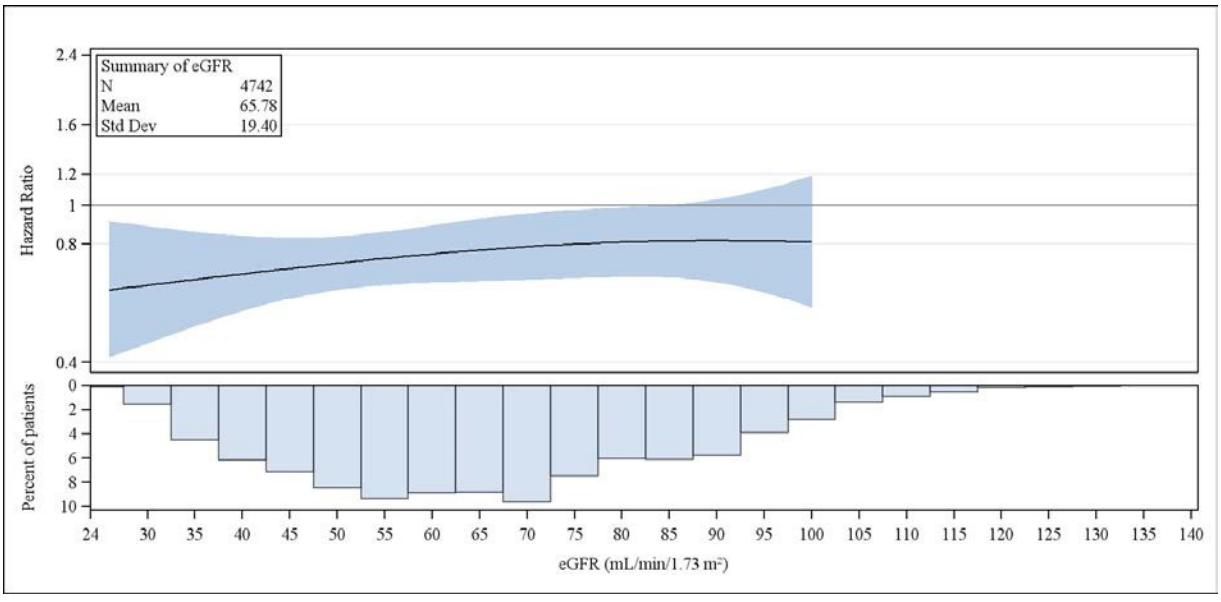
By diabetic and renal status

Figure 11 Hazard ratio of the primary endpoint by baseline HbA1c (FAS)



Hazard ratios for Dapa 10mg versus placebo at each point of continuous variable are calculated from Cox proportional hazards model stratified by T2DM status at randomisation, with factors for history of HF hospitalisation, the relevant continuous variable, the treatment group and the interaction between treatment group and the continuous variable. The continuous variable was transformed using a restricted cubic spline with 3 knots at 5th, 50th and 95th percentiles of the range before including in the model. Band on the plot shows 95% confidence interval calculated using the same model.

Figure 12 Hazard ratio of the primary endpoint by baseline eGFR (FAS)



Hazard ratios for Dapa 10mg versus placebo at each point of continuous variable are calculated from Cox proportional hazards model stratified by T2DM status at randomisation, with factors for history of HF hospitalisation, the relevant continuous variable, the treatment group and the interaction between treatment group and the continuous variable. The continuous variable was transformed using a restricted cubic spline with three knots at 5th, 50th and 95th

percentiles of the range before including in the model. Band on the plot shows 95% confidence interval calculated using the same model.

These post hoc analyses including HbA1c and eGFR as a continuous variable supports the results of the prespecified sub group analyses.

Supportive study(ies)

NA

2.4.3. **Discussion on clinical efficacy**

Dapagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor, previously approved for the treatment of patients with T1DM or T2DM. In the current variation, the MAH is applying for a new indication (*X is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fractio*n) based on the results of one pivotal phase III study; D1699C00001, hereafter referred to as DAPA-HF.

Design and conduct of clinical studies

Dose finding

No results of dose response studies for the administration in patients with heart failure were submitted. Pharmacokinetic and pharmacodynamics data previously showed that 10 mg dapagliflozin near maximally inhibits SGLT2 in the kidney. The marketed 10 mg dose of dapagliflozin has demonstrated a favourable benefit/risk balance for the treatment of T2DM in the clinical development programme. 10 mg once daily is the recommended dose in patients with T2DM. A dose of 10 mg once daily was also investigated in the cardiovascular outcome study (DECLARE) showing non-inferiority vs. placebo for the composite of cardiovascular death, myocardial infarction or ischaemic stroke. At baseline, 10.0% of patients in the study had a history of heart failure. Dapagliflozin 10 mg demonstrated superiority versus placebo in preventing the composite of hospitalisation for heart failure or cardiovascular death. The difference in treatment effect was driven by hospitalisation for heart failure, with no difference in cardiovascular death. Based on these data 10 mg once daily was selected as a dose to be investigated in the DAPA HF trial. In the CHMP advice, the MAH aimed for a 3 arm study, testing both the 5 and 10 mg dose of dapagliflozin. No in depth rational is given why the 5mg dose was eventually not included in the DAPA-HF. In addition, no dose finding studies have been performed.

Efficacy

The application was based on one pivotal trial (DAPA-HF trial (Study Code D1699C00001).

The MAH has not submitted any results from clinical studies supporting the mechanism of action of dapagliflozin in patients with heart failure (HF), but only a discussion based on published references. In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid have been discussed to be relevant for cardio-renal effects of dapagliflozin In the CHMP advice given in 2016, it was expected

that the results of the pivotal would be supported by adequate data to elucidate the mechanism of action. This advice has not been followed, but the issue is not further pursued based on the rather convincing results of the pivotal study.

The DAPA-HF study

DAPA-HF was a global, event-driven, randomised, double-blind, placebo-controlled Phase III study conducted at 410 sites across 20 countries, and included 4744 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 HF events, when added to background standard of care, in patients with HFrEF in NYHA class II-IV, with T2DM or without diabetes.

The primary variable was time from randomisation to the first event included in the composite endpoint of CV death, hospitalisation for HF, or urgent HF visit. Secondary variables included time to first occurrence of either component of the primary endpoint; total number of (first and recurrent) HF hospitalisations and CV death; change from baseline, measured at 8 months, in the total symptom score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ); time to first occurrence of any component of the composite ≥50% sustained decline in estimated glomerular filtration rate (eGFR), end stage renal disease, or renal death; and time to death from any cause. Eligible patients were randomised (1:1) to dapagliflozin or placebo; randomisation was stratified based on T2DM status. Following randomisation, study visits occurred at Day 14, 60, 120, 240, and then every fourth month.
The study was event-driven; 844 primary composite endpoint events were required to have 90% power to demonstrate superiority of dapagliflozin to placebo assuming a hazard ratio (HR) of 0.80.

The study aimed to include patients with HFrEF NYHA II- IV that were optimally treated according to guidelines and that did not have hypotension or recent worsening of the condition. Patients with eGFR <30 mL/min/1.73 m^2 were excluded.

The primary endpoint is relevant and in line with CHMP guidelines. It could have been more relevant to choose all cause instead of cardiovascular mortality and such an analysis was provided at CHMP request. However, ACM is included as a secondary endpoint. Recurrent HF hospitalisations are included as a secondary endpoint. This may be a complicated endpoint from a methodological point of view due to competing risks. The KCCQ is a well-defined PRO instrument for measuring the experience of HF patients. It has been validated in patients with HF since its initial development in the mid-1990s. The MAH has submitted justifications for the clinical relevance of a 5 point improvement as being clinically relevant.

Treatment compliance was comparable in both groups. Approx 11 % discontinued treatment, with similar reasons in both groups.

Efficacy data and additional analyses

Dose finding

The rationale for the dose selection appears to be reasonable. Based on the data as outlined above 10 mg once daily was selected as a dose to be investigated in the DAPA HF trial. Few patients received dapagliflozin 5 mg once daily or matching placebo at any time during the study 1.9% and 1.6% in the dapagliflozin and placebo group, respectively, mainly due to AEs. The small number of patients exposed to dapagliflozin 5 mg prevents conclusions about the efficacy of this dose in patients with HFrEF. Although investigating an

additional lower dose would have been of scientific interest, the lack of such data is not considered a major issue of concern.

Whereas the dose of 10 mg once daily matches the dose that is recommended for the treatment of T2DM, it is higher than the dose recommended in patients with T1DM (5 mg once daily). The lower dose in T1DM was recommended based on a lack of additional efficacy at higher dose and considering that in light of possible safety concerns (DKA) the lower dose might be more appropriate. Patients with T1DM were not included in the DAPA HF trial. In the absence of data on efficacy and safety, treatment of patients with T1DM and heart failure with dapagliflozin is not recommended.

Efficacy

The mean age of the study population was 66 years and the majority (77%) of the subjects were male. Almost 50% were recruited in Europe. The median eGFR was 64 ml/min/1.73m2, 15% had eGFR below 45. The inclusion criteria stated that time since diagnosis should be at least 2 months. However, the majority had their diagnosis of HF since at least 1 year. About 50% had been hospitalised because of HF. 67.5% / 31.6% of patients had NYHA class II / III at baseline respectively, while a very small proportion were in class IV (n=43, 1% of study population). Median LVEF was 32%, 56% had an ischemic aetiology, non-ischemic 35.6% and unknown in 8.1%. 24% had AF. 42 % had T2 diabetes. The treatment groups were well balanced for all these characteristics. Median NT-proBNP was 1437 (Q1, Q3 857, 2650). 93.6% were treated with an ACEi/ARB/ARNI, 96.1% with a beta blocker, 71.0% with an MRA, and 93.4% were treated with a diuretic, most commonly a loop diuretic. HF treatment at randomisation was balanced between treatment groups. Device therapy was balanced between treatment groups: CRT-D or CRT-P (n (%) Dapa vs. Placebo): 190 (8.0) vs. 164 (6.9), ICD: 467 (19.7) 486 (20.5), ICD or CRT-D: 622 (26.2) 620 (26.1). There was little change in the administration of concomitant heart failure specific additional therapy over the course of the study (24 months) in both treatment arms with the exception of a moderate increase in the administration of Neprilysin inhibitor/ARB (ARNI). Thus, baseline treatment seems to have been adequate and according to treatment guidelines.

Primary efficacy result:

Dapagliflozin was superior to placebo in reducing the incidence of the composite of CV death or a HF event with a 26% relative risk reduction (95% CI 15% to 35%), p<0.0001. The event rate of primary endpoint events was 11.6 in the dapagliflozin treatment group and 15.6 in the placebo group. The median duration of follow-up time was 18.2 months. The effect size is considered clinically relevant and sufficiently compelling to support an application based on one pivotal trial.

The performed sensitivity analysis did not have a large influence on the results

Results for the individual components

All 3 components of the primary composite endpoint individually contributed to the overall treatment effect observed, as evidenced by the lower incidence of CV deaths, hospitalizations for HF, and urgent HF visits in the dapagliflozin treatment group compared to placebo. Although not formally tested for significance, treatment with dapagliflozin was associated with an 18% (95% CI 2% to 31%) relative risk reduction in CV death, a 30% (95% 17% to 41%) relative risk reduction in hospitalization for HF, and a 57% (95% CI 10% to 80%) relative risk reduction in urgent HF visits, compared with placebo.

The major cause of death was cardiovascular. When adding deaths from other causes, the difference is still in favour of dapagliflozin.

Secondary efficacy results

Treatment with dapagliflozin was superior to placebo in time to first event of **CV death or hospitalisation** for HF. Dapa 10 mg (n = 2373) vs. Placebo (n = 2371), n = 382 vs. 495 events, HR 0.75 (0.65, 0.85) p <0.0001 and in reducing the total numbers of events in the **composite of CV death and recurrent HF hospitalisation**. There were 567 and 742 events of CV death or hospitalisation for HF in the dapagliflozin and placebo groups, respectively, corresponding to event rates per 100 patient-years of 16.3 and 21.6, respectively (p= 0.0002). Although the effect on recurrent events is not easily interpreted in the presence of terminal events it is in this case considered to support the analyses of time to first event endpoints.

The incidence of **all-cause mortality** was numerically lower in the dapagliflozin treatment group compared with the placebo group (nominal p-value 0.0217). There were 276 and 329 patients who died in the dapagliflozin 10 mg and placebo groups, respectively, corresponding to event rates per 100 patient-years of 7.9 and 9.5. In line with the predefined hierarchical testing procedure the result is considered exploratory only. The numerical difference was largely driven by CV deaths, but also the numbers non-CV deaths and of deaths of undetermined cause were lower in the dapagliflozin treatment group.

In the DAPA-HF study, the main PRO was the KCCQ, for which the MAH investigated the clinically meaningful levels of individual change from baseline at 8 months in KCCQ-TSS. A clinically relevant improvement or deterioration in KCCQ-TSS was defined as a change from baseline of ≥5 points. The difference in responders based on this cut off (as well as for the 10 and 15% improvement cut off) compared to placebo was of statistical significance.

There were no significant differences in the incidence of the composite of ≥50% sustained decline in estimated glomerular filtration rate (eGFR), end stage renal disease, or renal death; or death from any cause. However, the cases were few.

Subgroups

Overall, the results for the primary endpoint were consistent with the overall beneficial result in most but not all of the pre-defined subgroups (age, sex, race, geographical region, NYHA class, LVEF, NTproBNP, prior hospitalisation, MRA use, diabetes status, AF, aetiology, BMI, eGFR). Consistent results for most of the subgroups were observed for the heart failure events (hospitalization for HF or urgent visit). However, there was some heterogeneity for CV and all cause deaths that in turn translated into some heterogeneity for the primary efficacy endpoint. For the primary endpoint efficacy tended to be lower in the European population (HR 0.84 (0.69, 1.01)) than in other patients, which was due to a lack of an effect on CV mortality in the European population (HR 0.97 (0.76 – 1.25)). In addition, relative efficacy was lower in patients at advanced stages of heart failure as defined by higher NYHA class (NYHA class III or IV, p for interaction 0.0087) or higher baseline NT-proBNP levels (p for interaction 0.1238). This was due to a numerically higher rate of CV deaths in patients at NYHA stage III and IV (HR 1.09 (0.85-1.41 p value for interaction 0.0023). The MAH has carefully analysed the data, without finding any credible explanation to this finding. These findings are not supported by a biological rationale, and not consistently found when other disease severity markers (LVEF, NT-proBNP, MAGGIC score and KCCQ-TSS) are used. Further, an increased risk of mortality is not supported by other safety findings in the DAPA HF study.

In addition, data in this subgroup support a positive effect on reducing hospitalisations for HF which is indeed a clinically relevant outcome. Therefore, a benefit of treatment is expected also in patients with more severe heart failure.

