19 April 2012
EMA/431093/2021
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Procedure No. EMEA/H/C/WS1941

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/WS1941/0062
Edistride	dapagliflozin	EMEA/H/C/004161/WS1941/0043

Worksharing applicant (WSA): AstraZeneca AB

This application is in the area of: (Non-)Clinical RMP

Note

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

The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	28 Nov 2020	28 Nov 2020	☐
☐	CHMP Rapporteur Assessment Report	22 Jan 2021	22 Jan 2021	☐
☐	PRAC Rapporteur Assessment Report	29 Jan 2021	22 Jan 2021	☐
☐	PRAC members comments	03 Feb 2021	03 Feb 2021	☐
☐	Updated PRAC Rapporteur Assessment Report	04 Feb 2021	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	11 Feb 2021	11 Feb 2021	☐
☐	CHMP members comments	15 Feb 2021	15 Feb 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 Feb 2021	18 Feb 2021	☐
☐	Request for supplementary information	25 Feb 2021	25 Feb 2021	☐
☐	MAH responses by:	19 Mar 2021	19 Mar 2021	☐
☐	Re-Start of procedure	22 Mar 2021	22 Mar 2021	☐
☐	CHMP Rapporteur Assessment Report	20 Apr 2021	20 Apr 2021	☐
☐	PRAC Rapporteur Assessment Report	23 Apr 2021	20 Apr 2021	☐
☐	PRAC members comments	28 Apr 2021	28 Apr 2021	☐
☐	Updated PRAC Rapporteur Assessment Report	29 Apr 2021	26 Apr 2021	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	06 May 2021	06 May 2021	☐
☐	CHMP members comments	10 May 2021	10 May 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 May 2021	12 May 2021	☐
☐	2nd Request for supplementary information	20 May 2021	20 May 2021	☐
☐	MAH responses by:	27 May 2021	27 May 2021	☐
☐	Re-Start of procedure	28 May 2021	28 May 2021	☐
☐	CHMP Rapporteur Assessment Report	09 Jun 2021	10 Jun 2021	☐
☐	PRAC Rapporteur Assessment Report	09 Jun 2021	10 Jun 2021	☐
☐	PRAC/CHMP members comments	14 Jun 2021	14 Jun 2021	☐
☐	Updated PRAC Rapporteur Assessment Report	17 Jun 2021	17 Jun 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 Jun 2021	17 Jun 2021	☐

Status of this report and steps taken for the assessment				
☒	Opinion	24 Jun 2021	24 Jun 2021	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Table of contents

1. Background information on the procedure 6

2. Recommendations 6

3. EPAR changes 7

4. Scientific discussion 8

4.1. Introduction 8
4.1.1. Problem statement 8
4.1.2. About the product 8
4.1.3. The development programme/compliance with CHMP guidance/scientific advice 8
4.2. Non-clinical aspects 9
4.2.1. Ecotoxicity/environmental risk assessment 9
4.2.2. Conclusion on the non-clinical aspects 11
4.3. Clinical aspects 11
4.3.1. Introduction 11
4.3.2. Pharmacokinetics 11
4.3.3. Pharmacodynamics 16
4.3.4. Discussion on clinical pharmacology 16
4.3.5. Conclusion clinical pharmacology 17
4.4. Clinical efficacy 17
4.4.1. Main study 17
4.4.2. Discussion on clinical efficacy 58
4.4.3. Conclusions on the clinical efficacy 63
4.5. Clinical safety 65
4.5.1. Discussion on clinical safety 98
4.5.2. Conclusions on clinical safety 103
4.5.3. PSUR cycle 103

5. Risk management plan 103

6. Changes to the Product Information 106

6.1.1. User consultation 106

7. Benefit-Risk Balance 107

7.1. Therapeutic Context 107
7.1.1. Disease or condition 107
7.1.2. Available therapies and unmet medical need 107
7.1.3. Main clinical studies 107
7.2. Favourable effects 108
7.3. Uncertainties and limitations about favourable effects 108
7.4. Unfavourable effects 109
7.5. Uncertainties and limitations about unfavourable effects 111
7.6. Effects Table 112

7.7. Benefit-risk assessment and discussion 114
7.7.1. Importance of favourable and unfavourable effects 114
Balance of benefits and risks 115
7.8. Conclusions 116

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 9 November 2020 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, II and IIIB

Update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Forxiga and Edistride based on the results from the renal outcomes study D169AC00001 (DAPA-CKD). The Annex II.B and Package Leaflet of these products are updated accordingly. The DAPA-CKD study is a category 3, Post-Authorisation Safety Study (PASS) listed in the dapagliflozin RMP to evaluate the potential risk of lower limb amputation; it is a multicentre, event-driven, randomized, double-blind, parallel group, placebo-controlled study, evaluating the effect of dapagliflozin versus placebo, given once daily in addition to standard of care, to prevent the progression of chronic kidney disease (CKD) or cardiovascular (CV)/renal death.
In addition, the Risk Management Plan for dapagliflozin (version 25s3) has been updated.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II 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/0373/2018 of 7 December 2018 on the granting of a (product-specific) waiver for dapagliflozin (Forxiga), (EMEA-000694-PIP04-18) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did seek Scientific advice at the CHMP (see section 4.1.3).

2. Recommendations

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

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, II and IIIB

Extension of Indication to add the treatment of chronic kidney disease in adults. Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated for Forxiga and Edistride based on the results from the renal outcomes study D169AC00001 (DAPA-CKD), and the Annex II.B and Package Leaflet of these products are updated accordingly. The DAPA-CKD study is a category 3, Post-Authorisation Safety Study (PASS) listed in the dapagliflozin RMP to evaluate the potential risk of lower limb amputation; it is a multicentre, event-driven, randomized, double-blind, parallel group, placebo-controlled study, evaluating the effect of dapagliflozin versus placebo, given once daily in addition to standard of care, to prevent the progression of chronic kidney disease (CKD) or cardiovascular (CV)/renal death.
In addition, the Risk Management Plan for dapagliflozin (version 25s3) has been updated.

☒is recommended for approval.

Amendments to the marketing authorisation

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

3. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion Forxiga/ Edistride - EMEA/H/C/WS1941.

4. Scientific discussion

4.1. Introduction

This application is based upon the single pivotal trial DAPA-CKD (D169AC00001) which was designed to support a new indication for the use of dapagliflozin 10 mg for the treatment of CKD: *Dapagliflozin is indicated in adults for the treatment of chronic kidney disease.*

4.1.1. Problem statement

Disease or condition

CKD is a serious and progressive condition that is associated with CV disease and increased risk of adverse outcomes including HF (Dhingra et al 2011), premature death (Muntner et al 2002), ESRD, and the need for RRT (Webster et al 2017). Globally, the most common causes of CKD are diabetes (42%), hypertension (18%), and glomerulonephritis of varying aetiologies (18%) (Xie et al 2018). An estimated 700 million people worldwide live with CKD (GBD Collaborators 2018). The global prevalence of CKD stage 3 to 5 (defined as eGFR < 60 mL/min/1.73 m^2) is estimated at 10.6% (Hill et al 2016); and estimates of global incidence, prevalence, and mortality of CKD have all increased dramatically since 1990; an effect driven by population growth, ageing, and increased prevalence of diabetes and hypertension (Xie et al 2018).

Standard of care for CKD in patients with and without diabetes is represented by blood pressure control and reduction of proteinuria through RAAS blockade (ACE-I or ARB) combined with CV risk management and/or and glycaemic control as necessary (Inker et al 2014, KDIGO 2013).

Another SGLT2 inhibitor, canagliflozin, has demonstrated cardiorenal efficacy in patients with CKD and T2DM (Perkovic et al 2019), and is currently approved for the treatment of diabetes nephropathy, in addition to standard of care. These results have recently been recognised in the KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease which recommend initiation of an SGLT2 inhibitor in patients with CKD, T2DM and eGFR ≥ 30 mL/min/1.73 m^2 per year (KDIGO 2020).

However, interventional studies assessing the use of ACE-I or ARB for the treatment for DKD (Brenner et al 2001, Lewis et al 2001) indicate that patients treated with these drugs remain at risk of morbidity, mortality, and progression to ESRD. An unmet need remains for safe and effective therapies that further reduce CKD morbidity, mortality, and progression towards ESRD, irrespective of the presence or absence of diabetes or albuminuria.

4.1.2. About the product

Dapagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor, previously approved for the treatment of patients with T1DM or T2DM. Additionally, dapagliflozin has been recently approved for the treatment of heart failure in adult patients with HFrEF.

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

The MAH sought advice from the FDA and EMA on the proposed design of the DAPA-CKD trial in 2016. At the time feedback was sought, the trial was proposed as a 3-arm trial in which patients would be randomised 1:1:1 to Dapa 10 mg, Dapa 5 mg, or placebo. Subsequent advice has been sought from the FDA.

As a result of the interaction with the EMA in March 2016, it was suggested that the proposed 3-arm study design was changed to 2-arm, Dapa 10mg and placebo. Primary endpoint was adjusted to include a greater sustained reduction of eGFR (≥ 50%) and an altered definition of ESRD as well as the lower limit for albuminuria raised to 200 mg/g. Additional comments from the EMA included the removal of CV death from primary composite endpoint, titration of background treatment to obtain adequate BP control, collection of safety data based on known dapagliflozin safety profile and close monitoring of volume depletion.

As a result of the interaction with the FDA in June 2016, sample size was increased to provide 90% power at alpha of 0.05, the schedule for assessment of renal function was adjusted so that the first post-enrolment eGFR assessment would occur at 14 days and renal adverse events, amputations, and fractures were included as adverse events of special interest.

4.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

4.2.1. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) for the drug substance dapagliflozin (as FORXIGA™) has previously been evaluated and approved by the European Medicines Agency (EMEA/H/C/002322) with market authorization on 12 November 2012.

The present submission concerns an application for an additional indication for FORXIGA in adults for the treatment of chronic kidney disease. An Environmental Risk Assessment (ERA) has been undertaken for dapagliflozin in accordance with the EMA Guidance. The assessment, including the results from the environmental fate and effects testing is presented as part of the submission.

No new data are provided in this updated risk assessment. However, the assessment has been updated and include a recalculation of PEC surface water using default market penetration factor (0.01) as opposed to the previously used refined value. In addition, in the evaluation of the environmental effects of dapagliflozin to sediment dwelling organisms $PEC_{Sediment}$ for dapagliflozin is now estimated according to the ECHA Guidance and the NOEC for sediment dwelling species normalised to a "standard sediment" with an organic carbon content of 10%, in accordance with the EMA guidance.

Recalculated PEC surface water

$PEC_{surface\ water}$ = (10 mg x 0.01) / (200 L x 10) = 0.05 µg/L

Recalculated PEC sediment

The $PEC_{Sediment}$ for dapagliflozin is estimated according to the ECHA Guidance (Ref 19). This estimation relies in part on the PEC for dapagliflozin of 0.05 µg/L. The estimation of $PEC_{Sediment}$ uses the following equation.

$$PEC_{Sediment} = \frac{(K_{SUSP-WATER} \times PEC_{Surfacewater} \times 1000)}{RHO_{SUSP}}$$

$PEC_{Surface\ water}$ = 0.05 µg/L
RHO_{SUSP} = bulk density of suspended matter = 1150 kg/m^3 (Ref 19)
$K_{SUSP-WATER}$ = suspended matter/water partitioning coefficient (m^3.m^{-3}, see below) is calculated as follows:

$$K_{SUSP-WATER} = Fwater_{SUSP}^{\#} + Fsoild_{SUSP}^{\#} \times \frac{Kp_{SUSP}}{1000} \times RHOsolid^{\#}$$

Where # values are standard values from the ECHA guidance (Ref 19) and Kp_{SUSP} is the partition coefficient solid-water in suspended matter (L/kg). Kp_{SUSP} is calculated as:

$$Kp_{SUSP} = Foc \times Koc$$

The fraction of organic carbon (Foc) in suspended matter is 0.1 (Ref 19) and the solid-water partition coefficient is taken from the adsorption/desorption study. The Kd(ads) was 51 (taken from Report No. BL8614/B) and was used to estimate the likely removal of dapagliflozin by adsorption, during sewage treatment. The content of carbon in sewage is 37% (Ref. 11), therefore the equivalent Koc value would be: Koc = Kd(ads) / 0.37 = 51 /0.37 = 138 and therefore

$$Kp_{SUSP} = 0.1 \times 138$$

$$Kp_{SUSP} = 13.8$$

The $K_{SUSP-WATER}$ can therefore be calculated as:

$$K_{SUSP-WATER} = 0.9 + 0.1 \times (13.8/1000) \times 2500$$

$$K_{SUSP-WATER} = 4.35\ m^3.m^{-3}$$

The $PEC_{SEDIMENT}$ is therefore calculated as:

$$PEC_{Sediment} = \frac{(K_{SUSP-WATER} \times PEC_{Surfacewater} \times 1000)}{RHO_{SUSP}}$$

$$PEC_{Sediment} = \frac{(4.35 \times 0.05 \times 1000)}{1150}$$

$PEC_{Sediment}$ = **0.19 µg/kg**

Recalculated PNEC Sediment

In accordance with the EMA guidance (Ref: "ERA QA 2011")) the NOEC for sediment dwelling species is normalised to a "standard sediment" with an organic carbon content of 10% ($FOC_{standard\ sediment}$), according to the equation;

$$NOEC_{standard\ sediment} = NOEC_{measured} \times \left(\frac{f_{OC\ standard\ sediment}}{f_{OC\ measured}} \right)$$

The organic carbon content of the artificial sediment used in the previously submitted Chironomus riparius toxicity study was determined via loss on ignition to be 2.4% ($FOC_{measured}$) (Study report No BL8661/B). Therefore, the normalised $NOEC_{standard\ sediment}$ is 150000 × (10/2.4) = 625000 µg/kg dry weight.

$PNEC_{sediment}$ = $NOEC_{standard\ sediment}$ / 100 (Assessment factor)

$NOEC_{standard\ sediment}$ = 625000 µg/kg

$PNEC_{sediment}$ = **6250 µg/kg**

PEC/PNEC assessments

Recalculated Dapagliflozin – PEC/PNEC assessments			
	PEC (µg/L)	**PNEC (µg/L)**	**PEC/PNEC**
Microorganisms	0.05	10760 **)	4.7×10^{-6}
Surface water	0.05	100	5.0×10^{-4}
Groundwater	0.0125	1000	1.3×10^{-5}
Sediment *)	0.19 (µg/kg)	6250 (µg/kg)	3.0×10^{-5}

*) Value proposed in the present ERA with the $PEC_{Sediment}$ for dapagliflozin estimated according to the ECHA Guidance and the PNEC calculated using NOEC for sediment dwelling species normalised to a "standard sediment" with an organic carbon content of 10% in accordance with the EMA guidance.
**) calculated highest concentration in the test vessels, see Assessor's comments below.

The recalculated PEC/PNEC ratios for microorganisms (<0.1), groundwater (<1) and surface water (<1), as well as for sediment (<1) are all below the trigger points and no further studies are thus required.

4.2.2. Conclusion on the non-clinical aspects

In the present ERA the MAH proposes a new calculation of PECsediment and PNECsediment as compared to calculations used in the initial application approved in 2012. Both calculations are considered acceptable and do not change the risk assessment for sediment.

The previously calculated highest concentration in the test vessels of 107.6 mg/L has been used for calculation of PNEC microorganisms instead of the proposed 200 mg/L in the submitted ERA. This is in line with data presented in the original EPAR for Forxiga.

Considering the previously submitted data and the now submitted updated PEC and PNEC calculations, dapagliflozin is not expected to pose a risk to the environment.

4.3. Clinical aspects

4.3.1. Introduction

GCP

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

4.3.2. Pharmacokinetics

popPK analysis

One pre-dose PK sample per patient was collected at Week 52 in the DAPA-CKD study. Due to the sparseness of the dapagliflozin concentration measurements in this study with adult CKD patients, a previously

established popPK model for dapagliflozin in healthy subjects, and adult and paediatric patients with T2DM was used as a basis to estimate the PK exposure and properties in adult patients with CKD.

Aim popPk

The aim of this exploratory analysis was to:

1. Characterise the PK of dapagliflozin in patients with CKD using a popPK model previously established in adults with T2DM, paediatric patients with T2DM, and healthy subjects
2. Compare dapagliflozin systemic exposure between different patient populations, including CKD patients with T2DM or without diabetes and adult patients with T2DM.

Data

For DAPA-CKD, 0.056% of the PK samples were excluded due to uncertain dosing records. In addition, 7.1% of the samples were BLQ. Table 2 provides a summary of the data used in this popPK analysis. In total, 11480 plasma PK samples from 3101 subjects treated with dapagliflozin were available (placebo-treated patients were excluded from the analysis). From these samples, the majority (82.4%) were from the adult T2DM and healthy subject studies, 15.5% from DAPA-CKD and 2.1% from the paediatric T2DM study.

Table 2 Summary of Data Used in the Population PK Analysis of Dapagliflozin in CKD Patients (N (%)).

	Day 1 pre-dose concentration	Uncertain dosing information	High pre-dose concentration	Outlier	Below LLOQ	Used in PK analysis
DAPACKD	0 (0)	1 (0.0562)	172 (9.67)	0 (0)	127 (7.14)	1478 (83.1)
T2DM submission	412 (4.35)	2 (0.0211)	353 (3.73)	73 (0.771)	615 (6.5)	8011 (84.6)
Paediatric T2DM study	0 (0)	0 (0)	0 (0)	0 (0)	10 (4.24)	226 (95.8)
All subjects	412 (3.59)	3 (0.0261)	525 (4.57)	73 (0.636)	752 (6.55)	9715 (84.6)

N, number; LLOQ, lower limit of quantification; PK, pharmacokinetic.
Datasource: pooled_pk_data_CKD_T2DM.csv; r-script: s06_exploratory_data_analysis.R; 2020-09-28 20:38:00

A summary of the baseline covariates for the 3055 subjects used in the analysis is available in Table 3. Overall, the median age was similar and median eGFR lower in the CKD patients with T2DM or without diabetes compared with adult T2DM patients.

Table 3 Covariate Summary for all Studies Stratified on Population

Variable	All subjects	DAPACKD without DM	DAPACKD with T2DM	T2DM	Paediatric T2DM	Healthy subjects
n	3055	560	1218	1223	24	30
Age [years] - (median [range])	60 [11, 93]	58 [23, 91]	65 [31, 93]	57 [18, 79]	15 [11, 17]	34 [25, 42]
Bodyweight [kg] - (median [range])	84 [39, 168]	78 [40, 145]	81 [39, 158]	90 [42, 164]	94 [61, 168]	80 [66, 99]
eGFR - (median [range])	56 [19, 154]	40 [23, 78]	42 [19, 86]	90 [32, 154]	110 [82, 154]	107 [76, 121]
Body mass index [(kg/m2)] - (median [range])	30 [16, 66]	27 [17, 50]	30 [16, 66]	32 [17, 47]	36 [23, 52]	26 [22, 33]
Males - n (%)	1828 (59.8)	390 (69.6)	795 (65.3)	604 (49.4)	9 (37.5)	30 (100.0)
Race - n (%)						
Caucasian	2134 (69.9)	331 (59.1)	645 (53.0)	1132 (92.6)	11 (45.8)	15 (50.0)
Black	143 (4.7)	22 (3.9)	67 (5.5)	30 (2.5)	11 (45.8)	13 (43.3)
Asian	609 (19.9)	184 (32.9)	378 (31.0)	46 (3.8)	0 (0.0)	1 (3.3)
Other	169 (5.5)	23 (4.1)	128 (10.5)	15 (1.2)	2 (8.3)	1 (3.3)
CKD stage - n (%)						
eGFR 15-29	229 (7.5)	80 (14.3)	149 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)
eGFR 30-44	821 (26.9)	271 (48.4)	537 (44.1)	13 (1.1)	0 (0.0)	0 (0.0)
eGFR 45-59	613 (20.1)	159 (28.4)	373 (30.6)	81 (6.6)	0 (0.0)	0 (0.0)
eGFR 60-89	739 (24.2)	50 (8.9)	159 (13.1)	523 (42.8)	2 (8.3)	5 (16.7)
eGFR > 90	653 (21.4)	0 (0.0)	0 (0.0)	606 (49.6)	22 (91.7)	25 (83.3)

CKD, chronic kidney disease; DM, diabetes mellitus; T2DM, type 2 diabetes mellitus; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Datasource: pooled_pk_data_CKD_T2DM.csv; r-script: s06_exploratory_data_analysis.R; 2020-09-28 20:38:00

Final model

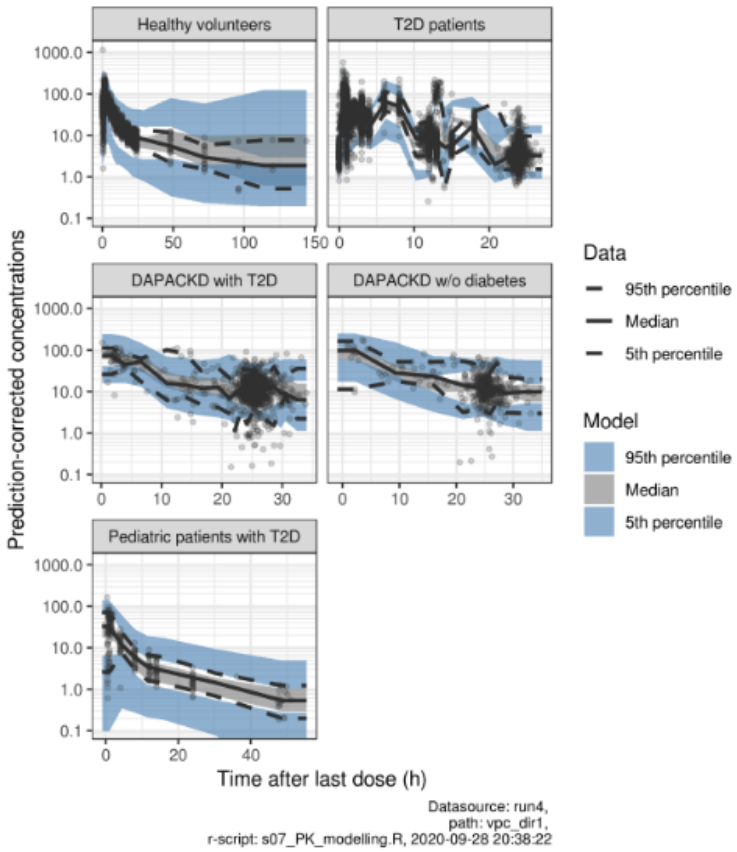
The final model was a two-compartment model with first-order absorption and first-order elimination. Exponential BSVwas estimated on CL/F and Vp/F. The BSV on KA was fixed to 8.52 from model estimated on adult T2DM and healthy subject data and the paediatric T2DM study. A combined error model was applied to account for residual variability and a separate residual variability was estimated for the paediatric patients. eGFR (higher CL/F with higher eGFR), and sex (higher CL/F for males), were used as covariates on CL/F. In addition, bodyweight (higher Vc/F with higher body weight) were used for Vc/F. The PK parameter estimates are presented in Table 5. CL/F was 21.6 L/h, which is very close to the previous estimate in T2DM patients and healthy subjects (22.9 L/h). The condition number was high, suggesting model simplification may be possible however the prediction-corrected visual predictive checks stratified on study are shown in Figure 8 indicated that the model could accurately describe the data.

Table 5 **Dapagliflozin PK Model Parameter Estimates for Final Model Based on CKD Patients With T2DM or Without Diabetes, adult T2DM Patients, Paediatric T2DM Patients and Healthy Subjects (Final Model – run4)**

OFV: -1732.921			
Condition number: 50500			
Parameters	**Units**	**Population Mean**	**RSE (%)**
KA	(h^{-1})	2.833	2.300
CL/F	(L/h)	21.56	1.400
Vc/F	(L)	73.47	1.500
Vp/F	(L)	168.5	8.000
Q/F	(L/h)	9.137	2.600
eGFR~CL/F	(-)	0.6374	3.300
SEX~CL/F	(-)	-0.1441	11.700
BWT~Vc/F	(-)	0.5424	12.700
EPI	(-)	0.5491	6.000
Between Subject variability			
CL/F	(-)	0.1136	4.200
Vp/F	(-)	0.8229	12.400
Residual variability			
Add Error (adults)	(-)	0.1849	0.800
Prop Error (adults)	(-)	0.2845	14.100
Prop Error (paediatrics)	(-)	0.2519	6.600
Datasource: run 4, r-script: s07_PK_modelling.R, 2020-09-28 20:41:04			

BWT, body weight; CL/F, apparent clearance; eGFR, estimated glomerular filtration rate; KA, first-order absorption rate constant; OFV, Objective Function Value; Q/F, apparent intercompartmental clearance; RSE, relative standard error; Vc/F, apparent central volume of distribution; Vp/F, apparent peripheral volume of distribution.

Figure 8 **Prediction-corrected Visual Predictive Check of Time After Last Dose of the Final Dapagliflozin PK Model for CKD Patients With T2DM or Without Diabetes, Adult T2DM Patients, Paediatric T2DM Patients and Healthy Subjects, Stratified by Population**

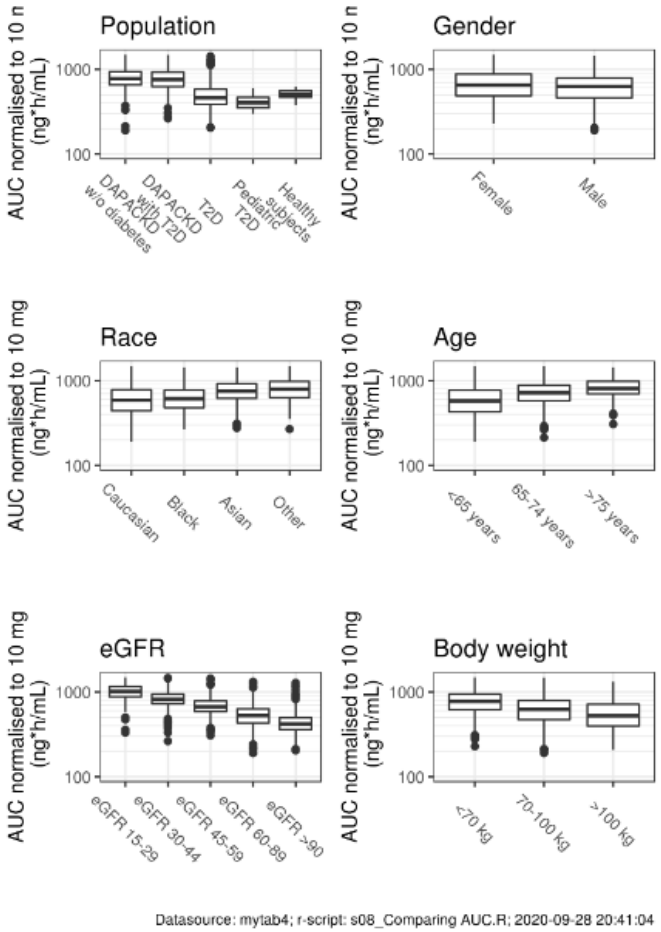


VPC, visual predictive check.
The solid and dashed lines represent the median, 5th, and 95th percentiles of observed (in black); the grey areas represent the 95% confidence interval of the median, 5th, and 95th percentiles of the simulated data.

Exposure in CKD patients

CKD patients with T2DM or without diabetes had similar model-derived AUC. Median AUC was approximately 1.6-fold higher in CKD patients compared to adults with T2DM but without CKD. No impact of race or gender was observed for AUC. Higher AUC was observed in patients with higher age or lower body weight. However, these differences were not considered to be clinically relevant.

Figure 9 **Dapagliflozin AUC Normalised to 10 mg Stratified on Different Covariates**



Datasource: mytab4; r-script: s08_Comparing AUC.R; 2020-09-28 20:41:04

AUC, area under dapagliflozin concentration-time profile, eGFR, estimated glomerular filtration rate.

4.3.3. Pharmacodynamics

No new information regarding biopharmaceutics is included in this application, which is considered acceptable.

4.3.4. Discussion on clinical pharmacology

The MAH proposed to add in section 5.2 of the SmPC:

"The effect of reduced renal function on systemic exposure was evaluated in a population pharmacokinetic model. Consistent with previous results, model predicted AUC was higher in patients with chronic kidney disease compared with patients with normal renal function and was not meaningfully different in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes."

This is supported by the popPK analysis. The stratified pcVPCs indicate that the model is satisfactory. VPCs stratified on eGFR could potentially have been useful. PK is however descriptive and the lack of such VPCs is not further perused. The update in section 5.2 in the SmPC is accepted.

4.3.5. Conclusion clinical pharmacology

The MAHs conclusion that the AUC was higher in patients with chronic kidney disease compared with patients with normal renal function and was not meaningfully different in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes, is accepted.

4.4. Clinical efficacy

4.4.1. Main study

A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease

Methods

DAPA-CKD was an international, multicentre, event-driven, randomized, double-blind, parallel-group, placebo-controlled study, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to standard of care, to prevent the progression of CKD and renal or CV death.