The effect did not seem to be influenced by eGFR at baseline, but patients with eGFR <30 were excluded from the study. Provided analyses do not indicate a risk of reduced effect based in patients with lower eGFR, but the fact that the experience is very limited is reflected in the SmPC.

2.4.4. **Conclusions on the clinical efficacy**

The MAH for dapagliflozin is applying for a new indication; *treatment of symptomatic heart failure with reduced ejection fractio*n based on one pivotal study. The study was large, multinational, randomised and placebo controlled and overall of acceptable design and conduct. Dapagliflozin was superior to placebo in reducing the incidence of the composite of CV death or a HF event with a 26% relative risk reduction (95% CI 15% to 35%), p<0.0001. This is considered as a clinically relevant effect. The effect was in general consistent in subgroups (eg in patients with and without type 2 diabetes), even if a beneficial effect on CV mortality was not seen in patients with more severe HF.

2.5. Clinical safety

Introduction

The current safety evaluation is based on data from the recently completed CV outcome study DAPA-HF.

The study population was patients with heart failure (HF) and reduced left ventricular ejection fraction (HFrEF) and included subjects with and without T2DM.

Patient exposure

The safety analysis set (SAS) included all randomised patients who received at least 1 dose of randomised study drug, i.e. 4,736 patients; 2,368 patients in the dapagliflozin group and the placebo group, respectively.

On-treatment: any event with an onset date on, or after, first dose of randomised study drug and on, or before, 30 days after last dose of study drug.

On and off treatment: any event with onset on, or after, first dose of randomised study drug regardless of whether the patient was on, or off, study treatment at the time of the event.

All summaries of AEs were presented for the SAS for both treatment periods and safety laboratory data were presented for the SAS for the on-treatment period.

Duration of exposure to study drug

The duration of exposure to study drug ranged from 0 to 28.3 months. In total, there were 3,310 patient-years of exposure to dapagliflozin in the study. The median duration of exposure to study drug was

similar between treatment groups: 17.8 months in the dapagliflozin treatment group and 17.6 months in the placebo group.

Table 19 Duration of exposure and cumulative exposure over time (SAS)

Characteristic	Statistic	Dapagliflozin 10 mg (n=2368)	Placebo (n=2368)
Duration of exposure (months)[a]	N	2368	2368
	Mean	16.8	16.6
	SD	6.3	6.5
	Minimum	0.0	0.0
	1st quartile	13.5	13.2
	Median	17.8	17.6
	Maximum	21.5	21.1
	Maximum	28.0	28.3
	Total treatment years	3310	3268
Cumulative exposure over time, n (%)[b]	≥1 day	2368 (100.0)	368 (100.0)
	≥1 month	2316 (97.8)	2317 (97.8)
	≥ 6 months	2152 (90.9)	2137 (90.2)
	≥12 months	1955 (82.6)	1905 (80.4)
	≥18 months	1168 (49.3)	1133 (47.8)
	≥24 months	261 (11.0)	255 (10.8)
Actual exposure (months)[c]	N	2368	2368
	Mean	16.6	16.4
	SD	6.3	6.5
	Minimum	0.0	0.0
	1st quartile	13.4	13.1
	Median	17.5	17.4
	Maximum	21.3	21.1
	Maximum	28.0	28.3
	Total treatment years	3285	3236

[a]Total exposure (months)= (last dose date - first dose date + 1)/30, regardless of interruptions. [b]Rows are cumulative and subjects are included if they have taken treatment up to and including that day. [c]Actual duration of exposure=Total duration of exposure, excluding interruptions

Study dose reduction

In specific cases, where a clinically relevant event of volume depletion, hypotension and/or unexpected worsening of kidney function was seen, and when these could not be resolved by reducing the dose of, or stopping concomitant, non-essential medications, reduction of dapagliflozin to 5 mg or matching placebo was allowed per protocol.

The number of patients with dose reduction of study drug was low and balanced between treatment groups. Less than 2% of patients in both treatment groups had dose reduction (45 [1.9%] patients in the dapagliflozin treatment group and 39 [1.6%] patients in the placebo group) and most of these patients did not return to the 10 mg dose of dapagliflozin or matching placebo.

The most frequent reason for dose reduction was AE: 42 (1.8%) patients in the dapagliflozin treatment group and 28 (1.2%) patients in the placebo group; SAEs that led to dose reduction were observed in 3 (0.1%) patients in the dapagliflozin treatment group and 1 (0.0%) patient in the placebo group. The most common AE that led to dose reduction of study drug was hypotension: 20 (0.8%) patients in the dapagliflozin treatment group and 11 (0.5%) patients in the placebo group.

Study drug interruption

The frequency of temporary interruption of study drug was lower in the dapagliflozin treatment group compared with the placebo group: 341 (14.4%) patients and 396 (16.7%) patients, respectively. Most patients had only 1 period of interruption. The median number of days per interruption was 13 days in the dapagliflozin treatment group and 18 days in the placebo group. The reasons for interruption were similar between treatment groups. The most common reason for interruption of study drug was AE: 277(11.7%) patients in the dapagliflozin treatment group and 330 (13.9%) patients in the placebo group. The only AE, by PT, that led to interruption of study drug in ≥1% patients overall was cardiac failure: 50 (2.1%) patients in the dapagliflozin treatment group and 78 (3.3%) patients in the placebo group.

Demographic and other characteristics of study population

At screening, the DAPA-HF study included patients with HFrEF in NYHA class II-IV, including patients with T2DM and without diabetes, and patients with baseline eGFR ≥30 mL/min/1.73 m^2.

Baseline patient characteristics were balanced between treatment groups and there were nearly equal proportions of patients with T2DM, 45.3% and 44.9%, in the dapagliflozin and placebo groups, respectively.

Adverse events

Data collection in this study focused on the following safety variables: serious AEs (SAEs), AEs leading to discontinuation (DAEs), AEs leading to dose interruption or dose reduction, and AEs of special interest, and clinical chemistry and haematological parameters.

A summary of AEs for subjects on-treatment and on and off treatment is presented in **Table 19**.

Table 20 Number of subjects with AEs in any category (SAS)

	Number (%) of subjects[a]			
	On-treatment		On and off treatment	
AE category	**Dapa 10 mg (N=2368)**	**Placebo (N=2368)**	**Dapa 10 mg (N=2368)**	**Placebo (N=2368)**
Any AE with outcome = death	227 (9.6)	250 (10.6)	286 (12.1)	333 (14.1)
Any SAE (including events with outcome death)	846 (35.7)	951 (40.2)	895 (37.8)	994 (42.0)
Any AE leading to discontinuation of IP	111 (4.7)	116 (4.9)	111 (4.7)	116 (4.9)
Any AE leading to dose interruption	284 (12.0)	349 (14.7)	284 (12.0)	349 (14.7)
Any AE leading to dose reduction	43 (1.8)	25 (1.1)	43 (1.8)	25 (1.1)
Any definite or probable diabetic ketoacidosis[b]	3 (0.1)	0	3 (0.1)	0
Any major hypoglycemic event[c]	4 (0.2)	4 (0.2)	4 (0.2)	4 (0.2)
Any event of symptoms of volume depletion[d]	170 (7.2)	153 (6.5)	178 (7.5)	162 (6.8)
Any fracture[d]	48 (2.0)	47 (2.0)	49 (2.1)	50 (2.1)
Any renal AE[d]	141 (6.0)	158 (6.7)	153 (6.5)	170 (7.2)
Any amputation[e]	11 (0.5)	11 (0.5)	13 (0.5)	12 0.5)

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories. [b] Events adjudicated as definite or probable diabetic ketoacidosis. [c] AE with the following criteria confirmed by the investigator: i) Symptoms of severe impairment in consciousness or behaviour ii) need of external assistance iii) intervention to treat hypoglycaemia iv) prompt recovery of acute symptoms following the intervention. [d] Based on pre-defined list of preferred terms. [e]Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma.

Serious adverse events and deaths

Deaths

During the on and off treatment period, the number of patients who died were fewer in the dapagliflozin treatment group compared with the placebo group: 286 (12.1%) patients and 333 (14.1%) patients, respectively. The 3 most commonly reported AEs with an outcome of death in the dapagliflozin treatment group were: cardiac failure, death and sudden death; and in the placebo group they were: cardiac failure, death and sudden cardiac death.

During the *on-treatment period*, there were 227 patients (9.6%) in the dapagliflozin treatment group and 250 patients (10.6%) in the placebo group who died.

For a summary of CV death, renal death, and all-cause mortality as efficacy endpoints, see the efficacy part of this report.

Serious adverse events

During the on-treatment period, the numbers of patients with SAEs were fewer in the dapagliflozin treatment group compared with the placebo group: 846 (35.7%) patients and 951 (40.2%) patients, respectively. The most frequently reported SAEs for dapagliflozin vs placebo were cardiac failure (10% vs 14%), pneumonia (3.0% vs 3.1%), cardiac failure congestive (2.4% vs 2.7%) and cardiac failure acute (1.5% vs 2.2%).

Table 21 Number of subjects with serious adverse events (frequency ≥ 0.5%) by preferred term - on treatment (SAS)

Preferred term	Number (%) of subjects[a]	
	Dapa 10mg (N=2368)	Placebo (N=2368)
Subjects with any SAE	846 (35.7)	951 (40.2)
Cardiac failure	238 (10.1)	325 (13.7)
Pneumonia	70 (3.0)	73 (3.1)
Cardiac failure congestive	57 (2.4)	65 (2.7)
Cardiac failure acute	36 (1.5)	51 (2.2)
Death	33 (1.4)	38 (1.6)
Acute myocardial infarction	32 (1.4)	32 (1.4)
Ventricular tachycardia	32 (1.4)	53 (2.2)
Cardiac failure chronic	24 (1.0)	26 (1.1)
Ischaemic stroke	24 (1.0)	24 (1.0)
Atrial fibrillation	23 (1.0)	37 (1.6)
Angina unstable	21 (0.9)	29 (1.2)
Acute kidney injury	20 (0.8)	41 (1.7)
Sudden cardiac death	17 (0.7)	27 (1.1)
Sudden death	17 (0.7)	7 (0.3)
Chronic obstructive pulmonary disease	14 (0.6)	22 (0.9)
Myocardial infarction	14 (0.6)	17 (0.7)

Transient ischaemic attack	13 (0.5)	7 (0.3)
Angina pectoris	12 (0.5)	12 (0.5)
Bronchitis	11 (0.5)	6 (0.3)
Peripheral arterial occlusive disease	11 (0.5)	9 (0.4)
Sepsis	10 (0.4)	11 (0.5)
Urinary tract infection	10 (0.4)	16 (0.7)
Cardiogenic shock	9 (0.4)	12 (0.5)
Acute respiratory failure	7 (0.3)	13 (0.5)
Cerebral infarction	7 (0.3)	11 (0.5)
Pulmonary embolism	7 (0.3)	13 (0.5)
Syncope	7 (0.3)	12 (0.5)
Non-cardiac chest pain	6 (0.3)	14 (0.6)

Adverse events of special interest and other analysis

AEs of special interest: AEs suggestive of volume depletion, renal AEs, diabetic ketoacidosis (DKA), major hypoglycaemic events and fractures.

Additional safety analysis: UTIs, genital infections and Fournier's gangrene.

Results from all pre-specified sub-group analyses (age [≤65, >65], baseline eGFR [<60, ≥60 mL/min/1.73 m^2], and baseline systolic BP [<130, ≥130 mmHg]) and additional post-hoc subgroup analyses (baseline renal function and baseline diabetes status) are presented in section Special populations.

AEs suggestive of volume depletion

During the on-treatment period, the frequency of any AEs suggestive of volume depletion was 7.2% (n=170) in the dapagliflozin treatment group and 6.5% (n=153) in the placebo group, corresponding to event rates of 5.09 and 4.64 events per 100 patient-years, respectively. DAEs were <0.5% patients in both treatment groups. There were fewer patients with SAEs in the dapagliflozin treatment group compared with the placebo group: 23 (1.0%) patients and 38 (1.6%) patients, respectively.

The most commonly reported AEs were hypotension, dehydration, and hypovolaemia. Results from sub-group analyses, see section Special population.

MAHs proposal to remove volume depletion from the SmPC

In the DECLARE study, in patients with T2DM, the event rates of volume depletion were 0.7 events per 100 patient-years in both the dapagliflozin treatment group and the placebo group. The event rate of volume depletion in the DAPA-HF study was substantially higher, corresponding to 5.1 and 4.6 events per 100 patient-years in the dapagliflozin treatment group and placebo group, respectively. The higher incidence of volume depletion reflects that HFrEF patients are susceptible to side effects like volume

depletion and renal events when treated with currently approved and guidelines recommended therapy. Despite this, the DAPA-HF study showed no increase in the incidence of volume depletion with dapagliflozin treatment compared with the placebo group. The numbers of AEs and DAEs suggestive of volume depletion were balanced between treatment groups and there were fewer patients with SAEs in the dapagliflozin treatment group (23 patients) compared with the placebo group (38 patients).

It is the MAH's position that the combined findings of these 2 CVOTs allow the conclusion that treatment with dapagliflozin does not increase the risk for volume depletion. This conclusion is supported by the fewer SAEs suggestive of volume depletion with dapagliflozin treatment in the DAPA-HF population, which was at high risk for volume depletion both due to the intercurrent condition and concomitant medication. Thus, the MAH considers that there is no longer a need for a recommendation to interrupt treatment with dapagliflozin in patients with volume depletion.

The Applicant was requested to provide a further justification for the removal of volume depletion from section 4.4.

Assessment of the Response concluded that in the DAPA-HF study, events suggestive of volume depletion was overall increased compared to the clinical development programme, most likely reflecting treatment in a more vulnerable patient population. However, the incidence of volume depletion was slightly higher for dapagliflozin compared with placebo in both the clinical development programme (1.1% vs 0.7%) and the DAPA-HF study (7.2% vs 6.5%), indicating that dapagliflozin contributes to the events of volume depletion; most of the events were non-serious.

The adverse event 'volume depletion' includes several predefined preferred terms, e.g. dehydration, hypovolaemia and hypotension. One single predefined PT might have been reported as a non-serious event; however, the consequence of the contributed volume depletion with dapagliflozin treatment is still considered to be a risk that could become serious, especially in vulnerable patients or in case of intercurrent conditions due to gastrointestinal illness. Moreover, the increased risk of haematocrit with dapagliflozin is most likely due to volume depletion. Therefore, the following warning in section 4.4 regarding the risk of volume depletion on an individual basis should be kept:
"*In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8)*"

Renal adverse events

During the on-treatment period, the frequency of renal events was 6.0% (n=141) in the dapagliflozin treatment group and 6.7% (n=158) patients in the placebo group, corresponding to event rates of 4.22 and 4.79 events per 100 patient-years, respectively. DAEs were <0.5% patients in both treatment groups. SAEs were fewer in the dapagliflozin treatment group compared with the placebo group: 34 (1.4%) patients and 58 (2.4%) patients, respectively.