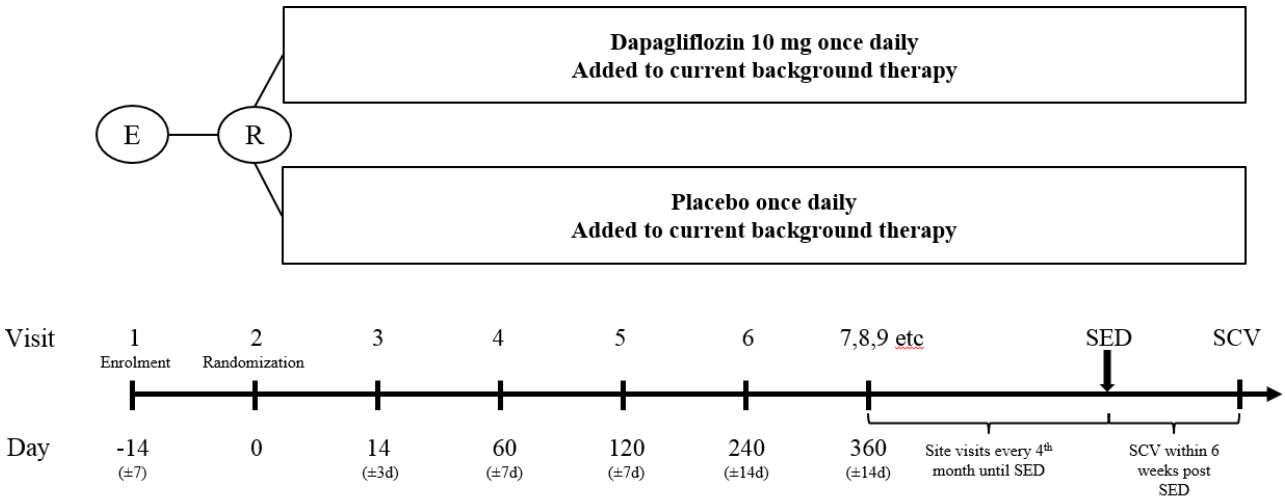
It was estimated that approximately 10000 patients at approximately 450 study sites in approximately 20 countries would be enrolled to reach the target of approximately 4000 randomized patients.

Study duration

The study was event-driven. The anticipated duration of the study was approximately 45 months with an estimated mean treatment period for a patient of 33 months. The study closure procedures were to be initiated when the predetermined number of primary endpoints were predicted to have occurred (n=681) (Figure 1). The study duration could be changed if the event rate or randomization rate were different than anticipated. The study could be terminated early if either a clear beneficial or harmful effect of the study

Figure 1: Study Design

treatment was detected during the Data Monitoring Committee (DMC) review.



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

Study participants

Adult patients were eligible to participate in the study if they had CKD defined as eGFR ≥ 25 and ≤ 75 mL/min/1.73 m2 (CKD-EPI Formula) at Visit 1, and evidence of increased albuminuria 3 months or more before Visit 1 and UACR ≥ 200 and ≤ 5000 mg/g at Visit 1.

UACR ≥ 200 mg/g was selected as the lower inclusion limit for UACR in-line with the principles of prognostic enrichment (FDA 2019). In addition, patients had to be on stable, maximum-tolerated labelled daily dose, of ACE-I or ARB for at least 4 weeks before Visit 1, if not medically contraindicated.

Inclusion criteria

Key inclusion criteria included:

- Provision of signed informed consent prior to any study specific procedures
- Female or male aged ≥ 18 years at the time of consent
- eGFR ≥ 25 and ≤ 75 mL/min/1.73 m2 (CKD-EPI Formula) at Visit 1
- Evidence of increased albuminuria 3 months or more before Visit 1 and UACR ≥ 200 and ≤ 5000 mg/g at Visit 1
- Stable, and for the patient maximum tolerated labelled daily dose, treatment with ACE-I or ARB for at least 4 weeks before Visit 1, if not medically contraindicated

Exclusion criteria

Subjects enrolled in this study were required to meet the following key exclusion criteria at screening (for full exclusion criteria, refer to the study protocol):

- Patients with known polycystic kidney disease
- Glomerulonephritis with flares (lupus or anti-neutrophil cytoplasmic antibodies associated vasculitis)

- Recent or ongoing renal inflammation (receiving cytotoxic therapy, immunosuppressive therapy or other immunotherapy for primary or secondary renal disease)
- Patients with type 1 diabetes mellitus
- CV events (eg, MI, stroke, coronary revascularisation procedures) within 12 weeks prior to enrolment
- New York Heart Association class IV Congestive HF at the time of enrolment

Medications/Therapies

All patients were to be treated for CV risk factors (eg, BP, lipids, and antithrombotic treatment), diabetes and CKD complications (eg, hyperphosphatemia, hyperparathyroidism, hyperkalaemia, acidosis and renal anaemia).

Treatment with non-steroidal anti-inflammatory drugs (NSAID) was, if possible, to be avoided during the study.

Concomitant treatment with open-label SGLT2 inhibitors eg, dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, tofogliflozin and luseogliflozin and fixed-dose combinations containing these drugs was prohibited.

CKD Medication

To be eligible, the patient needed to be on stable and for the patient maximum tolerated labelled daily dose of ACE-I or ARB for at least 4 weeks before Visit 1, if not medically contraindicated. If the patient was not on an ACE-I or ARB at the time of enrolment, the reason was to be recorded in the eCRF.

Details regarding the following CKD related treatments were to be recorded in the eCRF throughout the study:

- RAAS inhibition: ACE-I/ARBs, renin inhibitors, mineralocorticoid antagonists
- Diuretics: Loop diuretics, thiazide diuretics and other diuretics
- Treatment of underlying kidney disease: cytotoxic agents, immunosuppressive agents, other immunotherapy
- Phosphate binders
- Potassium binders

Diabetes Treatment

Patients with T2DM at randomisation in this study continued their T2DM treatment. Treatment was to be based on established guidelines and according to local laboratory values. Patients were eligible for adjustments in their anti-diabetes treatment at the discretion of their diabetes health care provider. Diabetes medications at baseline and any changes throughout the study, were to be recorded in the eCRF.

Treatments

At randomisation, Visit 2 (Day 0), eligible patients were randomly assigned to 1 of 2 treatments:

- Dapagliflozin 10 mg, given once daily per oral use

- Placebo – one placebo tablet to match dapagliflozin 10 mg, given once daily per oral use

Reduction of dose to dapagliflozin 5 mg was permitted if clinically indicated. If the dose was decreased, or interrupted, the dose was increased back, or re-introduced, to 10 mg dapagliflozin (or matching placebo), as soon as the patient's condition was stable, in the opinion of the investigator. All patients were required to be on current available standard of care treatment for CKD. Therefore, placebo was an appropriate comparator.

Objectives

Primary objective

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/1.73m2 and albuminuria (urine albumin creatinine ratio [UACR] ≥ 200 and ≤ 5000 mg/g).

Secondary objectives

To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the composite endpoints of worsening of renal function.

To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of the composite endpoint of CV death or hospitalisation for heart failure.

To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of all-cause mortality.

Safety objective

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

Outcomes/endpoints

Primary efficacy outcome:

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

1. ≥ 50% sustained* decline in eGFR
2. Reaching ESRD
    - Sustained eGFR < 15 mL/min/1.73 m2 or,
    - Chronic* dialysis treatment or,
    - Receiving a renal transplant
3. CV death
4. Renal death

Secondary efficacy outcomes:

- Time to the first occurrence of any of the components of this composite:
    - ≥ 50% sustained decline in eGFR
    - Reaching ESRD

    - Renal death
- Time to the first occurrence of either of the components of this composite:
    - CV death
    - Hospitalisation for heart failure
- Time to death from any cause

Safety outcome measures:

1. Serious adverse event (SAE)
2. Discontinuation of investigational product (IP) due to adverse event (DAE)s
3. Changes in clinical chemistry/haematology parameters
4. AEs of interest (volume depletion, renal events, major hypoglycaemic events, fractures, diabetic ketoacidosis (DKA), AEs leading to amputation and AEs leading to a risk for lower limb amputations ["preceding events"]

Exploratory outcome measures

- Time to the first occurrence of any of the components of this composite: chronic dialysis, receiving renal transplant or renal death)
- Time to the first occurrence of each of the individual components: ≥ 50% sustained decline in eGFR, reaching ESRD, CV death or Renal death
- Time to the first occurrence of two consecutive central laboratory values showing either of the following: ≥ 30% decline in eGFR from baseline, ≥ 40% decline in eGFR from baseline
- The effect on eGFR over time will be measured: from baseline to end of treatment, from first on treatment measurement to end of treatment.
- Proportion of patients with eGFR > 40 mL/min/1.73 m^2 at baseline that enter CKD 4 during the study.
- Changes in UACR from baseline.
- Time to the first occurrence of each of any of the following central laboratory levels of serum potassium:> 6.0 mmol/L, > 5.5 mol/L, < 3.5 mmol/L, < 3.0 mmol/L
- Time to the first occurrence of an event of doubling of serum creatinine (compared to the most recent central laboratory measurement)
- Proportion of patients without diabetes at baseline with a new diagnosis of T2DM during the study
- Changes in HbA1c from baseline
- Change in systolic BP from baseline
- Change in body weight from baseline
- Time to the first occurrence of any of the components of this composite: CV death, MI and Stroke
- Time to first hospitalization for heart failure
- Time to first fatal or non-fatal MI
- Time to first fatal or non-fatal stroke of any cause

- Change from baseline in the overall summary score of the KDQOL™-36
- Changes in health status measured by the EQ-5D-5L

Definitions and adjudications

Sustained eGFR decline of ≥ 50% from baseline and sustained eGFR < 15 ml/min/1.73 m^2 were based on 2 consecutive central laboratory values at least 28 days apart below the respective limit. These endpoints were derived from the central laboratory and were not adjudicated.

The following potential endpoints were recorded in the eCRF and submitted for central adjudication by a CEA Committee: all deaths, renal endpoints (dialysis, kidney transplantations, doubling of serum creatinine [compared to the most recent central laboratory measurement]), hospitalization for HF, cardiac ischemic events, and cerebrovascular events. Chronic dialysis was adjudicated as dialysis treatment ongoing for at least 28 days, or when the renal deterioration was deemed irreversible and the dialysis treatment was stopped before Day 28. To be included in the primary and secondary efficacy variables, events had to be confirmed by the CEA (with the exception of eGFR events).

Sample size

The study was event-driven. With an annual event rate of 7.5% in the placebo treatment group, 4000 patients were estimated to provide the required number of primary events, based on an anticipated recruitment period of 24 months and an average follow-up period of approximately 33 months. The assumed placebo event rate of 7.5% is based on a review of published data in the CKD population. The number of patients with incomplete follow-up of endpoints was expected to be small; hence, these were not considered in the determination of the sample size.

Assuming a true HR of 0.78 between dapagliflozin and placebo, using a one-sided alpha of 2.5%, 681 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. The assumed hazard ratio of 0.78 is considered as clinically relevant.

Randomisation

Randomization of patients was performed using an IxRS in balanced blocks to ensure an approximate balance between treatment groups. Patient recruitment was continuously monitored in order to achieve adequate proportions of patient subpopulations. Patients were randomized at 386 sites in 21 countries.

Patients were randomized in a 1:1 ratio to receive either 10 mg dapagliflozin once daily or placebo. Randomization was stratified by:

- T2DM status (with or without) at the time of randomization
- UACR > 1000 and ≤ 1000 mg/g.

The number of patients with eGFR 60 to 75 mL/min/1.73 m^2 at the time of randomization was also monitored to ensure that the number of patients in this subpopulation did not exceed approximately 10%. The number of randomized patients with and without T2DM was monitored in order to ensure a minimum of 30% in each subpopulation. Randomization was capped when the pre-determined limits were reached. Randomization of patients based on geographic region was monitored to ensure a global representation. Also, the proportion of patients not on ACE-I or ARB at randomization, due to intolerance, was monitored to ensure that the target population was reflected with regard to background therapy.

Blinding (masking)

The blinding of treatment was ensured by using a double-blind technique. The dapagliflozin tablets and the respective placebo tablets were identical in size, colour, smell, and taste. The bottles with IP were labelled with unique identification numbers.

No member of the extended MAH study team, site personnel, or any clinical research organization (CRO) handling study data had access to the randomization scheme during the study. The MAH personnel or delegate generating the randomization scheme and the Supply Chain Study Management were able to access the randomization scheme as appropriate.

Monitoring and adjudication committees

The Executive Committee was to make recommendations to the MAH with regard to early stopping or modifications of the study based on the information received from the DMC.

The National Lead Investigator (NLI) Committee was comprised of NLIs from each country where the study was conducted and was supervised by the Executive Committee.

An independent Data Monitoring committee (DMC) was appointed and reported to the Executive Committee. The DMC was responsible for safeguarding the interests of the patients in the study by assessing the safety of the IP, and for reviewing the overall conduct of the study. The DMC had access to the individual treatment codes and was able to merge these with the collected study data while the study was ongoing.

The role of the Clinical Event Adjudication (CEA) committee was to independently review, interpret and adjudicate potential endpoints experienced by the patients. Endpoints were identified preliminarily by the Investigators, and also by the MAH personnel or in the CEA process as specified in the CEA charter. The CEA committee members did not have access to individual treatment codes for any patient or clinical efficacy endpoint and safety events. The precise responsibilities and procedures applicable for the CEA were detailed in the CEA charter.

Statistical methods

Analysis sets

All patients who had been randomized to study treatment were included in the full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients were analysed according to their randomized IP assignment.

All patients who received at least one dose of randomized treatment were included in the safety population. Patients were analysed according to the treatment actually received.

Hypothesis

For the primary endpoint the following hypothesis was tested at the 2.5% one-sided level:

H0: HR [dapagliflozin:placebo]≥1 versus
H1: HR [dapagliflozin:placebo]<1.

For clarity, two-sided p-values were presented in the CSR and the alpha threshold for statistical significance used in the confirmatory testing was 0.05 (corresponding to one-sided alpha of 0.025).

Estimand

The primary and secondary objectives were evaluated under the treatment policy estimand to reflect the effect of the initially assigned randomized study drug, irrespective of adherence to randomized study

treatment. Specifically, the analysis was performed for the full analysis set including all events that occurred on or prior to the primary analyses censoring date (PACD), including events following premature discontinuation of study drug.

Primary analysis

Potential endpoint events and event dates were adjudicated by CEA committee. The eGFR events were not adjudicated. The primary variable was time to first event included in the primary composite endpoint. The primary analysis was based on the FAS using confirmed or adjudicated events.

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 randomization stratification factors (T2D, UACR), and adjusting for eGFR. The event rates (per 100 person-years), p-value, hazard ratio (HR) and 95% confidence interval (CI) were reported. In general, the analysis used each patient's last contact as the censoring date for patients without any primary events. Deaths adjudicated as 'cause undetermined' with regard to CV death or non-CV death were included in the analyses as CV deaths but were not considered as renal deaths. Patients who did not have an endpoint event were censored at the earliest of date of withdrawal of consent (WoC) or non-CV death or non-renal death when applicable, and otherwise at the earliest of date of last clinical event assessment and PACD.

The contribution of each component of the primary composite endpoint to the overall treatment effect was examined. The first event of the given type was included irrespectively of any preceding non-fatal composite event of a different type. Methods similar to those described for the primary analysis were used to separately analyse the time from randomization to the first occurrence of each component of the primary composite endpoint. Last contact was treated as the censoring date for patients without the endpoint of interest. Kaplan-Meier estimates of the cumulative incidence to the first occurrence of any event in the primary endpoint were calculated and plotted, for overall analysis and for the individual components.

Sensitivity analysis was performed for the primary endpoint 1) excluding chronic dialysis events ongoing less than 90 days, and 2) where deaths adjudicated as 'undetermined' cause were not included as CV deaths but treated as censoring events.

No hazard ratio estimates with confidence interval and p-values were given when less than 15 events in total, both treatment groups combined.

Missing data

The time-to-event analysis using the Cox regression depends 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 WoC, lost to follow-up or otherwise incomplete follow-up of endpoints. The amount of missing data was described e.g., in terms of the number of patients and patient time with incomplete follow-up. To assess the impact of missing data and the robustness of the results with regard to the assumption of non-informative censoring, sensitivity analysis was based on the evaluation of the missing follow-up and discussed in relation to the observed efficacy signal. This could include analysis where scenarios in terms of increased risk in censored patients were explored to identify a 'tipping point' where statistical significance would be lost.

Secondary and subgroup analyses

The secondary variables were analysed in the similar manner as the primary variable. Subgroup variables for the primary efficacy endpoint and secondary efficacy endpoints included demography (age, sex, race, geographic region) and baseline disease characteristics (T2D, UACR, eGFR, and Systolic blood pressure).

Interim analysis

An interim analysis was initially planned to be performed when 75% of the primary endpoints were adjudicated, using a Haybittle-Peto rule. However, the interim analysis was removed in accordance with protocol version 4.0 dated 17 March 2020.

On 26 March 2020, the DMC held a regular review meeting to assess data. Based on their review, the DMC recommended that the study be stopped early on the basis of positive efficacy results. The Executive Committee together with the MAH decided on 2 April 2020 to set the study end date (and the PACD) to 3 April 2020.

Multiplicity

A closed testing procedure of the primary and secondary endpoints was utilized in a pre-specified hierarchical order as given in the *Outcomes/endpoints* section. The Type I error was initially planned to be controlled at a one-sided 0.02496 level for multiplicity in consideration of the planned interim analysis. Since the interim analysis was removed, in accordance with protocol version 4.0, the alpha level was updated for the final analysis. The Type I error was controlled at a one-sided 0.025 level for multiplicity across the primary and the 3 secondary endpoints.

Retrospective evaluation

It was recognised that the informal analysis by the DMC and the unplanned early stop led to multiplicity. The MAH provided the following framework in order to assist with statistical interpretation of the efficacy results.

1) Primary endpoint

When evaluating the efficacy data in March 2020, the DMC referred to Haybittle-Peto boundary as the statistical criterion for the primary endpoint, in their deliberation leading to the recommendation for early stop. Although not considered to be required by the MAH, the same Haybittle-Peto boundary was prudent to use in evaluating the primary endpoint in the retrospective setting.

2) Secondary endpoints

Hung et al 2007 (Hung et al 2007) and Glimm et al 2010 (Glimm et al 2010) illustrated the complexity associated with the MTP for secondary endpoints, in a group sequential design (GSD), when the stopping criteria were primarily based on the primary endpoint. In particular, the FWER increases with higher correlation between the primary endpoint and the secondary endpoint(s). The FWER is also dependent on the magnitude of the treatment effect on the primary endpoint. Hung et al illustrated that using the full alpha does not always ensure strong control of the FWER, while using the same critical value (threshold) as in the stopping criteria for the primary endpoint is overly conservative and with reduced power. Glimm et al provided a general framework and benchmark for deriving MTP. The MAH adopted a framework similar to Glimm et al for the retrospective evaluation while recognising that their work was in the context of prospective GSD designs. The MAH claimed that a two-sided alpha threshold of 0.03 would ensure strong control of FWER, accounting for 3 analyses: DMC informal analysis for the primary endpoint only (408 primary endpoint events), current analysis (509 primary endpoint events) and planned final analysis (681 primary endpoint events). This result was conservatively based on the correlation of 0.87 between the primary endpoint and first secondary endpoint in testing hierarchy which was modelled as being approximately equal to the square root of the proportion of the joint events in the primary and first secondary endpoint (385 1st secondary endpoint events/509 primary endpoint events). It was presented that the maximum FWER associated with a threshold of 0.03 is 0.4984 (two-sided).

In conclusion, the primary and secondary efficacy endpoint results as reported in the CSR were statistically significant based on the pre-specified procedure as described in the SAP, and when the MAH's threshold of 0.03 was applied for ensuring FWER at two-sided 0.05.

Safety analyses

Safety analyses were performed by means of descriptive statistics using both on treatment observations and using all observations regardless of whether patients are on or off study treatment.

Changes to the pre-specified analyses

No changes to the analyses were made after the unblinding of study data.

The statistical analyses were performed according to the SAP version 2 (15 April 2020) after DBL (17 July 2020). The first SAP was authored prior to first patient enrolled. The major change in the SAP version 2 was removal of the pre-planned interim analyses as described above.

According to the first SAP version, the study had a group sequential design study with an interim analysis that would assess superiority of dapagliflozin to placebo on a one-sided alpha level of 0.001. If superiority was achieved, the DMC would evaluate the totality of the efficacy data, in particular ESRD and mortality, and safety data, to determine if benefit is unequivocal and overwhelming such that the DMC recommends ending the study. If the study was stopped for superiority, then testing of secondary endpoints would continue down the hierarchy at one-sided significance level 0.001.

Results

Participant flow

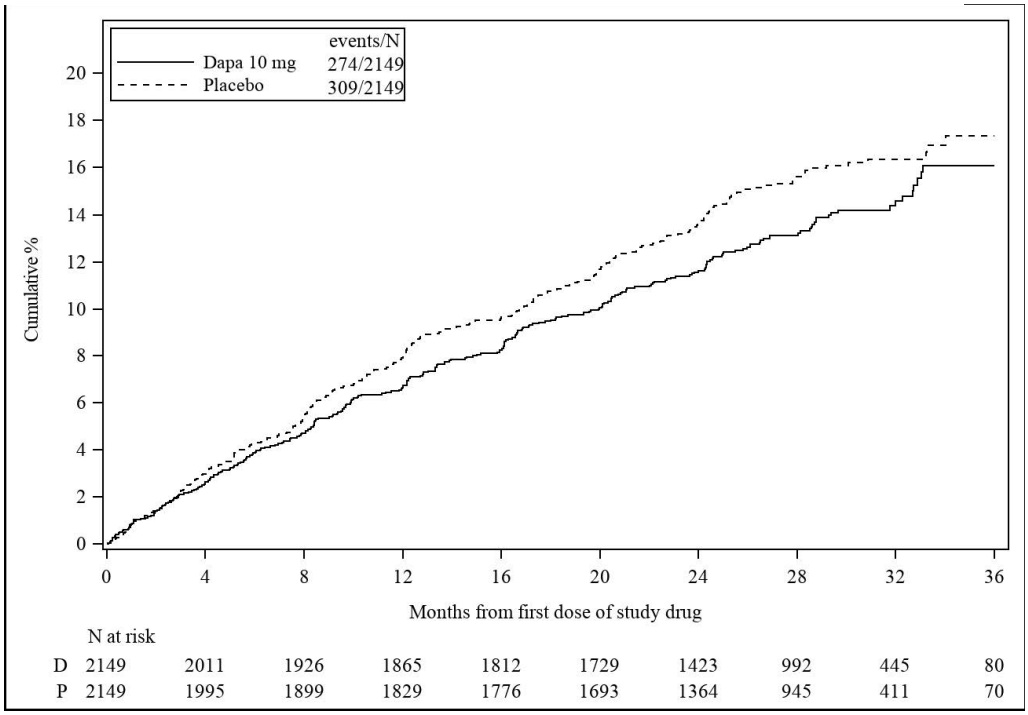
In total, 7517 patients were enrolled, 4304 patients were randomized, and 4289 patients completed the study. The median time in study until PACD was 27.6 months (range 0.1 to 38.2 months), and median time in study until last visit was 28.5 months (range 0.3 to 39.2 months). In total, 11 (0.3%) patients withdrew consent during the study and the proportions of patients who withdrew consent were balanced between treatment groups. Overall, 15 patients discontinued the study (10 in dapagliflozin, 5 in placebo). Vital status was unknown for 5 patients in total. There were 2142 (99.5%) and 2147 (99.8%) patients who completed the study in the dapagliflozin and placebo arms, respectively (Figure 3).

In total, few (13.5%) patients prematurely and permanently discontinued IP, with similar proportions in the dapagliflozin group (12.7%) and the placebo group (14.4%).

Recruitment

This study was conducted at 405 sites across 21 countries, and patients were randomized at 386 sites. The first patient was enrolled on 02 February 2017. Study closure visits started after the study end date (SED), which was also the primary analysis censoring date (PACD) for efficacy analyses (including events occurring on or prior to that date). On 02 April 2020, the PACD was set to 03 April 2020 by the executive committee. The last patient completed the last visit on 12 June 2020, and the database was locked on 17 July 2020.

Figure 2:Kaplan-Meier Plot of the Cumulative Percentage of Patients with Premature Permanent Discontinuation of Study Drug (SAS)



Conduct of the study

Protocol amendments

Version 1.0 of the CSP was dated 26 October 2016. There were 3 amendments to the CSP: Version 2.0 was dated 26 September 2017, Version 3.0 was dated 22 January 2020, and Version 4.0 was dated 17 March 2020. All amendments were made after the start of patient recruitment. All amendments were made after the start of patient recruitment. Protocol amendments and other significant changes to study conduct are shown in *Table 1*.

Table 1:Protocol Amendments and Other Significant Changes to Study Conduct

Number (Date of Internal Approval)	**Key Details of Amendment (Section of This Report Affected, If Applicable)**	**Reason for Amendment**	**Person(s)/ Group(s) Responsible for Amendment**
Amendments Made Before the Start of Subject Recruitment			
None			
Amendments Made After the Start of Subject Recruitment			

1 (26Sep2017)	Expanding the AE of interest category of amputations to also include:AEs leading to a risk for lower limb amputations ("preceding events").	Regulatory authority interaction	AstraZeneca Clinical Study Team
	Clarifying inclusion criteria number 4 and exclusion criteria number 11. Extending requirement for contraceptives (exclusion criteria 13)	Regulatory authority interaction and harmonisation with the ICF	AstraZeneca Clinical Study Team
	Handling of incorrectly randomised patients	Clarification	AstraZeneca Clinical Study Team
	Provision of additional guidelines regarding essential treatment in the setting of acute worsening of heart failure or other acute situations	Clarification	AstraZeneca Clinical Study Team
	Removal of parathyroid hormone (PTH) central laboratory assessment (Table 2) Change in table footnote a) and clarifying removal of 21 days window for optional lab assessment.	Analysis of PTH can be done, if applicable, using biomarker samples and no separate sampling is needed	AstraZeneca Clinical Study Team
	Additional information regarding investigator responsibility in terms of standard of care treatment after the patient stops study drug	Clarification	AstraZeneca Clinical Study Team
	Removal of requirement for adjudicating potential endpoints related to eGFR decline	The endpoint criteria did not justify adjudication of these events	AstraZeneca Clinical Study Team
	Additional information regarding what was considered an AE of special interest for renal events.	Clarification based on feedback	AstraZeneca Clinical Study Team
	Recording of AEs to not include potential renal endpoints that were based on laboratory results only, unless they fulfilled SAE or DAE criteria	Protocol mandated laboratory values were systematically analyzed	AstraZeneca Clinical Study Team

Number (Date of Internal Approval)	**Key Details of Amendment (Section of This Report Affected, If Applicable)**	**Reason for Amendment**	**Person(s)/ Group(s) Responsible for Amendment[a]**

	Only HF endpoints and fatal AEs were withheld from reporting to health authorities	To simplify SAE reporting and minimize the risk for withholding renal AEs of special interest, which should have been reported	AstraZeneca Clinical Study Team
	Added information about Medication Error definition and reporting	Additional information	AstraZeneca Clinical Study Team
	Use of open label treatment with SGLT2 inhibitors was not prohibited if the patient was not taking study medication, but was to be avoided	Clarification	AstraZeneca Clinical Study Team
	Inclusion of detailed recording of cardiovascular medications in the eCRF during the study	Additional information	AstraZeneca Clinical Study Team
	Possibility for the DMC to conduct more than one interim analysis of efficacy if necessary	Clarification	AstraZeneca Clinical Study Team
2 (22Jan2020)	New exploratory objective added: *To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of the composite endpoint of chronic dialysis, renal death or receiving a renal transplant*	To prespecify a renal composite objective that only included a hard renal and no surrogate (eGFR) endpoint	AstraZeneca Clinical Study Team
	New exploratory objective added: *To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of the composite endpoint of CV death, MI or stroke*	To prespecify a CV composite objective in order to better evaluate overall CV efficacy	AstraZeneca Clinical Study Team
	Changed wording for outcome measure of exploratory objective to determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of events of doubling of serum creatinine: time of first occurrence of an event instead of number of events	Correction so that the objective would reflect the statistical analysis to be used	AstraZeneca Clinical Study Team
3 (17Mar2020)	Removal of all text relating to interim analysis. Statistical testing level for endpoints changed to 2.5% instead of 2.496%	Outcome of planned interim analysis would be close to planned study end date	AstraZeneca Clinical Study Team

Protocols deviations

Important protocol deviations are summarized in *Table 2*. Overall, 2.6% of the patients had 1 or more important protocol deviation. The most frequent important protocol deviation was failed inclusion criteria related to stable ACE-I or ARB treatment, reported for in total 47 patients (1.1%) and equally distributed between treatment groups. The number of subjects with important protocol deviations in each treatment group was balanced with respect to both frequency and type of protocol deviations. All important protocol deviations were reviewed and agreed before database lock.

Table 2:Summary of Important Protocol Deviations (FAS)

	Number (%) of subjects		
	Dapa 10 mg (N=2152)	**Placebo (N=2152)**	**Total (N=4304)**
Important protocol deviation			
Number of patients with at least 1 important deviation	61 (2.8)	52 (2.4)	113 (2.6)
Randomised but did not fulfil all inclusion and exclusion criteria	52 (2.4)	46 (2.1)	98 (2.3)
Patient took incorrect investigational treatment ie, IP not allocated through IxRS	1 (0.0)	0 (0.0)	1 (0.0)
Patient received prohibited medications during IP period ie, SGLT2 Inhibitor a	8 (0.4)	6 (0.3)	14 (0.3)

Changes to Planned Analyses

Changes to the planned analyses are shown in *Table 3*. No changes were made after the unblinding of study data.