Table 22 Summary of renal adverse events – on treatment (SAS)

	Dapa 10mg (N=2368)	**Placebo (N=2368)**
	Number (%) of subjects	
Subjects with any renal AE	141 (6.0)	158 (6.7)
Event rate per 100 subject years	4.22	4.79
Any SAE	34 (1.4)	58 (2.4)

With outcome death	4 (0.2)	1 (0.0)
SAE excluding death	31 (1.3)	57 (2.4)
Any DAE	8 (0.3)	9 (0.4)
Any SAE leading to discontinuation of IP	5 (0.2)	5 (0.2)
Any AE leading to dose reduction	6 (0.3)	3 (0.1)
Any AE leading to interruption	19 (0.8)	30 (1.3)
Maximum intensity		
Mild	54 (2.3)	50 (2.1)
Moderate	77 (3.3)	71 (3.0)
Severe	22 (0.9)	44 (1.9)
Any AE possibly related to IP	33 (1.4)	28 (1.2)

Source: CSR Table 14.3.10.5

SAEs of AKI were reported for 20 [1.0%] patients in the dapagliflozin treatment group and 41 [1.7%] patients in the placebo group (**Table 20**).

The most commonly reported AEs for dapagliflozin vs placebo were renal impairment (2.8% vs 2.7%), AKI (1.8% vs 2.6%), and renal failure (1.6% vs 1.6%).

Results from sub-group analyses, see section Special population.

Diabetic ketoacidosis

All potential events of DKA were submitted to an independent, blinded DKA Adjudication Committee and assigned a likelihood of being DKA.

Three patients had an event adjudicated as definite DKA; no events were adjudicated as probable DKA. All 3 events were from the dapagliflozin treatment group during the on-treatment period.

All 3 patients were treated with anti-diabetic medication during the study, of which 1 patient was on concomitant insulin treatment. Contributing factors reported were: infection, illness, poor intake of food/drink, and dehydration.

One event had a fatal outcome. An elderly female patient with a history of T2DM treated with metformin and gliclazide, was hospitalised on day 399, after being found unconscious at home. At admission, the laboratory data revealed hyperglycaemia, ketonaemia, and ketonuria. The patient was suspected to have stopped her antidiabetic treatment. Concurrently, the patient was diagnosed with renal insufficiency and exacerbation of chronic pyelonephritis. The patient died 8 days later with a primary cause of death reported as diabetic ketoacidotic hyperglycaemic coma and secondary cause of death reported as polyorganic insufficiency.

Major hypoglycaemic events

Major hypoglycaemia was defined as an event that required assistance of another person to actively administer carbohydrates, glucagon, or to take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the corrective actions was considered sufficient evidence that the event was induced by a low plasma glucose concentration. Major hypoglycaemic episodes were recorded in the electronic case report form (eCRF) as an AE and on an additional eCRF page.

During the on-treatment period, there were 9 major hypoglycaemic events in 8 patients, 4 patients in each treatment group.

All patients with major hypoglycaemic events had T2DM at baseline; see section Special populations.

Patients with major hypoglycaemic events in both treatment groups were using sulphonylureas or insulin, or a combination, at the time of event, except for 1 patient in the placebo group who was not taking anti-diabetic medication at the time of the event.

Fractures

During the on and off treatment period, the frequency of fractures was 2.1% (n=49) in the dapagliflozin treatment group and 2.1% (n=50) in the placebo group, corresponding to event rates of 1.38 and 1.42 events per 100 patient-years, respectively.

Results from sub-group analyses, see section Special population.

Amputations

During the on and off treatment period, the number of patients who underwent at least 1 surgical amputation were balanced between treatment groups: 13 (0.5%) and 12 (0.5%) patients in the dapagliflozin and placebo groups, respectively. Most patients had one amputation (7 patients in the dapagliflozin treatment group and 9 patients in the placebo group); all were lower limb surgical amputations.

Table 23 Amputation by type of event and location – on and off treatment (SAS)

	Dapa 10m (N=2368)	Placebo (N=2368)
Category		
Subjects with at least one amputation	13 (0.5)	12 (0.5)
1 amputation	7 (0.3)	9 (0.4)
2 amputations	3 (0.1)	2 (0.1)
3 amputations	1 (0.0)	1 (0.0)
>3 amputations	2 (0.1)	0
Patients with event per 100 pat-years	0.37	0.34
Type of event		
Trauma by accident	0	0
Surgical amputation	13 (0.5)	12 (0.5)
Spontaneous/non-surgical amputation	0	0
Anatomic localisation		
Lower limb amputation	13 (0.5)	12 (0.5)
Big toe	3 (0.1)	2 (0.1)
Index toe	3 (0.1)	4 (0.2)
Middle toe	7 (0.3)	0
Fourth toe	4 (0.2)	1 (0.0)
Little toe	3 (0.1)	3 (0.1)
Trans metatarsal	2 (0.1)	1 (0.0)
Foot	0	0
Below knee	1 (0.0)	1 (0.0)
Above knee	4 (0.2)	1 (0.0)
Other	0	2 (0.1)

Source: CSR Table 14.3.11.5

Conditions that triggered amputation were similar between treatment groups. The most common condition that triggered amputation was infection, occurring in 9 patients in both the dapagliflozin and placebo groups.

Events leading to a risk for lower limb amputation ("preceding events")

Collection of data on events leading to a risk for lower limb amputations "preceding events", including cases that did not result in an amputation, was added as a regulatory requirement by the EMA/PRAC for all clinical trials which included SGLT2 inhibitors and were more than 12 weeks in duration.

During the on and off treatment period, the number of patients with "preceding events" was 155 (6.5%) patients in the dapagliflozin treatment group and 120 (5.1%) patients in the placebo group. Of these patients, the number of patients who underwent subsequent amputations was 13 patients in the dapagliflozin treatment group, and 10 patients in the placebo group.

Table 24 Adverse events related to risk for lower limb amputation by PRAC categories and preferred term - on and off treatment (SAS)

	Dapa 10mg (N=2368)	Placebo (N=2368)
Subjects with AE related to risk for lower limb amputation	**155 (6.5)**	**120 (5.1)**
Diabetic foot related AEs	**46 (1.9)**	**46 (1.9)**
Cellulitis	17 (0.7)	22 (0.9)
Diabetic foot	8 (0.3)	3 (0.1)
Osteomyelitis	7 (0.3)	3 (0.1)
Skin ulcer	7 (0.3)	9 (0.4)
Postoperative wound infection	3 (0.1)	1 (0.0)
Gangrene	2 (0.1)	6 (0.3)
Infected skin ulcer	2 (0.1)	1 (0.0)
Localised infection	2 (0.1)	4 (0.2)
Cellulitis gangrenous	1 (0.0)	0
Diabetic foot infection	1 (0.0)	0
Diabetic gangrene	1 (0.0)	0
Dry gangrene	1 (0.0)	1 (0.0)
Extremity necrosis	1 (0.0)	0
Skin erosion	1 (0.0)	0
Osteitis	0	1 (0.0)
Nervous System Disorders	**8 (0.3)**	**4 (0.2)**
Paraesthesia	4 (0.2)	1 (0.0)
Diabetic neuropathy	2 (0.1)	0
Hypoaesthesia	2 (0.1)	0
Autonomic neuropath y	0	1 (0.0)
Neuropathy peripheral	0	3 (0.1)
Vascular AEs	**39 (1.6)**	**21 (0.9)**
Peripheral arterial occlusive disease	18 (0.8)	13 (0.5)
Peripheral ischaemia	10 (0.4)	5 (0.2)
Peripheral artery occlusion	3 (0.1)	2 (0.1)
Peripheral artery stenosis	3 (0.1)	0
Intermittent claudication	2 (0.1)	0
Arterial stenosis	1 (0.0)	0
Peripheral coldness	1 (0.0)	0
Peripheral vascular disorder	1 (0.0)	0
Thrombosis	1 (0.0)	0
Diabetic vascular disorder	0	1 (0.0)
Iliac artery occlusion	0	1 (0.0)

Poor peripheral circulation	0	1 (0.0)
Volume depletion	**68 (2.9)**	**51 (2.2)**
Dehydration	35 (1.5)	29 (1.2)
Hypovolaemia	34 (1.4)	23 (1.0)
Wound/Infection	**9 (0.4)**	**9 (0.4)**
Wound infection	6 (0.3)	0
Impaired healing	1 (0.0)	0
Wound	1 (0.0)	4 (0.2)
Wound complication	1 (0.0)	1 (0.0)
Abscess limb	0	2 (0.1)
Skin infection	0	2 (0.1)

Additional safety analysis

Fournier's gangrene

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

Six cases indicating genital area infections or necrotizing fasciitis were identified for medical assessment; 3 cases in the dapagliflozin group and 3 cases in the placebo group. None of these events were confirmed as Fournier's gangrene.

Urinary tract infections

During the on-treatment period, the number of patients with SAEs and DAEs of UTI was 18 (0.8%) for dapagliflozin and 22 (0.9%) for placebo. Most patients only experienced 1 event (18 patients in the dapagliflozin group and 20 patients in the placebo group). Recurrent events were experienced by 2 patients, both of whom were in the placebo group.

The effect of diabetes status is discussed in section Special populations.

Genital infections

During the on-treatment period, SAEs and DAEs of genital infections were rare. Only 1 patient had an SAE of genital infection, in the placebo group. Seven patients, all in the dapagliflozin treatment group, had a DAE of genital infection.

The effect of diabetes status is discussed as an intrinsic factor in section Special populations.

Laboratory findings

Haematology

Mean haematocrit levels increased early and plateaued after month 4 in the dapagliflozin treatment group. The increase was not considered clinically relevant.

An increase from baseline to week 52 in haematocrit concentration was observed for dapagliflozin (7.3%) compared to placebo (0%). At 28 months, the increase was 4.9% for dapagliflozin relative 0% for placebo. Increased haematocrit is adequately labelled (frequency 'common') for dapagliflozin.

Table 25 Hematocrite 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
Hematocrit	ratio	Dapa 10mg (N=2368)	Baseline	2346	0.41	0.05	0.38	0.41	0.45	2346					
			14 days	2250	0.42	0.05	0.39	0.42	0.45	2244	0.01	0.03	-0.01	0.01	0.02
			2 Months	2188	0.43	0.05	0.40	0.43	0.47	2168	0.02	0.03	0.00	0.02	0.04
			4 Months	2148	0.44	0.05	0.41	0.44	0.47	2128	0.02	0.04	0.00	0.02	0.05
			8 Months	2031	0.44	0.05	0.41	0.44	0.47	2011	0.02	0.04	0.00	0.02	0.05
			12 Months	1946	0.44	0.05	0.41	0.45	0.47	1925	0.03	0.04	0.00	0.03	0.05
			16 Months	1596	0.44	0.05	0.41	0.44	0.48	1577	0.03	0.04	0.00	0.03	0.05
			20 Months	1082	0.44	0.05	0.41	0.44	0.47	1064	0.02	0.04	0.00	0.02	0.05
			24 Months	461	0.44	0.05	0.41	0.44	0.48	452	0.02	0.04	0.00	0.02	0.05
			28 Months	55	0.44	0.05	0.41	0.44	0.49	55	0.03	0.04	0.00	0.04	0.05
		Placebo (N=2368)	Baseline	2345	0.42	0.05	0.38	0.41	0.45	2345					
			14 days	2248	0.41	0.05	0.38	0.41	0.45	2239	-0.00	0.03	-0.02	0.00	0.01
			2 Months	2206	0.41	0.05	0.38	0.41	0.45	2188	-0.00	0.03	-0.02	0.00	0.02
			4 Months	2132	0.41	0.05	0.38	0.41	0.45	2114	-0.00	0.03	-0.02	0.00	0.02
			8 Months	2009	0.41	0.05	0.38	0.41	0.45	1992	-0.00	0.04	-0.02	0.00	0.02
			12 Months	1883	0.42	0.05	0.38	0.41	0.45	1868	-0.00	0.04	-0.02	0.00	0.02
			16 Months	1571	0.42	0.05	0.38	0.42	0.45	1557	0.00	0.04	-0.02	0.00	0.02
			20 Months	1060	0.42	0.05	0.38	0.42	0.45	1047	-0.00	0.04	-0.02	0.00	0.02
			24 Months	464	0.42	0.05	0.38	0.42	0.45	459	-0.00	0.04	-0.02	0.00	0.02
			28 Months	55	0.42	0.05	0.39	0.42	0.45	55	0.00	0.03	-0.02	0.00	0.03

Clinical chemistry

Mean changes in blood alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST), total bilirubin, blood urea nitrogen, serum creatinine, glycated haemoglobin (HbA1c), N-terminal pro b-type natriuretic peptide (NT-proBNP), phosphate, potassium, sodium, and eGFR were presented at baseline and over time.

There were no clinically relevant mean changes in blood ALT, ALP, AST, and total bilirubin, and blood urea nitrogen in either treatment group.

Creatinine/ eGFR

There were increases in mean serum creatinine in both treatment groups over time. This mean increase occurred early in the dapagliflozin treatment group. Consequently, there was a decrease in eGFR, which was initially more pronounced, in the dapagliflozin treatment group compared with the placebo group. At 20 months, change from baseline in eGFR was similar between the treatment groups.

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 10mg (N=2368)	Baseline	2367	104.0	29.7	83.0	99.0	120.0	2367					
			14 days	2306	110.8	33.5	86.6	105.0	128.0	2306	6.8	16.6	-2.0	6.0	14.0
			2 Months	2227	109.7	33.1	86.0	104.0	126.0	2226	5.6	18.0	-4.0	5.0	13.3
			4 Months	2184	109.0	33.7	86.8	103.0	126.0	2183	5.3	21.0	-4.0	4.0	13.3
			8 Months	2067	108.9	32.6	85.7	103.0	126.0	2066	5.5	19.8	-5.0	4.0	14.0
			12 Months	1966	109.3	34.4	86.0	102.0	126.0	1965	6.4	21.8	-4.4	5.0	15.0
			16 Months	1625	110.5	34.7	87.0	103.0	126.4	1625	7.8	23.1	-3.5	6.0	17.0
			20 Months	1115	110.8	36.3	86.0	103.0	127.0	1115	8.8	23.7	-4.0	6.0	18.0
			24 Months	477	111.6	34.8	88.0	103.0	128.0	477	9.1	24.4	-4.0	8.0	18.0
			28 Months	56	108.9	27.2	93.0	108.0	120.5	56	10.1	16.7	0.0	6.0	17.5
		Placebo (N=2368)	Baseline	2367	104.9	31.1	84.0	100.0	119.0	2367					
			14 days	2307	105.8	30.8	83.0	101.0	122.0	2306	0.9	15.2	-7.0	1.0	8.0
			2 Months	2244	105.3	31.6	83.0	100.0	120.0	2243	0.9	18.3	-7.0	0.0	9.0
			4 Months	2170	105.6	31.9	84.0	99.9	120.0	2169	1.2	18.9	-8.0	1.0	9.0
			8 Months	2043	107.6	33.2	84.0	102.0	123.8	2042	3.5	21.2	-7.0	2.0	12.0
			12 Months	1922	107.5	33.6	84.0	101.0	123.8	1921	4.0	22.5	-7.0	2.0	13.0
			16 Months	1602	108.8	35.0	85.0	102.0	126.0	1602	6.0	24.6	-6.0	4.0	15.0
			20 Months	1080	110.7	37.5	87.0	102.5	124.0	1080	6.5	28.3	-6.0	4.0	15.0
			24 Months	479	112.7	36.3	88.4	104.3	128.0	479	7.6	29.6	-5.3	4.0	15.0
			28 Months	55	117.7	40.3	85.7	104.0	155.0	55	9.3	29.2	-8.0	3.0	24.0

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/1.73m^2	Dapa 10mg (N=2368)	Baseline	2367	66.0	19.5	51.0	64.0	80.0	2367					
			14 days	2305	61.7	20.5	45.0	60.0	77.0	2305	-4.3	8.2	-9.0	-4.0	1.0
			2 Months	2227	62.5	20.7	46.0	60.0	78.0	2226	-3.5	9.4	-9.0	-3.0	2.0
			4 Months	2184	62.7	20.3	47.0	60.0	77.0	2183	-3.5	9.7	-9.0	-3.0	2.0
			8 Months	2067	62.6	20.4	47.0	60.0	77.0	2066	-3.7	10.3	-9.0	-3.0	2.0
			12 Months	1966	62.5	20.5	47.0	61.0	77.0	1965	-4.0	10.6	-10.0	-4.0	2.0
			16 Months	1629	61.3	19.9	46.0	60.0	76.0	1629	-5.2	11.2	-12.0	-5.0	1.0
			20 Months	1117	61.1	20.3	45.0	60.0	75.0	1117	-5.3	11.4	-12.0	-5.0	1.0
			24 Months	477	59.8	19.3	45.0	60.0	72.0	477	-6.0	11.7	-13.0	-6.0	1.0
			28 Months	56	59.5	18.5	45.0	56.0	69.5	56	-6.6	9.5	-11.0	-6.0	-0.5
		Placebo (N=2368)	Baseline	2367	65.6	19.3	51.0	64.0	79.0	2367					
			14 days	2309	64.5	20.1	49.0	63.0	78.0	2308	-1.1	8.0	-5.0	-1.0	3.0
			2 Months	2244	64.9	20.0	50.0	64.0	80.0	2243	-0.9	9.1	-6.0	-1.0	4.0
			4 Months	2170	64.6	19.9	50.0	64.0	79.0	2169	-1.2	9.1	-6.0	-1.0	4.0
			8 Months	2043	63.5	20.4	48.0	62.0	78.0	2042	-2.6	10.7	-8.0	-2.0	3.0
			12 Months	1923	63.5	20.5	48.0	62.0	78.0	1922	-2.9	11.0	-9.0	-2.0	4.0
			16 Months	1602	62.5	20.5	47.0	61.0	77.0	1602	-4.1	11.3	-11.0	-3.0	3.0
			20 Months	1080	60.7	19.3	46.0	59.0	73.5	1080	-4.5	11.2	-11.0	-4.0	2.0
			24 Months	479	59.3	19.1	45.0	59.0	74.0	479	-5.1	12.7	-12.0	-4.0	1.0
			28 Months	55	56.7	20.4	37.0	58.0	69.0	55	-3.8	13.1	-12.0	-2.0	4.0

There was an increase in serum creatinine (6.5% vs 0.9%) and a decrease in eGFR (-6.5% vs -1.7%) for dapagliflozin vs placebo 14 days after treatment was initiated. The eGFR values for dapagliflozin vs placebo changed over time as follows: At 2 months: -5.3% vs -1.4%, 4 months: -5.3% vs -2.0%, 8 months: -5.6% vs -4.1%, 12 months: -6.1% vs -4.7%, 16 months: -7.9% vs -6.6%, 20 months: -8.0% vs -7.0%, 24 months: -9.4% vs -8.1% and 28 months: -10% vs -7.9%). The serum creatinine increased similarly over time. In the DAPA-HF study, eGFR decreased over time in both the dapagliflozin and the placebo group. The change in eGFR was initially (within 2 weeks) more pronounced

for dapagliflozin compared to placebo (-6.5% vs -1.7%); however, the difference between dapagliflozin and placebo was less noticeable at month 20 (-8.0% vs -7.0%) and onwards.

HbA1C

Mean changes in glycated haemoglobin (HbA1c) was presented at baseline and over time.

Marked laboratory abnormalities

Marked laboratory abnormalities of ALT, AST and bilirubin below

Table 28 Marked abnormalities of ALT, AST and bilirubin

	Number (%) of subjects[a]	
	Dapa 10mg (N=2368)	**Placebo (N=2368)**
ALT (µkat/L) [a]		
Number of subjects with any on-treatment value	1869	1809
>3x ULN	5 (0.3)	5 (0.3)
>5x ULN	2 (0.1)	3 (0.2)
>10x ULN	1 (0.1)	1 (0.1)
>20x ULN	0	1 (0.1)
AST (µkat/L) [a]		
Number of subjects with any on-treatment value	1849	1783
>3x ULN	3 (0.2)	6 (0.3)
>5x ULN	2 (0.1)	3 (0.2)
>10x ULN	1 (0.1)	2 (0.1)
>20x ULN	0	2 (0.1)
Total bilirubin (µmol/L) [a]		
Number of subjects with any on-treatment value	1875	1816
>1.5x ULN	35 (1.9)	28 (1.5)
>2x ULN	9 (0.5)	8 (0.4)

There were 0.3% in both treatment groups meeting the criteria of ALT >3x upper limit of normal and 0.2% vs 0.3% for dapagliflozin vs placebo meeting the criteria of AST >3x ULN. Total bilirubin >3x ULN was 1.9% and 1.5% for dapagliflozin and placebo, respectively.

Vital signs and physical findings

Body weight

There was a decrease in mean body weight in the dapagliflozin treatment group compared to the placebo treatment group (-1.4 kg in the dapagliflozin treatment group and -0.0 kg in the placebo group at month 20).

Table 29 (update) Vital signs variables over time - on treatment (SAS); change in weight

				Result						Change from baseline					
Vital signs variable	SI-unit	Group	Time point	n	Mean	SD	Q1	Median	Q3	n	Mean	SD	Q1	Median	Q3
Weight	kg	Dapa 10mg (N=2368)	Baseline	2368	80.7	20.0	67.0	79.0	92.0	2368					
			14 days	2324	80.3	19.9	66.0	79.0	92.0	2324	-0.5	1.6	-1.0	0.0	0.0
			2 Months	2244	80.1	19.9	66.0	78.0	92.0	2244	-0.7	2.3	-2.0	-0.5	0.1
			4 Months	2199	80.1	19.9	66.0	78.0	91.4	2199	-0.7	3.6	-2.0	-0.6	1.0
			8 Months	2086	80.0	19.7	66.0	78.0	91.6	2086	-0.9	3.9	-3.0	-1.0	1.0
			12 Months	1983	79.8	19.7	66.0	78.0	91.0	1983	-1.1	4.4	-3.3	-1.0	1.0
			16 Months	1643	79.7	19.6	66.0	78.0	91.0	1643	-1.1	4.9	-4.0	-1.0	1.4
			20 Months	1117	80.8	19.4	67.0	80.0	92.0	1117	-1.4	5.2	-4.0	-1.0	1.2
			24 Months	478	81.6	19.3	67.8	80.0	93.9	478	-1.6	5.6	-4.7	-1.3	1.5
			28 Months	57	88.4	20.3	72.0	88.0	100.0	57	-3.0	6.9	-6.0	-3.0	-0.9
		Placebo (N=2368)	Baseline	2368	80.7	20.5	66.0	78.0	93.0	2368					
			14 days	2328	80.6	20.5	66.0	78.0	93.0	2328	0.0	1.7	-1.0	0.0	1.0
			2 Months	2258	80.8	20.6	66.0	78.6	93.0	2258	0.0	2.5	-1.0	0.0	1.0
			4 Months	2185	80.9	20.7	66.0	78.9	93.0	2185	0.0	3.2	-1.2	0.0	1.8
			8 Months	2065	81.0	20.7	67.0	79.0	93.9	2065	0.2	4.0	-2.0	0.0	2.0
			12 Months	1938	81.0	20.9	66.0	78.9	93.0	1938	0.1	4.5	-2.0	0.0	2.0
			16 Months	1612	81.2	20.3	67.0	79.0	93.0	1612	0.2	4.9	-2.1	0.0	3.0
			20 Months	1091	81.6	19.8	68.0	79.0	93.4	1091	0.0	5.5	-3.0	0.0	3.0
			24 Months	487	83.9	19.7	70.0	83.0	95.9	487	0.4	6.0	-3.0	0.0	3.0
			28 Months	56	88.5	21.1	72.0	84.0	97.3	56	-0.2	5.5	-3.0	-1.0	3.3

There was a decrease in mean body weight over time in the dapagliflozin group compared to placebo; -1.4% vs 0.1% at 16 months, -1.7% vs 0% at 20 months, -2.0% vs 0.2% at 24 months and -3.6% vs -0.2% at 28 months. Weight loss in HF patients could be associated with increased mortality. The Applicant was asked to present weight loss in different BMI-strata and to address if mortality was increased in subjects with weight loss. Assessment of the applicant`s response showed that weight loss over time was more pronounced in subjects with higher BMI at baseline (>35 and 30-35 kg/m2) compared with subjects with lower baseline BMI (25-30 and 20-25 kg/m2). However, the incidence of all-cause mortality was numerically lower in the dapagliflozin group compared with placebo; overall and across BMI strata.

Blood pressure

Systolic blood pressure (SBP) declined from baseline in the dapa group. The decline was most pronounced (-3.1 mmHg) early in the study (at Day 14). Thereafter, SBP tended to increase again with some fluctuation up to Month 20.

Table 30 SBP (update) [mmHg] change from baseline; baseline mean, 122.1 mmHg - Dapa 10mg

Time point	N	**Mean**	SD	Q1	Median	Q3
14 days	2326	**-3.1**	12.3	-10.0	-2.0	3.3
2 Months	2245	**-2.5**	13.7	-10.0	-2.0	5.3
4 Months	2201	**-2.6**	14.4	-11.0	-2.3	5.7
8 Months	2088	**-1.9**	14.9	-11.0	-1.3	7.3
12 Months	1985	**-2.3**	15.2	-11.7	-2.3	7.0
16 Months	1644	**-2.5**	15.7	-12.0	-3.0	7.3
20 Months	1120	**-2.7**	15.8	-11.7	-3.3	6.7
24 Months	478	**-3.5**	15.2	-13.3	-4.7	5.7
28 Months	57	**-4.8**	13.6	-10.7	-2.7	3.3

Source: CSR Table 14.3.15

Table 31 SBP (update) [mmHg] change from baseline; baseline mean, 121.6 mmHg - Placebo

Time point	n	**Mean**	SD	Q1	Median	Q3
14 days	2328	**-0.5**	12.0	-6.7	-0.3	6.0

2 Months	2258	**-0.4**	13.3	-8.0	-0.7	7.0
4 Months	2188	**-0.6**	13.9	-9.0	-0.3	7.7
8 Months	2070	**-0.3**	15.2	-9.3	-0.3	7.7
12 Months	1941	**-0.6**	15.1	-9.3	0.0	8.3
16 Months	1615	**-0.3**	15.5	-10.3	-0.3	9.3
20 Months	1091	**-0.4**	16.0	-10.0	-0.3	9.3
24 Months	487	**-1.9**	13.8	-10.0	-1.0	6.0
28 Months	56	**-6.2**	13.1	-14.7	-6.2	3.5

Source: CSR Table 14.3.15

Safety in special populations

Intrinsic factors

Effect of T2DM

At baseline, 2,136 (45.1%) patients had T2DM and 2,600 (54.9%) patients did not have diabetes. The effect of diabetes at baseline was analysed for SAEs, DAEs and the AEs of special interest and additionally for UTIs and genital infections (**Table 31**).

Table 32 Number of subjects with adverse events in any category – by diabetes status

	AE category	**T2DM at baseline: YES**		**T2DM at baseline: NO**	
		Number (%) subjects[a,b]		**Number (%) subjects[a,b]**	
		Dapa 10 mg (N=1073)	**Placebo (N=1063)**	**Dapa 10 mg (N=1,295)**	**Placebo (N=1,305)**
Any AE with outcome = death[e]		147 (13.7)	179 (16.8)	139 (10.7)	154 (11.8)
Any SAE (including events with outcome = death)[d]		426 (39.7)	496 (46.7)	420 (32.4)	455 (34.9)
Any AE leading to discontinuation of IP[d]		43 (4.0)	57 (5.4)	68 (5.3)	59 (4.5)
AEs of symptoms of volume depletion[c,d]	Any AE	79 (7.4)	80 (7.5)	91 (7.0)	73 (5.6)
	Any SAE	9 (0.8)	26 (2.4)	14 (1.1)	12 (0.9)
	Any DAE	4 (0.4)	4 (0.4)	5 (0.4)	4 (0.3)
Renal AEs[c,d]	Any AE	84 (7.8)	87 (8.2)	57 (4.4)	71 (5.4)
	Any SAE	22 (2.1)	32 (3.0)	12 (0.9)	26 (2.0)
	Any DAE	4 (0.4)	4 (0.4)	4 (0.3)	5 (0.4)
Urinary tract infections[c,d]	Any SAE	7 (0.7)	10 (0.9)	7 (0.5)	7 (0.5)
	Any DAE	2 (0.2)	2 (0.2)	3 (0.2)	3 (0.2)
Genital infections[c,d]	Any SAE	0	1 (0.1)	0	0
	Any DAE	2 (0.2)	0	5 (0.4)	0

Any definite or probable diabetic ketoacidosis[d,f]	Any AE	3 (0.3)	0	0	0
Any major hypoglycemic event[d,g]	Any AE	4 (0.4)	4 (0.4)	0	0
Any fracture[c, e]	Any AE	22 (2.1)	25 (2.4)	27 (2.1)	25 (1.9)
Any amputation[e,h]	Any AE	12 (1.1)	9 (0.8)	1 (0.1)	3 (0.2)

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than1 category are counted once in each of those categories. [b] Subject numbers for the on-treatment and on and off treatment groups were identical. [c] Based on pre-defined list of preferred terms. [d] Based on the on-treatment period. [e] Based on the on and off treatment period. [f] Events adjudicated as definite or probable diabetic ketoacidosis. [g]AE with the following criteria confirmed by the investigator: i) Symptoms of severe impairment in consciousness or behaviour ii) need of external assistance iii) intervention to treat hypoglycaemia iv) prompt recovery of acute symptoms following the intervention. [h] Surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma

Effect by renal function

Events suggestive of volume depletion and renal AEs were considered of particular clinical relevance to the HF population and, together with fractures, are discussed below.