Table 3: Changes to Planned Analyses

Key Details of Change (Section of this Report Affected, If Applicable)	**Reason for Change**	**Person(s)/ Group(s) Responsible for Change**
Changes made before unblinding of study data for SAP Version 2.0 15 April 2020		
eGFR endpoints were derived programmatically using serum creatinine values and were not adjudicated	Following protocol updates	MAH Clinical Study Team
AESI categories were expanded to include AEs leading to a risk for lower limb amputations	Following protocol updates	
Exploratory objectives added: MACE and composite endpoint of chronic dialysis/renal transplant/renal death	Following protocol updates	
Doubling of serum creatinine was analyzed as time to first event	Following protocol updates	

Interim analysis was removed and alpha level updated for the final analysis	Following protocol updates	
Time-to-event analyses were to contain 15 or more events to be produced.	Addition	
Baseline was defined in relation to date of randomization	Clarification	
ACE-I/ARB was removed as a sub-group variable due to small sample size on patients without ACE-I/ARB	Update	
Subgroup analyses were conducted for all secondary endpoints	Addition	

Interim Analysis

The original DAPA-CKD CSP included a planned interim analysis at 75% of endpoint events. The MAH took the decision to remove the planned interim analysis on 05 March 2020 as the anticipated timing of the planned interim analysis was expected to be close to the planned study end date and there was concern relating to the potential impact of the developing COVID-19 pandemic on study close-out. The DMC was informed of this decision on 11 March 2020, and CSP Version 4.0 was finalized on 17 March 2020. CSP amendment 4 removed text relating to the planned interim analysis and updated the statistical testing level for endpoints at the final analysis to 2.5% from 2.496%.

Early Stop

On 26 March 2020, the DMC held a regular review meeting to assess data. Based on their review, the DMC recommended that the study be stopped early on the basis of positive efficacy results. The decision was made public on 30 March 2020. The Executive Committee together with the MAH decided on 2 April 2020 to set the SED to 3 April 2020. The final database contained a total of 509 primary endpoint events in the FAS versus the originally planned 681 primary endpoint events.

Covid-19

Deviations from the clinical study protocol, procedures and guidance's due to COVID 19 were recorded in the CTMS. By DBL, a total of 2800 deviations related to COVID-19 had been reported. A listing by country, site, patient, treatment code, and category is provided in the clinical study report. None of the COVID-19-related protocol deviations were categorised as an important protocol deviation. Deviations were in general evenly distributed between treatment groups.

Baseline data

Patient demographic characteristics were balanced between the two treatment groups. In the overall patient population, 66.9% of patients were male, mean age was 61.8 years, and 57.8% were ≤ 65 and 42.2% were > 65 years old. Patients were randomized worldwide, with 28.6% of patients randomized in Europe, 18.9% in North America, 21.2% in Latin/South America, and 31.3% in Asia. Of the total study population, 53.2% of patients were White, 34.1% were Asian, and 4.4% were Black or African-American.

In total, 67.5% of patients in the study had T2DM and 32.5% did not have diabetes. There were equal proportions of patients with T2DM in the dapagliflozin and placebo group, respectively. Patient demographics and baseline subject characteristics in subgroups of patients with T2DM and patients without diabetes are shown in Table 4 and Table 5.

General patient characteristics and characteristics related to CKD, at baseline, are summarized in (Table 6). At baseline, mean eGFR was 43.1 mL/min/1.73 m2, 14.5% of patients had eGFR < 30 ml/min/1.73 m2, and 58.6% of patients had eGFR < 45 ml/min/1.73 m2. Median UACR was 949.3 mg/g and 51.7% of patients had UACR ≤ 1000 mg/g. Mean SBP was 137.1 mmHg.

The most common investigator judged causes of CKD were as follows: diabetic nephropathy (58.3%), hypertension (16.0%), and chronic glomerulonephritis (16.1%).

Concomitant Medication

All patients were to be treated for CV risk factors, diabetes and CKD complications during the study. At randomization, 97.0% of patients were treated with ACE-I or ARB and 94.1% of patients with T2DM were treated with diabetes medications. Overall, the most commonly used CV medications were: ACE-I (31.5%) or ARB (66.7%), lipid lowering agents (69.4%), calcium channel blockers (50.7%), and antithrombotic agents (47.4%). The most commonly used diabetes medication was insulin (55.4%).

The use of ACE-I and ARB after randomization was high and remained stable throughout the trial.

Table 4: Demographic characteristics by T2DM status (FAS)

T2DM subjects

Demographic characteristic		Dapa 10 mg (N=1455)	Placebo (N=1451)	Total (N=2906)
Age (years)	n	1455	1451	2906
	Mean	64.1	64.7	64.4
	SD	9.8	9.5	9.7
	Median	65.0	65.0	65.0
	Min	26	26	26
	Max	93	90	93
Age group (years) n (%)	≤ 65	770 (52.9)	737 (50.8)	1507 (51.9)
	> 65	685 (47.1)	714 (49.2)	1399 (48.1)
	≤ 65	770 (52.9)	737 (50.8)	1507 (51.9)
	66 - 75	508 (34.9)	528 (36.4)	1036 (35.7)
	> 75	177 (12.2)	186 (12.8)	363 (12.5)
	Total	1455	1451	2906
Sex n (%)	Male	961 (66.0)	980 (67.5)	1941 (66.8)
	Female	494 (34.0)	471 (32.5)	965 (33.2)
	Total	1455	1451	2906
Race n (%)	White	751 (51.6)	790 (54.4)	1541 (53.0)
	Black or African American	76 (5.2)	61 (4.2)	137 (4.7)
	Asian	481 (33.1)	451 (31.1)	932 (32.1)
	Native Hawaiian or other Pacific Islander	0	1 (0.1)	1 (0.0)
	American Indian or Alaska Native	53 (3.6)	58 (4.0)	111 (3.8)
	Other	94 (6.5)	90 (6.2)	184 (6.3)
	Total	1455	1451	2906
Ethnic group n (%)	Hispanic or Latino	398 (27.4)	396 (27.3)	794 (27.3)
	Not Hispanic or Latino	1057 (72.6)	1055 (72.7)	2112 (72.7)
	Total	1455	1451	2906
Region/ Country n (%)	Asia	438 (30.1)	403 (27.8)	841 (28.9)

Baseline diabetic status is defined as follows: Diabetes Medical history of T2DM or central laboratory HbA1c ≥ 6.5% at both visit 1 and visit 2.
Dapa Dapagliflozin. FAS Full analysis set. Max Maximum. Min Minimum. N Number of subjects in treatment group. n Number of subjects included in analysis. SD Standard deviation. T2DM Type 2 diabetes mellitus.

T2DM subjects

Demographic characteristic		Dapa 10 mg (N=1455)	Placebo (N=1451)	Total (N=2906)
	China	45 (3.1)	50 (3.4)	95 (3.3)
	India	81 (5.6)	78 (5.4)	159 (5.5)
	Japan	67 (4.6)	66 (4.5)	133 (4.6)
	Philippines	56 (3.8)	36 (2.5)	92 (3.2)
	South Korea	80 (5.5)	86 (5.9)	166 (5.7)
	Vietnam	109 (7.5)	87 (6.0)	196 (6.7)
	Europe	367 (25.2)	404 (27.8)	771 (26.5)
	Denmark	14 (1.0)	9 (0.6)	23 (0.8)
	Germany	39 (2.7)	45 (3.1)	84 (2.9)
	Hungary	46 (3.2)	66 (4.5)	112 (3.9)
	Poland	38 (2.6)	43 (3.0)	81 (2.8)
	Russia	73 (5.0)	72 (5.0)	145 (5.0)
	Spain	83 (5.7)	99 (6.8)	182 (6.3)
	Sweden	7 (0.5)	7 (0.5)	14 (0.5)
	UK	14 (1.0)	16 (1.1)	30 (1.0)
	Ukraine	53 (3.6)	47 (3.2)	100 (3.4)
	North America	308 (21.2)	315 (21.7)	623 (21.4)
	Canada	99 (6.8)	107 (7.4)	206 (7.1)
	USA	209 (14.4)	208 (14.3)	417 (14.3)
	Latin/South America	342 (23.5)	329 (22.7)	671 (23.1)
	Argentina	90 (6.2)	76 (5.2)	166 (5.7)
	Brazil	91 (6.3)	95 (6.5)	186 (6.4)
	Mexico	55 (3.8)	69 (4.8)	124 (4.3)
	Peru	106 (7.3)	89 (6.1)	195 (6.7)

Baseline diabetic status is defined as follows: Diabetes Medical history of T2DM or central laboratory HbA1c ≥ 6.5% at both visit 1 and visit 2.
Dapa Dapagliflozin. FAS Full analysis set. Max Maximum. Min Minimum. N Number of subjects in treatment group. n Number of subjects included in analysis. SD Standard deviation. T2DM Type 2 diabetes mellitus.

Non-T2DM subjects

Demographic characteristic		Dapa 10 mg (N=697)	Placebo (N=701)	Total (N=1398)
Age (years)	n	697	701	1398
	Mean	56.9	56.0	56.4
	SD	14.6	14.6	14.6
	Median	58.0	57.0	58.0
	Min	23	18	18
	Max	91	91	91
Age group (years) n (%)	≤ 65	477 (68.4)	502 (71.6)	979 (70.0)
	> 65	220 (31.6)	199 (28.4)	419 (30.0)
	≤ 65	477 (68.4)	502 (71.6)	979 (70.0)
	66 - 75	155 (22.2)	139 (19.8)	294 (21.0)
	> 75	65 (9.3)	60 (8.6)	125 (8.9)
	Total	697	701	1398
Sex n (%)	Male	482 (69.2)	456 (65.0)	938 (67.1)
	Female	215 (30.8)	245 (35.0)	460 (32.9)
	Total	697	701	1398
Race n (%)	White	373 (53.5)	376 (53.6)	749 (53.6)
	Black or African American	28 (4.0)	26 (3.7)	54 (3.9)
	Asian	268 (38.5)	267 (38.1)	535 (38.3)
	Native Hawaiian or other Pacific Islander	1 (0.1)	0	1 (0.1)
	American Indian or Alaska Native	9 (1.3)	16 (2.3)	25 (1.8)
	Other	18 (2.6)	16 (2.3)	34 (2.4)
	Total	697	701	1398
Ethnic group n (%)	Hispanic or Latino	124 (17.8)	154 (22.0)	278 (19.9)
	Not Hispanic or Latino	573 (82.2)	547 (78.0)	1120 (80.1)
	Total	697	701	1398
Region/ Country n (%)	Asia	254 (36.4)	251 (35.8)	505 (36.1)

Baseline diabetic status is defined as follows: Diabetes Medical history of T2DM or central laboratory HbA1c ≥ 6.5% at both visit 1 and visit 2.
Dapa Dapagliflozin. FAS Full analysis set. Max Maximum. Min Minimum. N Number of subjects in treatment group. n Number of subjects included in analysis. SD Standard deviation. T2DM Type 2 diabetes mellitus.

Non-T2DM subjects

Demographic characteristic		Dapa 10 mg (N=697)	Placebo (N=701)	Total (N=1398)
	China	59 (8.5)	56 (8.0)	115 (8.2)
	India	22 (3.2)	20 (2.9)	42 (3.0)
	Japan	61 (8.8)	50 (7.1)	111 (7.9)
	Philippines	8 (1.1)	15 (2.1)	23 (1.6)
	South Korea	65 (9.3)	63 (9.0)	128 (9.2)
	Vietnam	39 (5.6)	47 (6.7)	86 (6.2)
	Europe	243 (34.9)	219 (31.2)	462 (33.0)
	Denmark	12 (1.7)	10 (1.4)	22 (1.6)
	Germany	33 (4.7)	21 (3.0)	54 (3.9)
	Hungary	15 (2.2)	13 (1.9)	28 (2.0)
	Poland	11 (1.6)	11 (1.6)	22 (1.6)
	Russia	57 (8.2)	53 (7.6)	110 (7.9)
	Spain	42 (6.0)	36 (5.1)	78 (5.6)
	Sweden	15 (2.2)	11 (1.6)	26 (1.9)
	UK	14 (2.0)	16 (2.3)	30 (2.1)
	Ukraine	44 (6.3)	48 (6.8)	92 (6.6)
	North America	93 (13.3)	97 (13.8)	190 (13.6)
	Canada	34 (4.9)	40 (5.7)	74 (5.3)
	USA	59 (8.5)	57 (8.1)	116 (8.3)
	Latin/South America	107 (15.4)	134 (19.1)	241 (17.2)
	Argentina	31 (4.4)	38 (5.4)	69 (4.9)
	Brazil	49 (7.0)	67 (9.6)	116 (8.3)
	Mexico	14 (2.0)	16 (2.3)	30 (2.1)
	Peru	13 (1.9)	13 (1.9)	26 (1.9)

Baseline diabetic status is defined as follows: Diabetes Medical history of T2DM or central laboratory HbA1c ≥ 6.5% at both visit 1 and visit 2.
Dapa Dapagliflozin. FAS Full analysis set. Max Maximum. Min Minimum. N Number of subjects in treatment group. n Number of subjects included in analysis. SD Standard deviation. T2DM Type 2 diabetes mellitus.

Table 5: Subject characteristics by T2DM status (FAS)

T2DM subjects

Subject characteristic		Dapa 10 mg (N=1455)	Placebo (N=1451)	Total (N=2906)
eGFR (ml/min/1.73m^2)	n	1455	1451	2906
	Mean	44.0	43.6	43.8
	SD	12.6	12.6	12.6
	Median	43.0	42.0	42.0
	Min	19	20	19
	Max	86	82	86
eGFR (ml/min/1.73m^2) n (%)	n	1455	1451	2906
	<30	190 (13.1)	211 (14.5)	401 (13.8)
	30- <45	636 (43.7)	603 (41.6)	1239 (42.6)
	45- <60	450 (30.9)	468 (32.3)	918 (31.6)
	≥ 60	179 (12.3)	169 (11.6)	348 (12.0)
UACR (mg/g)	n	1455	1451	2906
	Mean	1474.9	1445.9	1460.4
	SD	1296.1	1245.4	1270.9
	Median	1024.5	1004.5	1016.5
	Min	23	124	23
	Max	11905	8963	11905
UACR (mg/g) n (%)	n	1455	1451	2906
	≤ 1000	714 (49.1)	719 (49.6)	1433 (49.3)
	>1000	741 (50.9)	732 (50.4)	1473 (50.7)
Most likely etiology of CKD n (%)	n	1455	1451	2906
	Diabetic Nephropathy	1271 (87.4)	1239 (85.4)	2510 (86.4)
	Ischaemic/Hypertensive Nephropathy	86 (5.9)	114 (7.9)	200 (6.9)
	Chronic Glomerulonephritis	47 (3.2)	50 (3.4)	97 (3.3)
	FSGS	6 (0.4)	16 (1.1)	22 (0.8)
	Iga Nephropathy	24 (1.6)	14 (1.0)	38 (1.3)

Baseline diabetic status is defined as follows: Diabetes Medical history of T2DM or central laboratory HbA1c ≥ 6.5% at both visit 1 and visit 2.
Pre-diabetes No history of T2DM and HbA1c ≥ 5.7% at visit 1 or at visit 2. Normo-glycemic No history of T2DM and HbA1c < 5.7% at both visit 1 and at visit 2.
CKD Chronic kidney disease. Dapa Dapagliflozin. DBP Diastolic blood pressure. eGFR Estimated glomerular filtration rate. FAS Full analysis set. Max Maximum. Min Minimum.
N Number of subjects in treatment group. n Number of subjects included in analysis. FSGS Focal Segmental Glomerulosclerosis. Other Glomerulonephritis Other Primary or Secondary Glomerulosclerosis.
SBP Systolic blood pressure. SD Standard deviation. T2DM Type 2 diabetes mellitus. UACR Urine albumin creatinine ratio.