Pre-specified analysis by baseline eGFR (<60, ≥60 mL/min/1.73 m^2)

In the pre-specified sub-group analysis by baseline eGFR (<60, ≥60 mL/min/1.73 m^2), adverse events were analysed, see table below.

Table 33 Number of subjects with adverse events in any category – eGFR <60, ≥60 mL/min/1.73 m^2

	AE category	**eGFR at baseline Number (%) of subjects**			
		<60 L/min/1.73m^2		**≥60 mL/min/1.73m^2**	
		Dapa (N=960)	**Placebo (N=962)**	**Dapa (N=1407)**	**Placebo (N=1405)**
Any AE with outcome = death		147 (15.3)	172 (17.9)	139 (9.9)	161 (11.5)
Any SAE (including events with outcome = death)		389 (40.5)	459 (47.7)	457 (32.5)	492 (35.0)
Any AE leading to discontinuation of IP		56 (5.8%)	59 (6.1)	55 (3.9)	57 (4.1)
AEs of symptoms of volume depletion	Any AE	89 (9.3)	80 (8.3)	81 (5.8)	73 (5.2)
	Any SAE	13 (1.4)	21 (2.2)	10 (0.7)	17 (1.2)
	Any DAE	8 (0.8)	2 (0.2)	1 (0.1)	6 (0.4)
Renal AEs	Any AE	88 (9.2)	112 (11.6)	53 (3.8)	46 (3.3)

	Any SAE	22 (2.3)	41(4.3)	12 (0.9)	17 (1.2)
	Any DAE	5 (0.7)	8(0.8)	3 (0.2)	1 (0.1)
DKA	Any AE	0	0	3 (0.2)	0
Major hypoglycaemic events	Any AE	3 (0.3)	0	1 (0.1)	4 (0.3)
Fractures	Any AE	28 (2.9)	25 (2.6)	21 (1.5)	25 (1.8)
Amputations	Any AE	8 (0.8)	9 (0.9)	5 (0.4)	3 (0.2)

Source: Table 14.3.8.5, Table 14.3.9.6 and Table 14.3.10.5 in the Clinical Study report

Post-hoc analysis by baseline eGFR (<45, ≥45 – <60, ≥60 mL/min/1.73 m^2)

Renal function was analysed through post-hoc sub-group analysis of baseline eGFR (<45, ≥45–<60, ≥60 mL/min/1.73 m^2) to further characterise the safety profile of dapagliflozin in patients with HF.

A summary of AEs for the sub-group analyses by baseline eGFR (<45, ≥45 –<60, ≥60 mL/min/1.73 m^2) is presented in **Table 33**.

The results of sub-group analysis by baseline eGFR (<45, ≥45 –<60, ≥60 mL/min/1.73 m^2) were generally consistent with the overall results. Similar to the overall results, there were fewer patients with SAEs suggestive of volume depletion and renal SAEs in the dapagliflozin treatment group. The number of patients with fractures was small, with numerically more patients in the dapagliflozin treatment group (15 [4.1%] patients) compared with the placebo group (10 [2.8%] patients) in the sub-group of baseline GFR <45mL/min/1.73 m^2. Manual review of fractures in this sub-group did not identify any patterns with regard to patient characteristics, time-to-onset, cause or type of fractures.

An eGFR ≥30 mL/min/1.73 m^2 at enrolment was an inclusion criterion and 24 patients with an eGFR <30 mL/min/1.73 m^2 at baseline were randomised. According to the Applicant, manual review of these patients did not reveal any safety concerns.

Table 34 Number of subjects with adverse events in any category – eGFR categories at baseline

	AE category	**eGFR at baseline Number (%) of subjects**					
		<45 L/min/1.73m²		**≥45–<60 L/min/1.73m²**		**≥60 mL/min/1.73m²**	
		Dapa (N=362)	**Placebo (N=357)**	**Dapa (N=598)**	**Placebo (N=605)**	**Dapa (N=1407)**	**Placebo (N=1405)**
Any AE with outcome = death		64 (17.7)	76 (21.3)	83 (13.9)	96 (15.9)	139 (9.9)	161 (11.5)
Any SAE (including		153 (42.3)	189 (52.9)	236 (39.5)	270 (44.6)	457 (32.5)	492 (35.0)

events with outcome = death)							
Any AE leading to discontinuation of IP		18 (5.0)	24 (6.7)	38 (6.4)	35 (5.8)	55 (3.9)	57 (4.1)
AEs of symptoms of volume depletion	Any AE	39 (10.8)	37 (10.4)	50 (8.4)	43 (7.1)	81 (5.8)	73 (5.2)
	Any SAE	5 (1.4)	11 (3.1)	8 (1.3)	10 (1.7)	10 (0.7)	17 (1.2)
	Any DAE	4 (1.1)	1 (0.3)	4 (0.7)	1 (0.2)	1 (0.1)	6 (0.4)
Renal AEs	Any AE	46 (12.7)	58 (16.2)	42 (7.0)	54 (8.9)	53 (3.8)	46 (3.3)
	Any SAE	12 (3.3)	24 (6.7)	10 (1.7)	17 (2.8)	12 (0.9)	17 (1.2)
	Any DAE	3 (0.8)	5 (1.4)	2 (0.3)	3 (0.5)	3 (0.2)	1 (0.1)
DKA	Any AE	0	0	0	0	3 (0.2)	0
Major hypoglycaemic events	Any AE	1 (0.3)	0	2 (0.3)	0	1 (0.1)	4 (0.3)
Fractures	Any AE	15 (4.1)	10 (2.8)	13 (2.2)	15 (2.5)	21 (1.5)	25 (1.8)
Amputations	Any AE	3 (0.8)	5 (1.4)	5 (0.8)	4 (0.7)	5 (0.4)	3 (0.2)

Effect by age

Pre-specified sub-groups by age (≤65, >65 years) were analysed for the AEs suggestive of volume depletion, renal AEs and fractures.

Of the 4,744 patients in the DAPA-HF study, 42.8% were ≤65 years old and 57.2% were >65 years old.

≤65-year sub-group

The results for the ≤65-year sub-group for the pre-defined AEs of special interest are presented in **Table 34**.

Table 35 Summary of AEs suggestive of volume depletion, renal AEs and fractures in patients ≤65 years (SAS)

AE of special interest	**AE category**	**≤65-year sub-population Number (%) subjects**	
		Dapa 10 mg (N=2368)	**Placebo (N=2368)**
		1029	997
AEs of symptoms of volume depletion	Any AE	60 (5.8)	51 (5.1)

	Any SAE	6 (0.6)	15 (1.5)
	Any DAE	1 (0.1)	5 (0.5)
Renal AE	Any AE	59 (5.7)	44 (4.4)
	Any SAE	15 (1.5)	14 (1.4)
	Any DAE	1 (0.1)	2 (0.2)
Fractures	Any AE	13 (1.3)	12 (1.2)
	Any SAE	6 (0.6)	5 (0.5)
	Any DAE	1 (0.1)	0

>65-year group

The results for the >65-year sub-group for the pre-defined AEs of special interest are presented in **Table 35**.

Table 36 Summary of AEs suggestive of volume depletion, renal AEs and fractures in patients >65 years (SAS)

AE of special interest	**AE category**	**>65-year sub-population Number (%) subjects**	
		Dapa 10 mg (N=2368)	**Placebo (N=2368)**
		1339	1371
AEs of symptoms of volume depletion	Any AE	110 (8.2)	102 (7.4)
	Any SAE	17 (1.3)	23 (1.7)
	Any DAE	8 (0.6)	3 (0.2)
Renal AE	Any AE	82 (6.1)	144 (8.3)
	Any SAE	19 (1.4)	44 (3.2)
	Any DAE	7 (0.5)	7 (0.5)
Fractures	Any AE	36 (2.7)	38 (2.8)
	Any SAE	23 (1.7)	21 (1.5)

	Any DAE	0	0

Effect by sex

Of the 4,744 patients in the DAPA-HF study, 76.6% were male and 23.4% were female. Pre-specified sub-group analysis by sex was performed for fractures. The number of patients with fractures in the sub-group analysis by sex were in females 3.4% vs 2.2% and in males 1.7% vs 2.1%, for dapagliflozin vs placebo.

Effect by baseline blood pressure

Pre-specified sub-group analysis by systolic blood pressure at baseline (<130, ≥130 mmHg) was performed for AEs suggestive of volume depletion. The incidence of volume depletion was 8.3% vs 7.2% (SAEs: 1.2% vs 1.6%) in subjects <130 mmHg and 4.7% vs 4.7% (SAEs: 0.4% vs 1.6%) in subjects ≥130 mmHg for dapagliflozin vs placebo.

Extrinsic factors

No extrinsic factors were analysed in the DAPA-HF 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. No new information is available on the potential impact on safety of such interactions in HFrEF patients.

Discontinuation due to adverse events

During the on-treatment period, the number of patients with DAEs were 111 (4.7%) patients and 116 (4.9%) patients in the dapagliflozin and placebo groups, respectively (**Table 36**). The most common AEs that led to permanent discontinuation of study drug were cardiac failure, dizziness and hypotension for the dapagliflozin treatment group and cardiac failure, cardiac failure congestive and renal impairment for the placebo group.

Table 37 Number of subjects with adverse events (frequency ≥0.1%) leading to discontinuation of investigational product by preferred term - on treatment (SAS)

Preferred term	Number (%) of subjects[a]	
	Dapa 10mg (N=2368)	Placebo (N=2368)
Subjects with any AE leading to discontinuation	111 (4.7)	116 (4.9)
Cardiac failure	17 (0.7)	15 (0.6)

Dizziness	4 (0.2)	4 (0.2)
Hypotension	4 (0.2)	4 (0.2)
Urinary tract infection	4 (0.2)	2 (0.1)
Acute kidney injury	3 (0.1)	3 (0.1)
Haematuria	3 (0.1)	0
Hypovolaemia	3 (0.1)	1 (0.0)
Nausea	3 (0.1)	0
Pruritus	3 (0.1)	1 (0.0)
Acute myocardial infarction	2 (0.1)	0
Decreased appetite	2 (0.1)	0
Lung neoplasm malignant	2 (0.1)	1 (0.0)
Malaise	2 (0.1)	1 (0.0)
Renal failure	2 (0.1)	1 (0.0)
Renal impairment	2 (0.1)	5 (0.2)
Septic shock	2 (0.1)	0
Cardiac failure chronic	1 (0.0)	2 (0.1)
Cardiac failure congestive	1 (0.0)	6 (0.3)
Chronic kidney disease	1 (0.0)	2 (0.1)
Cystitis	1 (0.0)	3 (0.1)
Fatigue	1 (0.0)	3 (0.1)
Ventricular tachycardia	1 (0.0)	3 (0.1)
Cardiac failure acute	0	3 (0.1)
Cerebral infarction	0	2 (0.1)
Ischaemic stroke	0	3 (0.1)
Pancreatic carcinoma	0	2 (0.1)
Syncope	0	2 (0.1)
Urosepsis	0	3 (0.1)

Use in pregnancy and lactation

Pregnant patients were excluded from participating in the DAPA-HF study. There were no pregnancies reported during the DAPA-HF study.

Overdose

There were no events of overdose of study drug during the DAPA-HF study.

Drug abuse

The potential for drug abuse for dapagliflozin has not been studied.

Withdrawal and rebound

The effect of dapagliflozin withdrawal and rebound has not been studied.

Post marketing experience

Post-marketing experience in the approved indications is summarised in regular periodic benefit-risk evaluation reports (PBRERs) that are submitted to regulatory authorities worldwide. The annual dapagliflozin PBRER with data lock 04 October 2019, including approximately 7,926,295 patient-years of post-marketing exposure (cumulative until 30 September 2019), is currently under preparation. At the data lock of the dapagliflozin PBRER (04 October 2019), there was according to the Applicant no new information to alter the overall positive benefit-risk profile for dapagliflozin in the approved indications.

2.5.1. Discussion on clinical safety

The established safety profile of dapagliflozin is based on the original dapagliflozin (submission for treatment of T2DM), including the DECLARE CV outcome study. The evaluation of the DAPA-HF CV outcome study provides information on the safety profile of dapagliflozin in subjects with heart failure and reduced ejection fraction. The study population included patients with T2DM (45%) and without diabetes (55%).

In study DAPA-HF, 2,368 subjects were treated with dapagliflozin for a total exposure of 3,310 PY, regardless of interruptions (i.e. 'on and off' treatment), with 1,955 subjects (83%) for at least 52 weeks, 1,168 subjects (49%) for at least 1,5 years and 261 subjects (11%) for at least 2 years. The mean duration of exposure was 16.8 and 16.6 months and the median duration of exposure was 17.8 and 17.6 months for dapagliflozin and placebo, respectively. 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 3,285 PY for dapagliflozin. The median duration of follow-up was 18.2 months.

Data collection in this study focused on serious AEs, AEs leading to discontinuation (DAEs) and AEs of special interest. The safety profile with regards to SAEs did not differ in any substantial way between patients with diabetes and the new target population, i.e. non-diabetic patients.

The number of SAEs was lower in the dapagliflozin group than in the placebo group. The most frequently reported SAEs for dapagliflozin vs placebo were cardiac failure (10% vs 14%), pneumonia (3.0% vs 3.1%), cardiac failure congestive (2.4% vs 2.7%) and cardiac failure acute (1.5% vs 2.2%).

Urinary tract infections

The incidence of SAEs of UTI was low and balanced for dapagliflozin vs placebo (0.6% vs 0.7%), including the subgroups *with T2DM* (0.7% vs 0.9%) and *without T2DM* (0.5% vs 0.5%). There were 4 SAEs of pyelonephritis; 3 cases in the dapagliflozin group. The incidence of events of UTI leading to discontinuation was balanced and equal in the overall population and two subgroups with and without T2DM (0.2% vs 0.2%).

Genital infections

Only 1 SAE of genital infections (placebo group) in a subject with T2DM was reported. Seven patients (0.3%), all in the dapagliflozin treatment group, had an event of genital infection leading to discontinuation.

Volume depletion

The incidence of adverse events suggestive of volume depletion was slightly increased for dapagliflozin vs placebo (7.2% vs 6.5%). However, there were fewer subjects with SAEs in the dapagliflozin treatment group (1.0%) compared with the placebo group (1.6%).

Events of volume depletion was reported more frequently with dapagliflozin (7.0%) than with placebo (5.6%) in subjects *without T2DM* (7.0% vs 5.6%) and was reported equally frequent in subjects with *T2DM* (7.4% vs 7.5%).