T2DM subjects

Subject characteristic		Dapa 10 mg (N=1455)	Placebo (N=1451)	Total (N=2906)
	Membranous Nephropathy	3 (0.2)	7 (0.5)	10 (0.3)
	Minimal Change	2 (0.1)	0	2 (0.1)
	Other Glomerulonephritis	12 (0.8)	13 (0.9)	25 (0.9)
	Chronic Interstitial Nephritis	7 (0.5)	6 (0.4)	13 (0.4)
	Chronic Pyelonephritis (Infectious)	5 (0.3)	7 (0.5)	12 (0.4)
	Renal Artery Stenosis	1 (0.1)	2 (0.1)	3 (0.1)
	Obstructive Nephropathy	1 (0.1)	4 (0.3)	5 (0.2)
	Unknown	26 (1.8)	21 (1.4)	47 (1.6)
	Other	11 (0.8)	8 (0.6)	19 (0.7)
T2DM n (%)[a]	n	1455	1451	2906
	Yes	1455 (100.0)	1451 (100.0)	2906 (100.0)
Duration of diabetes (years)	n	1438	1439	2877
	Mean	14.9	15.1	15.0
	SD	9.8	9.7	9.7
	Median	13.7	13.8	13.8
	Min	0	0	0
	Max	75	55	75
SBP (mmHg)	n	1455	1451	2906
	Mean	138.8	139.6	139.2
	SD	17.6	17.1	17.3
	Median	138.0	138.7	138.0
	Min	90	82	82
	Max	216	209	216
SBP (mmHg) n (%)	n	1455	1451	2906
	≤130	455 (31.3)	418 (28.8)	873 (30.0)
	>130	1000 (68.7)	1033 (71.2)	2033 (70.0)

Baseline diabetic status is defined as follows: Diabetes Medical history of T2DM or central laboratory HbA1c ≥ 6.5% at both visit 1 and visit 2.
Pre-diabetes No history of T2DM and HbA1c ≥ 5.7% at visit 1 or at visit 2. Normo-glycemic No history of T2DM and HbA1c < 5.7% at both visit 1 and at visit 2.
CKD Chronic kidney disease. Dapa Dapagliflozin. DBP Diastolic blood pressure. eGFR Estimated glomerular filtration rate. FAS Full analysis set. Max Maximum. Min Minimum.
N Number of subjects in treatment group. n Number of subjects included in analysis. FSGS Focal Segmental Glomerulosclerosis. Other Glomerulonephritis Other Primary or Secondary Glomerulosclerosis.
SBP Systolic blood pressure. SD Standard deviation. T2DM Type 2 diabetes mellitus. UACR Urine albumin creatinine ratio.

T2DM subjects

Subject characteristic		Dapa 10 mg (N=1455)	Placebo (N=1451)	Total (N=2906)
DBP (mmHg)	n	1455	1451	2906
	Mean	76.5	76.5	76.5
	SD	10.4	9.9	10.1
	Median	76.7	76.7	76.7
	Min	35	43	35
	Max	122	117	122
Pulse (bpm)	n	1455	1451	2906
	Mean	73.8	73.2	73.5
	SD	11.4	11.6	11.5
	Median	73.0	72.7	73.0
	Min	44	41	41
	Max	122	122	122
Height (cm)	n	1453	1447	2900
	Mean	165.3	165.6	165.5
	SD	10.2	10.0	10.1
	Median	166.0	166.0	166.0
	Min	135	116	116
	Max	195	196	196
Weight (kg)	n	1454	1450	2904
	Mean	83.2	83.8	83.5
	SD	20.9	21.2	21.0
	Median	80.0	81.0	80.6
	Min	39	41	39
	Max	158	174	174
Body Mass Index (kg/m^2)	n	1453	1446	2899
	Mean	30.2	30.4	30.3

Baseline diabetic status is defined as follows: Diabetes Medical history of T2DM or central laboratory HbA1c ≥ 6.5% at both visit 1 and visit 2.
Pre-diabetes No history of T2DM and HbA1c ≥ 5.7% at visit 1 or at visit 2. Normo-glycemic No history of T2DM and HbA1c < 5.7% at both visit 1 and at visit 2.
CKD Chronic kidney disease. Dapa Dapagliflozin. DBP Diastolic blood pressure. eGFR Estimated glomerular filtration rate. FAS Full analysis set. Max Maximum. Min Minimum.
N Number of subjects in treatment group. n Number of subjects included in analysis. FSGS Focal Segmental Glomerulosclerosis. Other Glomerulonephritis Other Primary or Secondary Glomerulosclerosis.
SBP Systolic blood pressure. SD Standard deviation. T2DM Type 2 diabetes mellitus. UACR Urine albumin creatinine ratio.

T2DM subjects

Subject characteristic		Dapa 10 mg (N=1455)	Placebo (N=1451)	Total (N=2906)
	SD	6.2	6.3	6.3
	Median	29.0	29.0	29.0
	Min	16	18	16
	Max	66	57	66
Body Mass Index group (kg/m^2) n (%)	n	1453	1446	2899
	<30	736 (50.7)	726 (50.2)	1462 (50.4)
	≥30	717 (49.3)	720 (49.8)	1437 (49.6)

Table 6: Subject Characteristics (FAS)

Subject characteristic		Dapa 10 mg (N=2152)	Placebo (N=2152)	Total (N=4304)
eGFR (ml/min/1.73m^2)	n	2152	2152	4304
	Mean	43.2	43.0	43.1
	SD	12.3	12.4	12.4
	Median	41.0	42.0	41.0
	Min	19	20	19
	Max	86	85	86
eGFR (ml/min/1.73m^2) n (%)	n	2152	2152	4304
	< 30	293 (13.6)	331 (15.4)	624 (14.5)
	30- < 45	979 (45.5)	919 (42.7)	1898 (44.1)
	45- < 60	646 (30.0)	682 (31.7)	1328 (30.9)
	≥ 60	234 (10.9)	220 (10.2)	454 (10.5)
UACR (mg/g)	n	2152	2152	4304
	Mean	1370.6	1356.4	1363.5
	SD	1197.9	1171.5	1184.7
	Median	964.8	933.8	949.3
	Min	23	124	23
	Max	11905	8963	11905
UACR (mg/g) n (%)	n	2152	2152	4304
	≤ 1000	1104 (51.3)	1121 (52.1)	2225 (51.7)
	> 1000	1048 (48.7)	1031 (47.9)	2079 (48.3)
Most likely etiology of CKD n (%)	n	2152	2152	4304
	Diabetic Nephropathy	1271 (59.1)	1239 (57.6)	2510 (58.3)
	Ischaemic/Hypertensive Nephropathy	324 (15.1)	363 (16.9)	687 (16.0)
	Chronic Glomerulonephritis	343 (15.9)	352 (16.4)	695 (16.1)
	FSGS	53 (2.5)	62 (2.9)	115 (2.7)
	IgA Nephropathy	137 (6.4)	133 (6.2)	270 (6.3)
	Membranous Nephropathy	19 (0.9)	24 (1.1)	43 (1.0)

Subject characteristic		Dapa 10 mg (N=2152)	Placebo (N=2152)	Total (N=4304)
	Minimal Change	7 (0.3)	4 (0.2)	11 (0.3)
	Other Glomerulonephritis	127 (5.9)	129 (6.0)	256 (5.9)
	Chronic Interstitial Nephritis	33 (1.5)	20 (0.9)	53 (1.2)
	Chronic Pyelonephritis (Infectious)	30 (1.4)	39 (1.8)	69 (1.6)
	Obstructive Nephropathy	13 (0.6)	12 (0.6)	25 (0.6)
	Renal Artery Stenosis	6 (0.3)	4 (0.2)	10 (0.2)
	Unknown	110 (5.1)	104 (4.8)	214 (5.0)
	Other	22 (1.0)	19 (0.9)	41 (1.0)
T2DM n (%)[a]	n	2152	2152	4304
	Yes	1455 (67.6)	1451 (67.4)	2906 (67.5)
	No	697 (32.4)	701 (32.6)	1398 (32.5)
SBP (mmHg)	n	2152	2152	4304
	Mean	136.7	137.4	137.1
	SD	17.5	17.3	17.4
	Median	135.7	136.3	136.0
	Min	90	82	82
	Max	216	217	217
DBP (mmHg)	n	2152	2152	4304
	Mean	77.5	77.5	77.5
	SD	10.7	10.3	10.5
	Median	77.8	77.7	77.7
	Min	35	43	35
	Max	122	136	136
Body Mass Index (kg/m^2)	n	2149	2147	4296
	Mean	29.4	29.6	29.5
	SD	6.0	6.3	6.2
	Median	29.0	29.0	29.0
	Min	15	16	15
	Max	66	57	66

[a] Baseline diabetic status is defined as follows: Diabetes: Medical history of T2DM or central laboratory HbA1c ≥ 6.5% at both Visit 1 and Visit 2.

CKD, chronic kidney disease; Dapa, dapagliflozin; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FSGS, Focal Segmental Glomerulosclerosis; HbA1c, Glycated haemoglobin; IgA, immunoglobulin A; Max, maximum; Min, minimum; N, number of subjects in treatment group; n, number of subjects included in analysis; Other Glomerulonephritis, other primary or secondary glomerulosclerosis; SBP, systolic blood pressure; SD, standard deviation; T2DM, Type 2 diabetes mellitus; UACR, urine albumin creatinine ratio.

Any use of systemic glucocorticoids during the study was less common in patients treated with dapagliflozin (6.9%) compared with placebo (8.2%) but use of other immunosuppressive treatment was overall balanced between treatment groups.

A total of 34 (0.8%) patients were treated with open-label SGLT2 inhibitors during the study, of which 14 cases were classified as prohibited medication use (ie, taken concomitantly with IP) and reported as important protocol deviations. The use of prohibited medications was balanced between treatment groups.

Treatment Compliance

Compliance with the randomised study drug was high and similar between treatment groups. Median (IQR) compliance was 98.6% (96.0 to 99.9%) and 98.6% (95.5 to 99.9%) in the dapagliflozin and placebo groups, respectively. In the dapagliflozin and placebo groups, 82.9% and 80.2% of patients, respectively, had a compliance of > 80%, and 77.7% and 74.6%, respectively, had a compliance of > 90%. If information regarding the number of tablets dispensed or the number of tablets returned was missing for at least one observation, compliance was not calculated for that subject. If physical return of tablets was not possible due to remote SCV during the COVID-19 pandemic, information regarding compliance was collected verbally.

Numbers analysed

The analysis sets and the number of subjects in each analysis set are summarized in Table 7.

The full analysis set (FAS) includes all randomised patients assessed according to their randomised study drug assignment (2152 patients in in each treatment arm). 6 patients did not receive IP and were therefore excluded from the safety analysis set (SAS). All decisions on the inclusion or exclusion of subjects from analyses were made while the data were still blinded.

All patients who were randomized to study treatment were included in the FAS irrespective of their protocol adherence and continued participation in the study.

Table 7:Analysis Sets

	Number of subjects	
	Dapa 10 mg	**Placebo**
Subjects randomized	2152	2152
Subjects included in full analysis set	2152	2152
Subjects included in safety analysis set [a]	2149	2149

Of the 4304 randomized patients, only 15 patients prematurely discontinued the study and there were only 5 patients with unknown vital status at the end of study.

Outcomes and estimation

Summary of Testing Hierarchy and Overall Efficacy Results

The study met the primary and secondary objectives. Dapagliflozin was superior to placebo in reducing the incidence of the composite of ≥ 50% sustained decline in eGFR, ESRD, and renal or CV death. All components contributed to the observed treatment effect. Demonstration of superiority for the primary efficacy endpoint initiated sequential testing of the secondary efficacy endpoints, see overview of

confirmatory analysis in Table 8. Dapagliflozin was superior to placebo for the reduction of all the secondary endpoints: (1) renal composite endpoint without CV death, (2) composite of CV death and hospitalisation for HF, and (3) all-cause mortality.

Table 8: Overview of Confirmatory Analysis of Primary and Secondary Endpoint Hierarchy (FAS)

		Dapa 10 mg (N = 2152)	Placebo (N = 2152)			
Variable	**Type of endpoint**	**Subjects with event n (%)**	**Subjects with event n (%)**	**Hazard ratio**	**95% CI**	**p-value**
Composite of ≥ 50% eGFR decline, ESRD and renal or CV death	Primary	197 (9.2)	312 (14.5)	0.61	(0.51, 0.72)	< 0.0001
Composite of ≥ 50% eGFR decline, ESRD and renal death	Secondary	142 (6.6)	243 (11.3)	0.56	(0.45, 0.68)	< 0.0001
Composite of CV death and hospitalisation for HF	Secondary	100 (4.6)	138 (6.4)	0.71	(0.55, 0.92)	0.0089
Death from any cause	Secondary	101 (4.7)	146 (6.8)	0.69	(0.53, 0.88)	0.0035

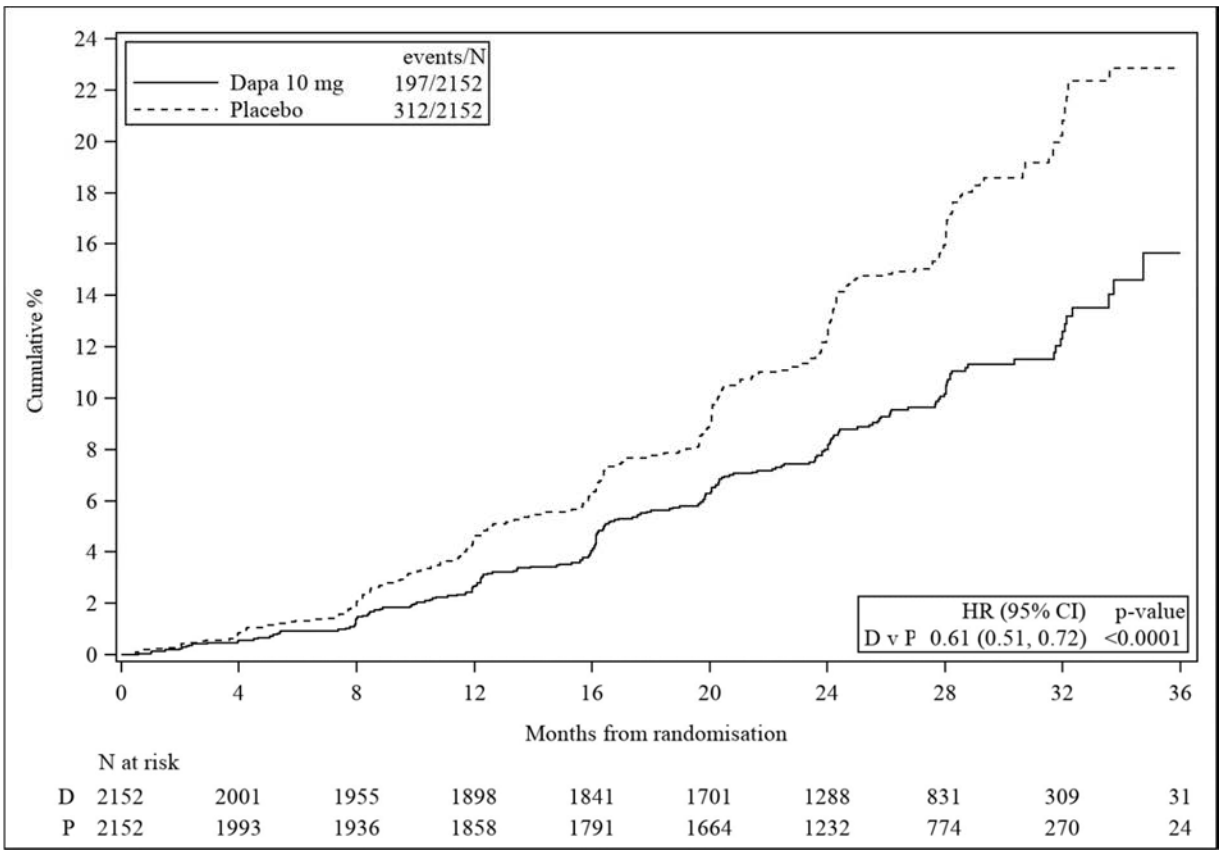
Primary Outcome: Composite of ≥ 50% Sustained Decline in eGFR, ESRD, and Renal or CV Death

Treatment with dapagliflozin was superior to placebo in reducing the incidence of the primary composite endpoint of ≥ 50% sustained decline in eGFR, ESRD, and renal or CV death (HR 0.61 [95% CI 0.51, 0.72], p < 0.0001) (

Table 9). There were 197 and 312 patients with any event of the composite endpoint in the dapagliflozin and placebo groups, respectively, corresponding to event rates per 100 patient-years of 4.6 and 7.5. The contributing events analysis showed that the treatment effect on the primary composite was not driven by first events of ≥ 50% eGFR decline alone.

The KM curves of the primary endpoint for placebo and dapagliflozin groups began to separate early (4 months) and continued to separate over the course of the study (Figure 4). The number needed to treat per 27 months was 19 (95% CI 15, 27).

Figure 3:Kaplan-Meier Plot of the Composite of ⩾ 50% eGFR Decline, ESRD, and Renal or CV Death (FAS)



Results for each of the individual components of the primary composite endpoint are summarised in

Table 9. All components of the primary composite endpoint individually contributed to the overall treatment effect observed (

Table 9). The benefit of dapagliflozin on the primary endpoint consisted of reductions in the incidence of the single components ≥ 50% eGFR sustained decline (HR 0.53 [95% CI 0.42, 0.67]) (Figure 4 and

Table 9), ESRD (HR 0.64 [95% CI 0.50, 0.82]) (

Table 9 and Figure 4), and CV death (HR 0.81 [95% CI 0.58, 1.12]) (see Table 5 and Figure 5). Renal deaths were few, 8 events in total (2 in dapagliflozin, 6 in placebo group) and therefore not analysed as an individual component, in accordance with the statistical analysis plan which specified that only events > 15 in total were to be analysed. (HR 0.81 [95% CI 0.58, 1.12]) (

Table 9 and Figure 4). Renal deaths were few, 8 events in total (2 in dapagliflozin, 6 in placebo group) and therefore not analysed as an individual component, in accordance with the statistical analysis plan which specified that only events > 15 in total were to be analysed.

Table 9: Time to First Event of the Composite Endpoint of ≥ 50% eGFR Decline from Baseline, ESRD, and Renal or CV Death (FAS)

	Dapa 10 mg (N=2152)		Placebo (N=2152)				
Variable	**Subjects with events n (%)**	**Event rate**	**Subjects with events n (%)**	**Event rate**	**Hazard ratio**	**95% CI**	**p-value**
Composite of ≥ 50% eGFR decline, ESRD, and renal or CV death	197 (9.2)	4.6	312 (14.5)	7.5	0.61	(0.51, 0.72)	< 0.0001[b]
≥ 50% decline in eGFR	112 (5.2)	2.6	201 (9.3)	4.8	0.53	(0.42, 0.67)	< 0.0001
ESRD	109 (5.1)	2.5	161 (7.5)	3.8	0.64	(0.50, 0.82)	0.0004
eGFR < 15mL/min/1.73 m^2	84 (3.9)	1.9	120 (5.6)	2.8	0.67	(0.51, 0.88)	0.0045
Chronic dialysis[a]	68 (3.2)	1.5	99 (4.6)	2.2	0.66	(0.48, 0.90)	0.0080
Receiving renal transplant[a]	3 (0.1)	0.1	8 (0.4)	0.2			
Renal death[a]	2 (<0.1)	0.0	6 (0.3)	0.1			
CV death[a]	65 (3.0)	1.4	80 (3.7)	1.7	0.81	(0.58, 1.12)	0.2029

Figure 4: Kaplan-Meier Plot of ≥ 50% eGFR Decline (FAS

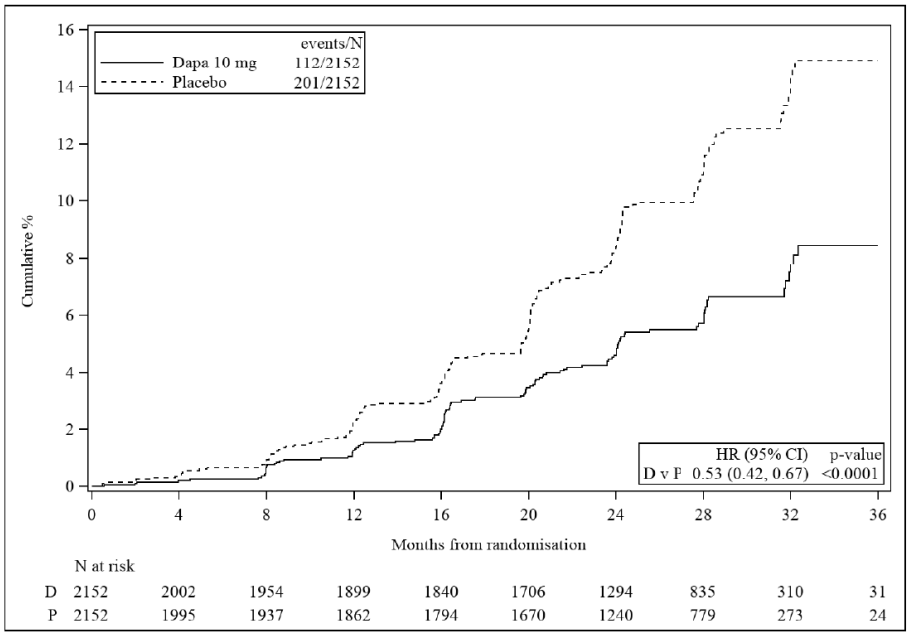


Figure 6: Kaplan-Meier Plot of ESRD (FAS)

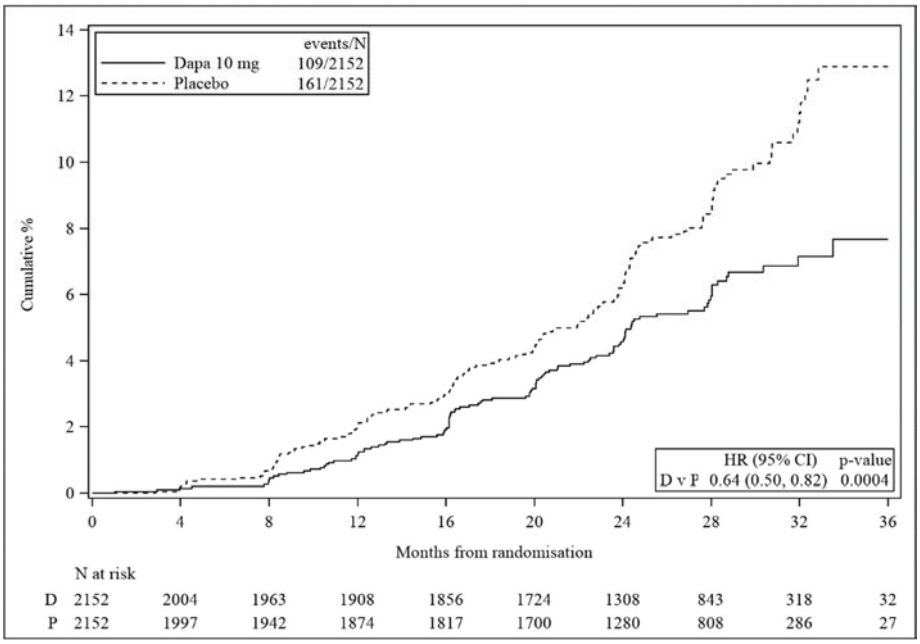
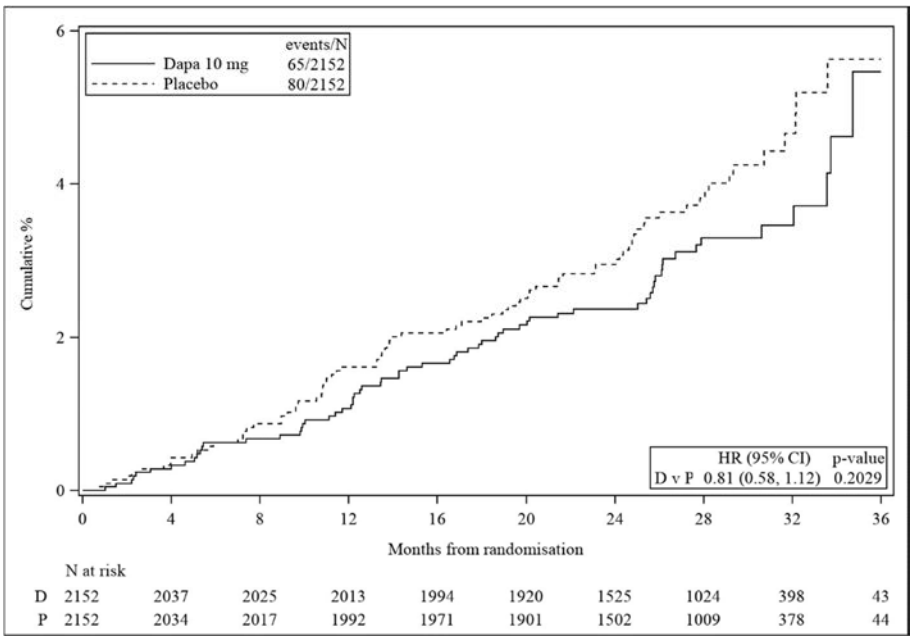


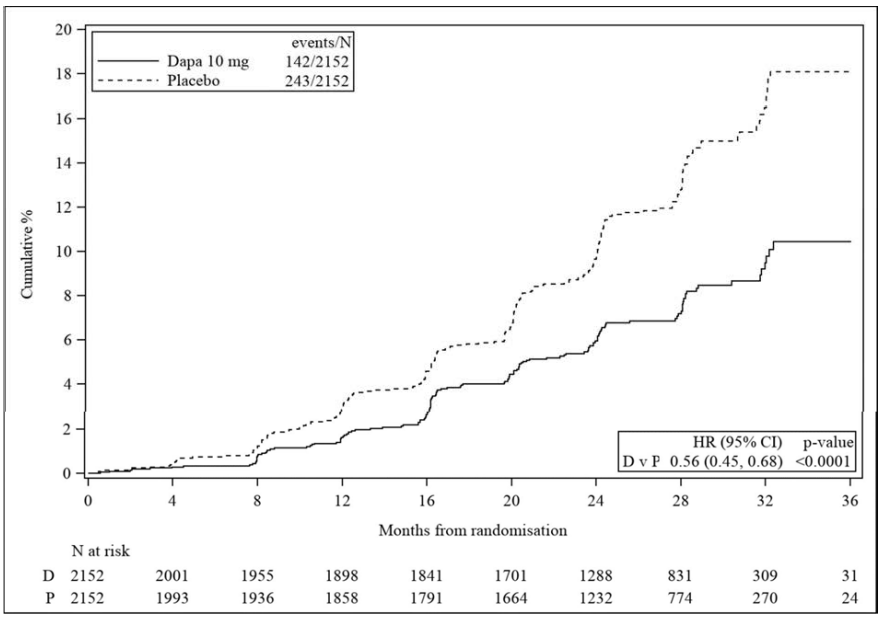
Figure 5: Kaplan-Meier Plot of CV Death (FAS)



Secondary Outcome: Composite of ≥ 50% Sustained Decline in eGFR, ESRD, and Renal Death

Dapagliflozin was superior to placebo in reducing the incidence of the composite of ≥ 50% sustained decline in eGFR, ESRD, and renal death (HR 0.56 [95% CI 0.45, 0.68], p < 0.0001) (Table 8). There were 142 and 243 patients with any event of the composite endpoint in the dapagliflozin and placebo groups, respectively, corresponding to event rates per 100 patient-years of 3.3 and 5.8. The results for this secondary endpoint were consistent with those for the primary endpoint. The KM curves began to separate early and continued to separate over the course of the study (Figure 7). The single components of the composite endpoint are discussed above.

Figure 7: Kaplan-Meier Plot of Composite of ⩾ 50% eGFR Decline, ESRD and Renal Death (FAS)



Secondary Outcome: Composite of CV Death and Hospitalisation for Heart Failure

Dapagliflozin was superior to placebo for the reduction of the composite of CV death and hospitalisation for HF (HR 0.71 [95% CI 0.55, 0.92]) (Table 8). There were 100 and 138 patients with any event of the composite endpoint in the dapagliflozin and placebo groups, respectively, corresponding to event rates per 100 patient-years of 2.2 and 3.0. The curves of the KM plot for placebo and dapagliflozin groups for this endpoint began to separate early and continued to separate over the course of the study, however crossing of KM curves towards the end of the study occurred due to high censoring rate and small number of patients at risk (Figure 8).