Across the eGFR strata, the incidence of volume depletion for dapagliflozin relative placebo was slightly increased: *eGFR ≥60 mL/min/1.73 m^2* (5.8% vs 5.2%), *eGFR 60–45 mL/min/1.73 m^2* (8.4% vs 7.1%) and *eGFR <45 mL/min/1.73 m^2* (11% vs 10%).

Renal events

Renal events occurred slightly more frequently in the placebo group (6.7%) than in the dapagliflozin group (6.0%) in the overall population and for subjects *with T2DM* (7.8% vs 8.2% for DAPA vs placebo) and *without T2DM* (4.4% vs 5.4% for DAPA vs placebo). SAEs of renal events were also higher in the placebo relative the dapagliflozin group; overall and in both subgroups. The same pattern was observed for AEs and SAEs of acute kidney injury, i.e. more frequently reported for placebo than for dapagliflozin.

The frequency of renal events was higher for placebo relative dapagliflozin in subjects with *eGFR <45 mL/min/1.73 m^2* (13% vs 16%) and *eGFR 60–45 mL/min/1.73 m^2* (7.0% vs 8.9%) and was slightly increased for dapagliflozin (3.8%) vs placebo (3.3%) in subjects with *eGFR ≥60 mL/min/1.73 m^2*.

Fractures

The incidence of fractures was balanced between the dapagliflozin and placebo group in the overall population (2.1% respectively), in subjects *with T2DM* (2.1% vs 2.4%) and *without T2DM* (2.1% vs 1.9%) and in subjects with *eGFR 60–45 mL/min/1.73 m^2* (2.2% vs 2.5%) and *eGFR ≥60 mL/min/1.73 m^2* (1.5% vs 1.8%). However, in subjects with *eGFR <45 mL/min/1.73 m^2* (4.1% vs 2.8%), the incidence of fractures was increased for dapagliflozin compared to placebo. In this subgroup, no obvious differences between the treatment groups were identified with regards to subject characteristics, apart from more subjects with osteoporosis in the medical history in the dapagliflozin group (5 of 15) compared with the placebo group (1 of 10). Most of the cases for dapagliflozin was caused by fall; however, none of the subjects had reported events suggestive of volume depletion (e.g. dehydration, orthostatic hypotension) that could have contributed to or caused the fall.

Pre-specified sub-group analysis by sex was performed for fractures. The number of patients with fractures in the sub-group analysis by sex were in females 3.4% vs 2.2% and in males 1.7% vs 2.1%, for dapagliflozin vs placebo.

Diabetic ketoacidosis

In total 5 subjects had an event adjudicated as an DKA, all in the dapagliflozin group; 3 events were adjudicated as a definite DKA (all serious of which one fatal outcome) and 2 events as a possible DKA (both non-serious). All subjects had T2DM and were treated with anti-diabetic medication of which 4 subjects were on concomitant insulin treatment. The 3 events adjudicated as a definite DKA occurred in subjects with eGFR ≥60 mL/min/1.73 m^2.

Major hypoglycaemic events

In the DAPA-HF study only major hypoglycaemic events were collected. Subjects with major hypoglycaemic events were balanced; 0.2% in the dapagliflozin (n=4) and placebo (n=4) group, respectively. One serious case in the placebo group and none in the dapagliflozin group. No subject discontinued due to any major hypoglycaemic event. All patients with major hypoglycaemic events had T2DM at baseline.

Based on the mechanism of action, it is not expected that dapagliflozin poses an unwarranted risk of hypoglycaemia in subjects without diabetes. Dapagliflozin acts insulin-independently and does not impair normal endogenous glucose production. Thus, the amount of glucose excreted into the urine is not considered sufficient to induce hypoglycaemia in normoglycemic subjects. Reassuringly, HbA1c was not reduced in non-diabetic subjects.

Amputations

The incidence of surgical amputations was overall low and balanced (0.5% vs 0.5%); however, slightly more subjects in the T2DM group (1.1% vs 0.8%) than in the non-T2DM group (0.1% vs 0.2%) experienced any amputation for dapagliflozin vs placebo. The event rate for dapagliflozin vs placebo was 0.62 vs 0.43 amputation evets per 100 subject years in the total population and 1.31 and 0.77 amputation events per 100 subject years in the T2DM subjects. The SmPC has been appropriately reworded .

In the eGFR ≥60 mL/min/1.73 m^2 group there was a higher incidence of amputations for dapagliflozin (0.4%) compared to placebo (0.2%); however, in the eGFR 60–45 mL/min/1.73 m^2 the incidence was balanced (0.8% vs 0.7%) and in the eGFR <45 mL/min/1.73 m^2 the incidence was higher in the placebo (1.4%) group relative dapagliflozin (0.8%).

The number of patients with an AE related to risk for lower amputation was 6.5% for dapagliflozin and 5.1% for placebo. All subjects in the dapagliflozin group (13/13) and most of the subjects in the placebo group (10/12) who experienced amputation/-s had preceding events, i.e. AEs related to risk for lower limb amputations. Diabetic foot related conditions and vascular events/PAD were the most predominating reported preceding events and occurred equally frequent in the dapagliflozin group and placebo group.

Fournier's gangrene

In total 6 cases with any SAE or DAE indicating genital area infections or necrotising fasciitis were identified; 3 (0.1%) in the dapagliflozin groups (1 anal abscess, 1 penile infection and 1 rectal abscess) and 3 (0.1%) in the placebo group (2 anal abscess and 1 Fournier's gangrene). However, none of the events was confirmed by the Applicant as Fournier's gangrene.

Laboratory findings/ vital signs

In the DAPA-HF study, eGFR decreased over time in both the dapagliflozin and the placebo group. The change in eGFR was initially (within 2 weeks) more pronounced for dapagliflozin compared to placebo (-6.5% vs -1.7%); however, the difference between dapagliflozin and placebo was less noticeable at month 20 (-8.0% vs -7.0%) and onwards.

In T2DM subjects, the glycaemic effect of dapagliflozin over time was modest (placebo-adjusted LS mean difference in HbA1c reduction of -0.2% to -0.3% during the study). However, this could be explained by the low mean baseline HbA1c (7.41%) for dapagliflozin and slightly higher use of antidiabetic drugs as concomitant medication in the placebo group.

There was a decrease in mean body weight over time in the dapagliflozin group compared to placebo; -1.4% vs 0.1% at 16 months, -1.7% vs 0% at 20 months, -2.0% vs 0.2% at 24 months and -3.6% vs -0.2% at 28 months. Weight loss over time was more pronounced in subjects with higher BMI at baseline (>35 and 30-35 kg/m^2) compared with subjects with lower baseline BMI (25-30 and 20-25 kg/m^2). The incidence of all-cause mortality was numerically lower in the dapagliflozin group compared with placebo; overall (11.6% vs 13.9%) and across BMI strata, including the subgroups with BMI >35 kg/m^2 (11.6% vs 15.1%) and 30-35 kg/m^2 (9.4% vs 12.4%). Reassuringly, there is no indication that all-cause mortality was increased with weight loss in dapagliflozin-treated subjects.

Subgroups

Effect by age

In the DAPA-HF study, 43% were ≤65 years of age, 36% were 66-75 years of age and 21% were >75 years old. The study included 1,003 subjects >75 years of age, of which 516 were treated with dapagliflozin. Pre-specified sub-groups by age (≤65, >65 years) were analysed for the AEs suggestive of volume depletion, renal AEs and fractures. A slightly higher reporting rate was noted in the older age group; however, the safety profile for dapagliflozin did not differ in the older age group compared to the younger age group.

Effect by sex

Pre-specified sub-group analysis by sex was performed for fractures. The number of patients with fractures in the sub-group analysis by sex were in females 3.4% vs 2.2% and in males 1.7% vs 2.1%, for dapagliflozin vs placebo.

Effect by baseline blood pressure

Pre-specified sub-group analysis by systolic blood pressure at baseline (<130, ≥130 mmHg) was performed for AEs suggestive of volume depletion. The incidence of volume depletion was 8.3% vs 7.2% (SAEs: 1.2% vs 1.6%) in subjects <130 mmHg and 4.7% vs 4.7% (SAEs: 0.4% vs 1.6%) in subjects ≥130 mmHg for dapagliflozin vs placebo.

Effect by renal function

The incidence of any SAE was higher in the eGFR <45 mL/min/1.73 m^2 subgroup (48%) compared to the eGFR 60–45 mL/min/1.73 m^2 (42%) and eGFR ≥60 mL/min/1.73 m^2 (34%) subgroups; the incidence was higher in the placebo group vs the dapagliflozin group in all subgroups. Overall, subjects with eGFR <45 mL/min/1.73 m^2 had a higher incidence of volume depletion, renal events and fractures compared to subjects with eGFR 60–45 mL/min/1.73 m^2 and eGFR ≥60 mL/min/1.73 m^2.

There was no indication of a worsening of the safety profile with declining renal function apart from events of fractures (4.1% vs 2.8%) that were more common in subjects with eGFR <45 mL/min/1.73 m^2 treated with dapagliflozin than in those on placebo. The incidence of fractures was balanced in subjects with eGFR 60–45 mL/min/1.73 m^2 and eGFR ≥60 mL/min/1.73 m^2. In this subgroup, no obvious differences between the treatment groups were identified with respect to subject characteristics, apart from more subjects with osteoporosis in the medical history in the dapagliflozin group (33%) compared with the placebo group (10%).

Effect of T2DM

The incidence of any SAE was higher in the T2DM subgroup (43%) compared to the non-diabetes subgroup (34%); however, the incidence was higher in the placebo group vs the dapagliflozin group in both subgroups.

Apart from events suggestive of *volume depletion*, that were increased for dapagliflozin vs placebo in subjects without T2DM (7.0% vs 5.6%) and were balanced in subjects with T2DM (7.4% vs 7.5%), there was no difference in safety profile for subjects with and without T2DM.

The incidence of *UTI* and *fractures* were balanced for dapagliflozin relative placebo in subjects with and without T2DM. Slightly more subjects in the T2DM group (balanced; 1.1% vs 0.8%) than in the non-T2DM group (more events for placebo; 0.1% vs 0.2%) experienced any *amputation*. Subjects with T2DM had a higher frequency of *renal events* compared to subjects with non-diabetes; however, the incidence of renal events was higher in the placebo group in both subgroups.

There were no events of *genital infections*, *major hypoglycaemic events* or *DKA* in the non-T2DM group.

Effect of NYHA class

Due to the limited number of subjects with NYHA IV (n=43) included in the study, no conclusions could be drawn regarding safety in this subgroup. The safety profile for dapagliflozin, with regards to SAEs, volume depletion renal events and fractures, was similar in the NYHA II and NYHA III subgroups, and in line with to the overall population (**Table** 37). The incidence of SAEs was lower with dapagliflozin compared with placebo in subjects with NYHA II and was more balanced between the groups in subjects with NYHA III. In the NYHA II and NYHA III groups, adverse events suggestive of volume depletion occurred with a slightly higher incidence for dapagliflozin relative placebo while renal events were somewhat less frequent with dapagliflozin than with placebo. The rate of fractures was balanced in the subgroup with NYHA II and slightly imbalance in the NYHA III group (favouring placebo).

Table 38 Number of Subjects with Adverse Events in Specific Categories - By Baseline NYHA Class – On-treatment (SAS)

	NYHA II		NYHA III		NYHA IV	
	Number (%) of subjects[a]		Number (%) of subjects[a]		Number (%) of subjects[a]	
AE category	Dapa 10 mg (N = 1601)	Placebo (N = 1595)	Dapa 10 mg (N = 747)	Placebo (N = 750)	Dapa 10 mg (N = 20)	Placebo (N = 23)
Any SAE (including events with outcome = death)	498 (31.1)	587 (36.8)	338 (45.2)	347 (46.3)	10 (50.0)	17 (73.9)
Any event of symptoms of volume depletion[b]	113 (7.1)	105 (6.6)	55 (7.4)	47 (6.3)	2 (10.0)	1 (4.3)

Any renal AE[b]	87 (5.4)	99 (6.2)	52 (7.0)	59 (7.9)	2 (10.0)	0
Any fracture[b]	32 (2.0)	28 (1.8)	15 (2.0)	19 (2.5)	1 (5.0)	0

2.5.2. **Conclusions on clinical safety**

The DAPA-HF study provides information on the safety profile of dapagliflozin in subjects with heart failure and reduced ejection fraction. No new safety concerns arise from the provided data.

The overall safety profile for dapagliflozin in the DAPA-HF study was similar compared with previously identified adverse drug reactions. The safety profile with regards to SAEs did not differ in any substantial way between patients with diabetes and the new target population, i.e. non-diabetic patients. Based on the mechanism of action, it is not expected that dapagliflozin poses an unwarranted risk of hypoglycaemia in subjects without diabetes. Reassuringly, HbA1c was not reduced in non-diabetic subjects.

In T2DM subjects, there was a numerical imbalance in subjects suffering amputation between the dapagliflozin and the placebo group (1.1% (n=12) vs 0.8% (n=9)). Furthermore, the number of patients undergoing more than one amputation was higher for dapagliflozin compared with placebo (6 vs 3) with an event rate of 1.31 vs. 0.77 amputation events per 100 subject years for dapagliflozin vs placebo. The numerical imbalances together with the assumption of a class effect should be reflected in the SmPC. Rewording of the SmPC is considered appropriate.

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

The incidence of SAEs and renal events was higher in subjects with T2DM compared to subjects without T2DM; however, the safety profiles did not differ in the subgroups. The glycaemic effect of dapagliflozin over time was modest. This might be explained by the low mean baseline HbA1c for dapagliflozin and slightly higher use of antidiabetic drugs as concomitant medication in the placebo group.

The incidence of SAEs, events of volume depletion, renal events and fractures increased with decreasing baseline eGFR. However, there was no indication of a worsening of the safety profile with declining renal function apart from events of fractures that were more common in subjects with eGFR <45 mL/min/1.73 m^2 treated with dapagliflozin than in those on placebo. In this subgroup, no obvious differences between the treatment groups were identified with regards to subject characteristics, apart from more subjects with osteoporosis in the medical history in the dapagliflozin group (33%) compared with the placebo group (10%).

There was a decrease in mean body weight over time in the dapagliflozin group compared to placebo. Weight loss over time was more pronounced in subjects with higher BMI at baseline (>35 and 30-35 kg/m^2) compared with subjects with lower baseline BMI (25-30 and 20-25 kg/m^2). However, the incidence of all-cause mortality was numerically lower in the dapagliflozin group compared with placebo; overall and across BMI strata. Reassuringly, there is no indication that all-cause mortality was increased with weight loss in dapagliflozin-treated subjects.

Only a limited number of subjects with NYHA IV (n=43) were included in the study, which did not allow to draw conclusions regarding the safety profile specifically in this subgroup. Use in patients with NYHA

class IV has been included as missing information in the RMP. The safety profile for dapagliflozin, with regards to SAEs, volume depletion renal events and fractures, was similar in the NYHA II and NYHA III subgroups, and in line with to the overall population.

The Applicant has submitted an updated RMP with this application. No new safety concerns have been raised. The proposed changes are discussed in section 2.6 of this report.

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 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version **19.6** is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version **19.6** with the following content:

Safety concerns

Important identified risks	Urinary tract infection Renal impairment Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	Liver injury Bladder cancer Breast cancer Prostate cancer Lower limb amputation
Missing information	Use in patients with NYHA class IV

Pharmacovigilance plan

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Retrospective Cohort Study on the Risk of Diabetic Ketoacidosis (DKA). (planned)	Determine the effectiveness of additional risk minimization measures in place for DKA in Europe by assessing the impact of the RMMs on the risk of DKA in T1DM patients who are treated with dapagliflozin in Europe.	diabetic ketoacidosis in T1DM	Protocol submission Feasibility assessment Populations size update Submission of interim report(s) Submission of final data	June 24, 2019 June 24, 2019 Annual Q4 2023 (estimated) Q4 2025 (estimated) Q4 2026 (estimated)
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
MB102103 (D1690R00008)- Observational study: Complications of UTI in Patients on Dapagliflozin Ongoing	Assess the incidence of hospitalization or emergency department visit for severe complications of UTI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Severe complications of UTI	Submission of interim data Submission of final data	2016, 2019 2020
MB102104 (D1690R00005) - Observational study: Acute Liver Injury in Patients on Dapagliflozin Ongoing	To assess the incidence of hospitalization for ALI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Risk of acute hepatic failure	Submission of Interim data Submission of final data	2016,2019 2020
MB102110 (D1690R00004) - Observational study: Acute Kidney Injury in Patients on	To assess the incidence of hospitalization for AKI among new users of dapagliflozin compared to those who are new users of	Risk of AKI	Submission of Interim data Submission of final data	2016,2019 2020

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
Dapagliflozin and Other Antidiabetic Medications Ongoing	certain other antidiabetic drugs.			
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 Ongoing	Studies aimed to elucidate the metabolic adaptations in term of glucose flux, lipolysis, and ketogenesis following insulin withdrawal in subjects with diabetes mellitus and absolute or relative endogenous insulin deficiency, when treated with dapagliflozin.	Ketoacidosis	Submission of final data	When available
D169AC00001 dapaCKD A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease Ongoing	To determine if dapagliflozin is superior to placebo in reducing the incidence of the primary composite endpoint of ≥50% sustained decline in estimated glomerular filtration rate (eGFR), reaching end stage renal disease (ESRD), CV or renal death when added to current background therapy in patients with eGFR ≥25 and ≤75 mL/min/1.73m^2 and albuminuria (urine albumin creatinine ratio [UACR] ≥200 and ≤5000 mg/g).	Lower limb amputation	Submission of final data	Q4 2020
D169EC00001 Determine HFpEF Short Title: DETERMINE-preserved – Dapagliflozin EffecT on ExeRcise capacity	To determine whether dapagliflozin is superior to placebo in patients with chronic HF NYHA Functional Class II-IV and preserved ejection fraction (LVEF>40%) [HFpEF] in:	Lower limb amputation	Submission of final data	Q1 2021

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
using a 6-MINutE walk test in patients with heart failure with preserved ejection fraction	• reducing patient-reported HF symptoms • reducing patient-reported physical limitation • improving exercise capacity			
D169EC00002 Determine HFrEF Short Title: DETERMINE-reduced – Dapagliflozin EffecT on ExeRcise capacity using a 6-MINutE walk test in patients with heart failure with reduced ejection fraction	To determine whether dapagliflozin is superior to placebo in patients with chronic HF NYHA Functional Class II-IV and reduced ejection fraction (LVEF≤40%) [HFrEF] in: • reducing patient-reported HF symptoms • reducing patient-reported physical limitation • improving exercise capacity	Lower limb amputation	Submission of final data	Q1 2021
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

Risk minimisation measures

Safety concern	Risk minimisation measures
Important identified risks	
Urinary tract infection	Routine risk minimisation measures: SmPC section: 4.8 PL section: 4

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). Additional risk minimisation for T1DM included for Forxiga 5 mg only: Information included that T1DM patients will be informed of the risk of DKA, risk factors, signs and symptoms, and that DKA may occur even if blood glucose levels are not elevated, in a mandatory education session. Recommendation on education about use of blood ketone monitoring, including directions to seek prompt medical attention in case of suspected ketoacidosis (SmPC section 4.4, PL section 2). Information on how to detect symptoms of DKA and instructions to seek prompt medical attention (PL section 2, 4). Recommendation that T1DM patients with BMI < 27 kg/m^2 should not be initiated on dapagliflozin. Additional risk minimisation measures: Educational materials for HCPs and patients/carers. Additional risk minimisation measures: Educational materials for HCPs and patients/carers.
Renal impairment	Routine risk minimisation measures: Guidance is provided on monitoring renal function (SmPC section 4.4 and PL section 2).
Important potential risks	
Liver injury	No risk minimisation measures.
Bladder cancer	No risk minimisation measures.
Breast cancer	No risk minimisation measures.
Prostate cancer	No risk minimisation measures.
Lower limb amputation	No risk minimisation measures.
Missing information	

Safety concern	Risk minimisation measures
Use in patients with NYHA class IV	Routine risk minimisation measures: SmPC section 4.4

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template.

2.7.1. **User consultation**

The results of the user consultation with target patient groups on the package leaflet submitted by the WSA show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. **Disease or condition and available therapies/unmet need**

The prevalence of heart failure (HF) is estimated at 1% to 2% in the Western world. The core symptoms of HF include shortness of breath, fatigue, and peripheral oedema and hospitalisations due to decompensations are frequently occurring. Current standard of care includes renin-angiotensin system (RAS) blockade, Beta blockade, mineralocorticoid receptor antagonists (MRAs) (if deemed appropriate). In addition to these therapies, diuretics are used to reduce symptoms from fluid overload and cardiac glycosides improve hospitalisation rate and provide symptomatic relief. More recently, neprilysin inhibition (in conjunction with RAS blockade) has been approved as a treatment option. Despite these treatments, mortality rates in patients with reduced ejection fraction (HFrEF) remain high.

Dapagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor, previously approved for the treatment of patients with T1DM or T2DM. In the current variation, the MAH is applying for a new indication (*X is indicated in adults for the treatment of symptomatic heart failure with reduced ejection fraction*) based on the results of one pivotal phase III study; D1699C00001, hereafter referred to as DAPA-HF.

3.1.2. **Main clinical study**

DAPA-HF was a global, event-driven, randomised, double-blind, placebo-controlled Phase III study conducted at 410 sites across 20 countries including 4744 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 HF events, when added to background standard of care, in patients with HFrEF in NYHA class II-IV, with T2DM or without diabetes.
Secondary variables included time to first occurrence of either component of the primary endpoint; total number of (first and recurrent) HF hospitalisations and CV death; change from baseline, measured at 8 months, in the total symptom score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ); time to first occurrence of any component of the composite ≥50% sustained decline in estimated glomerular filtration rate (eGFR), end stage renal disease, or renal death; and time to death from any cause.
The study was event-driven; 844 primary composite endpoint events were required to have 90% power to demonstrate superiority of dapagliflozin to placebo assuming a hazard ratio (HR) of 0.80.
The study aimed to include patients with HFrEF, NYHA II- IV that were optimally treated according to guidelines and that did not have hypotension or recent worsening of the condition. Patients with eGFR <30 mL/min/1.73 m^2 were excluded.

The mean age of the study population was 66 years and the majority (77%) of the subjects were male. Almost 50% of the subjects were recruited in Europe. 67.5% / 31.6% of patients had NYHA class II / III at baseline respectively, while a very small proportion were in class IV (n=43, 1% of study population). Median LVEF was 32%, aetiology of heart failure was ischemic in 56.4%, non-ischemic in 35.6% and unknown in 8.1% of cases. Twenty-four percent of the patients had atrial fibrillation and 42 % of the subjects had type 2 diabetes. Patients with type 1 diabetes were not included in the trial. The treatment groups were well balanced for all these characteristics. The vast majority of patients were treated with ACEi/ARB/ARNI and beta blocker in line with the inclusion criteria. In addition, 71% were on MRA and 93% were treated with diuretics.

3.2. Favourable effects

Dapagliflozin was superior to placebo in reducing the incidence of the composite of **CV death or a HF event** (hospitalisation for heart failure or urgent heart failure related visit) with a 26% relative risk reduction (95% CI 15% to 35%), p<0.0001. All three components of the primary endpoint contributed to the effect; HR for CV death 0.82 (95% CI 0.69 to 0.98); HR for hospitalisation for HF and urgent HF visits 0.70 (95% CI 0.59 to 0.83). The event rate of primary endpoint events was 11.6 in the dapagliflozin treatment group and 15.6 in the placebo group. The major cause of death was cardiovascular. When adding deaths from other causes, the difference in favour of dapagliflozin was preserved.

Treatment with dapagliflozin was superior to placebo in reducing the total numbers of events in the composite of CV death or recurrent HF hospitalisation/urgent HF visits. There were 567 and 742 events of CV death or hospitalisation for HF/ urgent HF visits in the dapagliflozin and placebo groups, respectively, corresponding to event rates per 100 patient-years of 16.3 and 21.6, respectively (p= 0.0002).

For the evaluation of the KCCQ questionnaire, the MAH investigated the clinically meaningful levels of individual change from baseline at 8 months in KCCQ-TSS. A clinically relevant improvement or deterioration in KCCQ-TSS was defined as a change from baseline of ≥5 points. The difference in

responders based on this cut off (as well as for the 10 and 15% improvement cut off) compared to placebo was of statistical significance.

In the pre specified subgroups (age, sex, race, geographical region, NYHA class, LVEF, NTproBNP, prior hospitalisation, MRA use, diabetes status, AF, aetiology, BMI, eGFR) the effect in most of the groups was consistent with the one in the overall population. Subgroup analyses supported that neither diabetic status nor BMI influenced the results.

3.3. Uncertainties and limitations about favourable effects

The MAH has not submitted any results from studies supporting the mechanism of action of dapagliflozin in patients with heart failure (HF), but only a discussion based on published references. The most plausible relevant mechanism in patients with HF is the known propensity of dapagliflozin to induce osmotic diuresis. In the CHMP advice given in 2016, it was expected that the results of the pivotal would be supported by adequate data to elucidate the mechanism of action. The MAH has referred to published data discussing the mechanism of action in relation to treatment of heart failure. The MAH´s interpretation of these results is that dapagliflozin inhibits SGLT2 in the proximal tubules of the kidneys, leading to glucosuria and increased sodium delivery to more distal parts of the nephron, which leads to restored tubuloglomerular feedback, and osmotic diuresis. This leads to a decrease in volume overload, and reduced blood pressure, reducing preload and afterload of the heart. This off-loading of the left ventricle leads to beneficial effects on cardiac remodelling, which leads to improved diastolic parameters.

No imaging data or information on cardiac function was submitted and echo data from the public domain were not considered meaningful. An echocardiographic substudy was included in Dapa HF but, data were insufficient to draw any conclusions. This issue is not further pursued in this procedure.

There were no significant differences in the incidence of the composite of ≥50% sustained decline in estimated glomerular filtration rate (eGFR), end stage renal disease, or renal death; or death from any cause, but the cases were few.

The effect did not seem to be influenced by eGFR at baseline, but patients with eGFR <30 was excluded from the study. Provided analyses do not indicate a risk of reduced effect based in patients with lower eGFR, but the fact that the experience is very limited is reflected in the SmPC.

In the subgroup analyses, the result of the primary endpoint was less convincing in patients with severe heart failure i.e. patients in NYHA class III-IV and patients with higher baseline NT-proBNP levels compared to the total study population. In particular, the estimate for CV death was above 1 (HR 1.09, 95%CI 0.85-1.41) compared to 0.82 (95%CI 0.69-0.98) in the total population. The MAH has carefully analysed the data, without finding a credible explanation to this finding. These findings are not supported by a biological rationale, and not consistently found when other disease severity markers (LVEF, NT-proBNP, MAGGIC score and KCCQ-TSS) are used.

The number of patients with NYHA class IV was very limited (only 1% of the study population). Information has been included in the SmPC.

No specific reason was detected for the lower efficacy in the European population that was mainly due to a lack of efficacy on the CV mortality component. Some factors at least numerically associated with a lower efficacy were more frequently present in the European population: NYHA class distribution was less

favourable in European patients than overall, atrial fibrillation and ischaemic aetiology were more common. Possibly the lower efficacy observed in the European patients was related to the higher representation of these subgroups where efficacy was at least numerically lower.

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. For the treatment of T1DM, dapagliflozin is also approved (add on insulin, BMI >= 27 kg/m2) but at a lower recommended dose of 5 mg once daily. In the absence of data on efficacy and safety at the 10 mg once daily dose, B/R cannot be considered positive in this population. Treatment of these patients is not recommended, therefore.

3.4. Unfavourable effects

In total in the HF-study, 2,368 subjects were treated with dapagliflozin for a total exposure of 3,310 PY, with 1,955 subjects (83%) for at least 52 weeks and 1,168 subjects (49%) for at least 1,5 years and 261 subjects (11%) for at least 2 years. The median duration of exposure was 17.8 and 17.6 months for dapagliflozin and placebo, respectively. The median duration of follow-up was 18.2 months.

The number of SAEs was lower in the dapagliflozin group than in the placebo group. The most frequently reported SAEs for dapagliflozin vs placebo were cardiac failure (10% vs 14%), pneumonia (3.0% vs 3.1%), cardiac failure congestive (2.4% vs 2.7%) and cardiac failure acute (1.5% vs 2.2%).

The incidence of SAEs of *urinary tract infections* (0.6% vs 0.7%) and events of UTI leading to discontinuation (0.2% vs 0.2%) were low and balanced. There were 4 SAEs of pyelonephritis; 3 cases in the dapagliflozin group.

Only 1 SAE of *genital infections* (placebo group) was reported. Seven patients (0.3%), all in the dapagliflozin treatment group, had an event of genital infection leading to discontinuation.

Events of *volume depletion* was reported slightly more frequently with dapagliflozin (7.2%) than with placebo (6.5%). However, there were fewer patients with SAEs in the dapagliflozin treatment group (1.0%) compared with the placebo group (1.6%).

Renal events occurred slightly more frequently in the placebo group (6.7%) than in the dapagliflozin group (6.0%). The incidence of SAEs of renal events were also higher in the placebo relative the dapagliflozin group.

The incidence of *fractures* was balanced between the dapagliflozin and placebo group in the overall population (2.1% respectively).

In total 5 subjects had an event adjudicated as an *DKA*, all in the dapagliflozin group; 3 events were adjudicated as a definite DKA (all serious of which one fatal outcome) and 2 events as a possible DKA (both non-serious). All subjects had T2DM and were treated with anti-diabetic medication of which 4 subjects were on concomitant insulin treatment.

In the DAPA-HF study only *major hypoglycaemic events* were collected. Subjects with major hypoglycaemic events were balanced; 0.2% in the dapagliflozin (n=4) and placebo (n=4) group, respectively. One serious case in the placebo group and none in the dapagliflozin group. No subject discontinued due to any major hypoglycaemic event. All patients with major hypoglycaemic events had T2DM at baseline.

The incidence of surgical *amputations* was overall low and balanced (0.5% vs 0.5%); however, slightly more subjects in the T2DM group (1.1% vs 0.8%) than in the non-T2DM group (0.1% vs 0.2%) experienced any amputation for dapagliflozin vs placebo. The event rate for dapagliflozin vs placebo was 0.62 vs 0.43 amputation evets per 100 subject years in the total population and 1.31 and 0.77 amputation events per 100 subject years in the T2DM subjects. Rewording of the SmPC is considered appropriate.

Laboratory findings/ vital signs

In the DAPA-HF study, eGFR decreased over time in both the dapagliflozin and the placebo group. The change in eGFR was initially (within 2 weeks) more pronounced for dapagliflozin compared to placebo (-6.5% vs -1.7%); however, the difference between dapagliflozin and placebo was less noticeable at month 20 (-8.0% vs -7.0%) and onwards.

There was a decrease in mean body weight over time in the dapagliflozin group compared to placebo; -1.7% vs 0% at 20 months and -3.6% vs -0.2% at 28 months. Weight loss over time was more pronounced in subjects with higher BMI at baseline (>35 and 30-35 kg/m^2) compared with subjects with lower baseline BMI (25-30 and 20-25 kg/m^2). However, the incidence of all-cause mortality was numerically lower in the dapagliflozin group compared with placebo; overall and across BMI strata. Reassuringly, there is no indication that all-cause mortality was increased with weight loss in dapagliflozin-treated subjects.

Subgroups

Pre-specified sub-groups by age (≤65, >65 years) were analysed for the AEs suggestive of volume depletion, renal AEs and fractures. A slightly higher reporting rate was noted in the older age group; however, the safety profile for dapagliflozin did not differ in the older age group compared to the younger age group.

Overall, subjects with eGFR <45 mL/min/1.73 m^2 had a higher incidence of volume depletion, renal events and fractures compared to subjects with eGFR 60–45 mL/min/1.73 m^2 and eGFR ≥60 mL/min/1.73 m^2. There was no indication of a worsening of the safety profile with declining renal function apart from events of fractures that were more common in subjects with eGFR <45 mL/min/1.73 m^2 treated with dapagliflozin (4.1%) than in those on placebo (2.8%). No obvious differences between the treatment groups were identified with regards to subject characteristics in this subgroup, apart from more subjects with osteoporosis in the medical history in the dapagliflozin group (33%) compared with the placebo group (10%).

The incidence of any SAE was higher in the T2DM subgroup (43%) compared to the non-diabetes subgroup (34%); however, the incidence was higher in the placebo group vs the dapagliflozin group in both subgroups. There was no difference in safety profile for subjects with and without T2DM apart from events suggestive of *volume depletion* that were increased for dapagliflozin vs placebo in subjects without T2DM (7.0% vs 5.6%) and were balanced in subjects with T2DM (7.4% vs 7.5%). In diabetic subjects, the glycaemic effect of dapagliflozin over time was modest (placebo-adjusted LS mean difference in HbA1c reduction of -0.2% to -0.3% during the study). However, this could be explained by the low mean baseline HbA1c (7.41%) for dapagliflozin and slightly higher use of antidiabetic drugs as concomitant medication in the placebo group.

The incidence of SAEs was lower with dapagliflozin compared with placebo in subjects with NYHA II (31% vs 37%) and was more balanced between the groups in subjects with NYHA III (45% vs 46%). Adverse events suggestive of volume depletion occurred with a slightly higher incidence for dapagliflozin relative

placebo (7.1% vs 6.6% and 7.4% vs 6.3% for NYHA II and NYHA III, respectively) while renal events were somewhat less frequent with dapagliflozin than with placebo for NYHA II (5.4% vs 6.2%) and NYHA III (7.0% vs 7.9%). The rate of fractures was low (≤2%) and balanced in the subgroup with NYHA II and slightly imbalance in the NYHA III group (favouring placebo). Due to the limited number of subjects with NYHA IV included in the study (n=43), no conclusions could be drawn regarding safety in this subgroup.

3.5. Uncertainties and limitations about unfavourable effects

The data collection in this study focused on serious AEs and AEs of special interest. The safety profile with regards to SAEs did not differ in any substantial way between patients with diabetes and the new target population, i.e. non-diabetic patients. Based on the mechanism of action, it is not expected that dapagliflozin poses an unwarranted risk of hypoglycaemia in subjects without diabetes. Dapagliflozin acts insulin-independently and does not impair normal endogenous glucose production. Thus, the amount of glucose excreted into the urine is not considered sufficient to induce hypoglycaemia in normoglycemic subjects. Reassuringly, HbA1c was not reduced in non-diabetic subjects.

The incidence of SAEs and renal events was higher in subjects with T2DM compared to subjects without T2DM and in subjects with NYHA II compared with NYHA III; however, the safety profile for dapagliflozin within the subgroups, respectively, was in line with the overall population. No conclusions could be drawn regarding safety in the NYHA IV subgroup due to the limited number of subjects.

In T2DM subjects, there was a numerical imbalance in subjects suffering amputation between the dapagliflozin and the placebo group (1.1% (n=12) vs 0.8% (n=9)). Furthermore, the number of patients undergoing more than one amputation was higher for dapagliflozin compared with placebo (6 vs 3) with an event rate of 1.31 vs. 0.77 amputation events per 100 subject years for dapagliflozin vs placebo. The numerical imbalances together with the assumption of a class effect are reflected in the SmPC.

3.6. Effects Table

Table 1. Effects Table

Effect	Short description	Unit	Treatment (DAPA)	Control (Plc)	Uncertainties / Strength of evidence	References
Favourable Effects						
CV death or a HF event		%	11.6	15.6	**HR 0.74** (95% CI 0.65 to 0.85)	DAPA-HF study
CV death			6.5	7.9	**HR 0.82** (95% CI 0.69 to 0.98)	DAPA-HF study
HF event	Hospitalisation or urgent HF visit		7.1	10.1	**HR 0.70** (95% CI 0.59 to 0.83)	DAPA-HF study
Unfavourable Effects						
Any SAE	On-treatment	n (%)	846 (36%)	951 (40%)		DAPA-HF study
Volume		n (%)	170 (7.2%)	153 (6.5%)		DAPA-HF

Effect	Short description	Unit	Treatment (DAPA)	Control (Plc)	Uncertainties / Strength of evidence	References
depletion						
Renal events		n (%)	141 (6.0%)	158 (6.7%)		DAPA-HF
Fractures		n (%)	48 (2.0%)	47 (2.0%)		DAPA-HF
Major hypo-glycaemic events		n (%)	4 (0.2%)	4 (0.2%)		DAPA-HF
DKA, adjudicated		n (%)	3 (0.1%)	0		DAPA-HF
Amputations		n (%)	11 (0.5%)	11 (0.5%)		DAPA-HF
Effect of T2DM						
Any SAE						
with T2DM		n (%)	426 (39.7%)	496 (46.7%)		DAPA-HF
without T2DM		n (%)	420 (32.4%)	455 (34.9%)		DAPA-HF
Volume depletion						
with T2DM		n (%)	79 (7.4%)	80 (7.5%)		DAPA-HF
without T2DM		n (%)	91 (7.0%)	73 (5.6%)		DAPA-HF
Renal events						
with T2DM		n (%)	84 (7.8%)	87 (8.2%)		DAPA-HF
without T2DM		n (%)	57 (4.4%)	71 (5.4%)		DAPA-HF
Fractures						
with T2DM		n (%)	22 (2.1%)	25 (2.4%)		DAPA-HF
without T2DM		n (%)	27 (2.1%)	25 (1.9%)		DAPA-HF
Effect of renal function						
Any SAEs						
eGFR <45		n (%)	153 (42.3%)	189 (52.9%)		DAPA-HF
eGFR ≥45-<60		n (%)	236 (39.5%)	270 (44.6%)		DAPA-HF
eGFR ≥60		n (%)	457 (32.5%)	492 (35.0%)		DAPA-HF
Volume depletion						
eGFR <45		n (%)	39 (10.8%)	37 (10.4%)		DAPA-HF
eGFR ≥45-<60		n (%)	50 (8.4%)	43 (7.1%)		DAPA-HF
eGFR ≥60		n (%)	81 (5.8%)	73 (5.2%)		DAPA-HF
Renal events						
eGFR <45		n (%)	46 (12.7%)	58 (16.2%)		DAPA-HF
eGFR ≥45-<60		n (%)	42 (7.0%)	54 (8.9%)		DAPA-HF
eGFR ≥60		n (%)	53 (3.8%)	46 (3.3%)		DAPA-HF
Fractures						
eGFR <45		n (%)	15 (4.1%)	10 (2.8%)		DAPA-HF
eGFR ≥45-<60		n (%)	13 (2.2%)	15 (2.5%)		DAPA-HF
eGFR ≥60		n (%)	21 (1.5%)	25 (1.8%)		DAPA-HF

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite the availability of a number of treatments for patients with HFrEF, morbidity and mortality are high and new treatment options are welcomed. Dapagliflozin reduced the incidence of CV death and HF worsening with 26% compared to placebo in a population with HFrEF on adequate background treatment

in line with current treatment recommendations. Use of ARNIs increased to some degree during the course of the study, but otherwise HF medication did not change much and patients in the placebo group had a relevant treatment with 94 % being treated with diuretics. Thus, it is likely that a reduced incidence of the primary variable could have been achieved in the placebo group with increased use of diuretics or other HF treatments.

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.

The effect was consistent in subgroups such as patients with and without type 2 diabetes. However, analyses in patients with severe heart failure (NYHA III- IV) indicate a lower effect compared to patients with NYHA II. Actually, the incidence of all cause and CV death was higher in patients treated with dapagliflozin compared to placebo. The MAH has carefully analysed the data, without finding any credible explanation to this finding. These findings are not supported by a biological rationale, and not consistently found when other disease severity markers (LVEF, NT-proBNP, MAGGIC score and KCCQ-TSS) are used. Further, an increased risk of mortality is not supported by other safety findings in the DAPA HF study.

In addition, data in this subgroup support a positive effect on reducing hospitalisations for HF which is indeed a clinically relevant outcome. Therefore, a benefit of treatment is expected also in patients with more severe heart failure.

Data collection in this study focused on serious AEs and AEs of special interest. No new safety concerns arise from the data provided. In the overall population and in the additional subgroup analyses on baseline diabetes status, renal function and NYHA class, the number of SAEs was lower in the dapagliflozin group than in the placebo group. The incidence of SAEs and renal events was higher in subjects with T2DM compared to subjects without T2DM and in subjects with NYHA II compared with NYHA III . However, the safety profile for dapagliflozin within the subgroups, respectively, was in line with the overall population, though no conclusions could be drawn regarding safety specifically in the NYHA IV subgroup due to the limited number of subjects. Use in patients with NYHA class IV has been included as missing information in the RMP, as requested by the CHMP.

In conclusion, the safety profile in patients with HF seems to be rather similar to the one previously documented in patients with diabetes and does not differ in any substantial way between patients with and without diabetes or between patients with moderate (NYHA II) and severe heart failure (NYHA III). Dapagliflozin acts insulin-independently and does not impair normal endogenous glucose production. Thus, the amount of glucose excreted into the urine is not considered sufficient to induce hypoglycaemia in normoglycemic subjects. Reassuringly, HbA1c was not reduced in non-diabetic subjects. However, it should be remembered that the safety profile of dapagliflozin is not innocuous; e.g. there is an increased risk of DKA (confirmed also in the current study), lower limb amputation and initial decline of eGFR.

3.7.2. **Balance of benefits and risks**

The documented benefits in the study population included in the DAPA HF trial are considered to be of clinical relevance and to outweigh risks. With respect to patients with NYHA III-IV, a somewhat less pronounced effect was observed. However, the totality of data do not support that the observation of an increased risk of mortality in patients with more severe HF is a finding considered robust enough to exclude this subgroup. In addition, data support a positive effect on reducing hospitalisations for HF which is indeed a clinically relevant outcome. Since the safety profile is considered similar irrespective of NYHA class, this benefit outweighs the uncertainty regarding risk in patients with more severe HF.

3.7.3. **Additional considerations on the benefit-risk balance**

The vast majority of the study population in the pivotal study was treated with standard background therapy according to treatment guidelines. The MAH was requested to discuss the adequacy of restricting the indication to patients on standard therapy. The MAH did not find this adequate considering that the data of DAPA-HF support a positive treatment effect of dapagliflozin that is independent of which background HF treatment a patient receives and that the observation that neither of these agents modified the response to dapagliflozin supports the view that SGLT2 inhibition acts in a mechanistically independent and complementary way to other therapies for HFrEF.
The argumentation is not fully agreed with; a statement in section 4.1 that dapagliflozin is an add-on treatment does not contradict the specific mechanism of dapagliflozin. However, it can be agreed that the aim of the DAPA-HF was not to study a specific combination. Thus, other medications can be seen as "background therapy" rather than "combination therapy" and may therefore not necessarily be included in section 4.1. Further, other recently approved heart failure treatments have information about background treatment in section 4.2 and not in section 4.1.. Thus, the proposed indication has been accepted by the CHMP considering the updated text in 4.2 *(In the DAPA-HF study, dapagliflozin was administered in conjunction with other heart failure therapies (see section 5.1).*

3.8. Conclusions

The benefit/risk balance is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning 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, IIIA and IIIB

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC for Edistride and Forxiga to add a new indication for the treatment of symptomatic heart failure with reduced ejection fraction in adults. The Package Leaflet and Labelling are updated in accordance.
The RMP version 19.6 is agreed as part of this procedure.
Furthermore, the PI is brought in line with the latest QRD template version 10.1, as well as editorial

change (addition of SI unit for blood glucose).

Amendments to the marketing authorisation

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the WSA, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

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.

Summary

Please refer to Scientific Discussion 'Forxiga-H-C-002322-WS1737' and 'Edistride-H-C-04161/WS1737'

Attachments

1. SmPC Labelling Package Leaflet (changes highlighted) of Forxiga 5mg and 10 mg,film-coated tablets, as a relevant example with changes highlighted as adopted by the CHMP on 15 October 2020.

Appendix

1. CHMP AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies

Reminders to the WSA

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by **30 October 2020**. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf.

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by **30 October 2020**. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The WSA is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. The WSA is reminded that, at the same time as the submission on the eCTD closing sequence mentioned above, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

4. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the

RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the WSA is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.