Both components contributed to the treatment effect on the composite endpoint. The incidence of the single component hospitalisation for HF was reduced in the dapagliflozin group, compared with placebo (HR 0.51

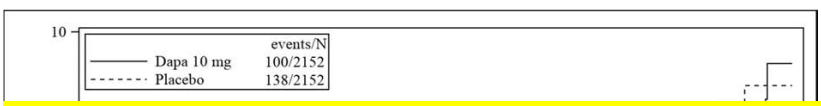
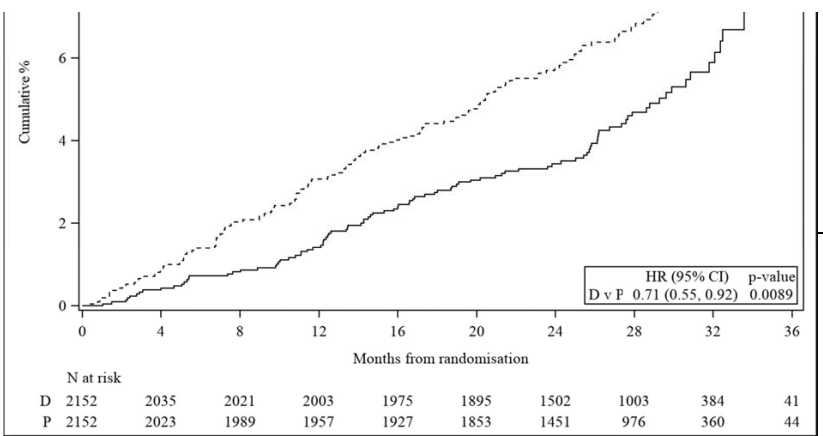


Figure 8: Kaplan-Meier Plot of Composite of CV Death and HF Hospitalisation (FAS)



[95% CI 0.34, 0.76]). The incidence of CV death as a single component was numerically reduced by dapagliflozin (HR 0.81 [95% CI 0.58, 1.12]), (Table 8).

Secondary Outcome: Death from Any Cause

Dapagliflozin was superior to placebo in reducing all-cause mortality (HR 0.69 [95% CI 0.53, 0.88]) (Table 8). There were 101 and 146 deaths in the dapagliflozin and placebo groups, respectively, corresponding to event rates per 100 patient-years of 2.2 and 3.1. The curves of the KM plot for placebo and dapagliflozin groups for all-cause mortality began to separate early and continued to separate over the course of the study (Figure 9).

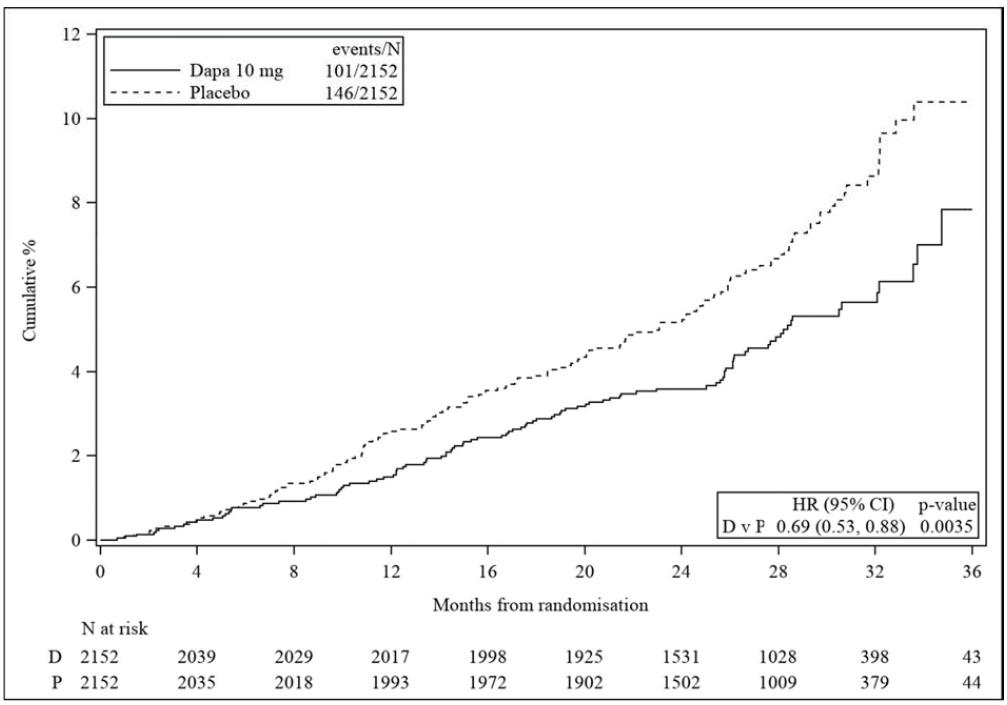
Adjudicated death causes are presented in Table 10. The benefit of dapagliflozin on all-cause mortality was driven by reductions in both deaths from non-CV causes (mainly infections, malignancies, renal deaths) and deaths from CV causes (mainly HF). Deaths of undetermined causes also contributed to the overall effect.

Overall, the most common cause of death in the study was non-CV deaths (102 in total, 36 in dapagliflozin, 66 in placebo). Of the non-CV deaths, the most common categories were deaths due to infections (46 in total; 18 in dapagliflozin, 28 in placebo), malignancies (27 in total; 8 in dapagliflozin, 19 in placebo) and renal deaths (8 in total; 2 in dapagliflozin, 6 in placebo). In total, there were 91 cases of CV deaths (41 in dapagliflozin, 50 in placebo), of which there were 51 patients with sudden cardiac death and 14 cases of deaths due to HF. In total, 54 deaths were categorised as of undetermined cause (24 in dapagliflozin, 30 in placebo).

Dapagliflozin reduced the number of patients who progressed to ESRD (in total 270; 109 in dapagliflozin, 161 in placebo) (

Table 9), and in these patients deaths from all causes were more frequent (15.9%) than in the overall study

Figure 9: Kaplan-Meier Plot of Death of Any Cause (FAS)



population (5.7%), Table 10.

Table 10: Summary of Adjudicated Death Classification (FAS)

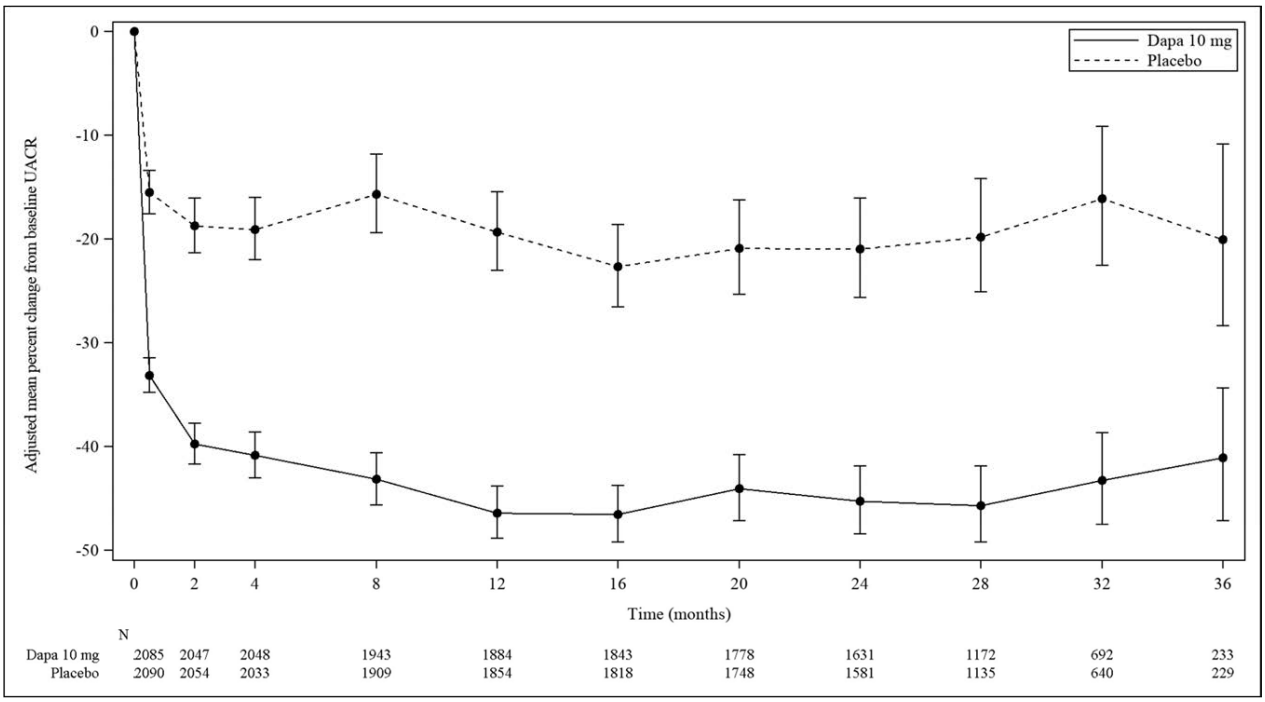
	Dapa 10 mg (N = 2152)	**Placebo (N = 2152)**	**Total (N = 4304)**
All deaths	101 (4.7)	146 (6.8)	247 (5.7)
CV death	41 (1.9)	50 (2.3)	91 (2.1)
Death due to acute myocardial infarction	6 (0.3)	5 (0.2)	11 (0.3)
Sudden cardiac death	24 (1.1)	27 (1.3)	51 (1.2)
Death due to heart failure	3 (0.1)	11 (0.5)	14 (0.3)
Death due to stroke	5 (0.2)	5 (0.2)	10 (0.2)
Death due to cardiovascular procedures	0	1 (0.0)	1 (0.0)
Death due to cardiovascular haemorrhage	1 (0.0)	0	1 (0.0)
Death due to other cardiovascular causes	2 (0.1)	1 (0.0)	3 (0.1)
Non-CV death	36 (1.7)	66 (3.1)	102 (2.4)
Pulmonary failure	3 (0.1)	1 (0.0)	4 (0.1)
Renal	2 (0.1)	6 (0.3)	8 (0.2)
Gastrointestinal causes	2 (0.1)	2 (0.1)	4 (0.1)
Hepatobiliary	0	3 (0.1)	3 (0.1)
Pancreatic	0	0	0
Infection (includes sepsis)	18 (0.8)	28 (1.3)	46 (1.1)
Non-infectious (e.g. SIRS)	0	0	0
Haemorrhage neither CV bleeding or stroke	0	4 (0.2)	4 (0.1)
Non-CV procedure or surgery	0	0	0
Trauma	3 (0.1)	1 (0.0)	4 (0.1)
Suicide	0	1 (0.0)	1 (0.0)
Non-prescription drug reaction or overdose	0	0	0
Prescription drug reaction or overdose	0	0	0
Neurological (non-cardiovascular)	0	0	0
Malignancy	8 (0.4)	19 (0.9)	27 (0.6)
Inflammatory/immune	0	0	0
Other	0	1 (0.0)	1 (0.0)
Undetermined cause of death	24 (1.1)	30 (1.4)	54 (1.3)

Exploratory Variables

UACR (Urine Albumin-to-Creatinine Ratio)

A greater reduction in UACR for dapagliflozin compared to placebo that was observed from 14 days and onwards. At 36 months, the adjusted mean percent change from baseline in UACR (mg/g) was -41.1% in patients treated with dapagliflozin and -20.08% in patients treated with placebo, giving a difference between treatment groups of -26.31% ([95% CI -36.82, -14.04]) (Figure 11)

Figure 10: Adjusted Mean Percent Change from Baseline UACR and 95% CIs from Repeated Measures Model (FAS)



Doubling of Serum Creatinine

Doubling of serum creatinine was used as an estimate of the effect on acute kidney injury. Dapagliflozin reduced the incidence of time to first doubling of serum creatinine levels compared to placebo (HR 0.68 [95% CI 0.49, 0.94]).

eGFR

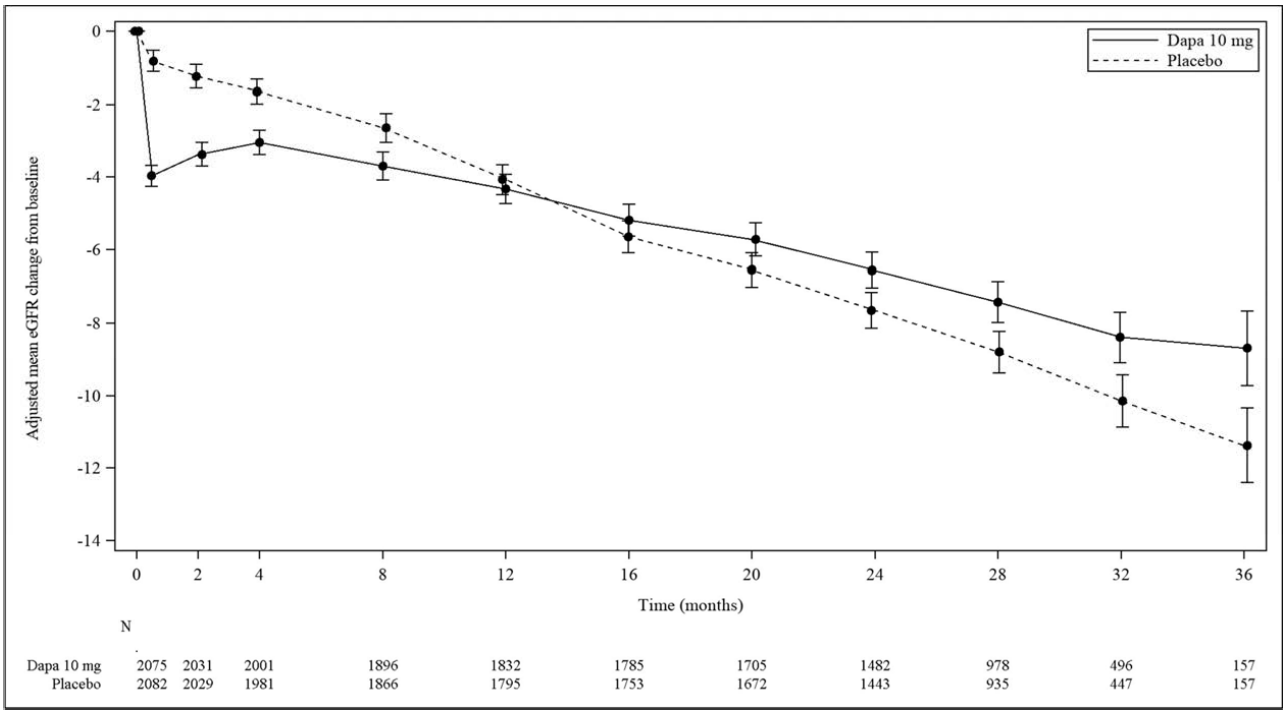
There was an initial drop in eGFR in the dapagliflozin group compared with placebo. Thereafter, the rate of decline in renal function was reduced in the dapagliflozin group compared to the placebo group. Thereafter, the rate of decline in renal function was reduced in the dapagliflozin group compared to the placebo group (Figure 12).

Dapagliflozin reduced events of ≥ 30% eGFR decline (HR 0.76 [95% CI 0.67, 0.87]) and ≥ 40% eGFR decline (HR 0.63 [95% CI 0.53, 0.74]) compared to placebo). This reduction was consistent with events of ≥ 50% decline in eGFR, as a single component of the primary composite endpoint (

Table 9).

Analysis of the proportion of patients with eGFR > 40 mL/min/1.73 m^2 that entered CKD stage 4, (sustained eGFR < 30 mL/min/1.73 m^2), showed that dapagliflozin reduced the incidence of patients that reached CKD4, compared with placebo, with an odds ratio of 0.59 ([95% CI 0.44, 0.80])

Figure 11: Adjusted Mean eGFR (CKD-EPI) Change from Baseline and 95% CIs from Repeated Measures Model (FAS)



SBP

Analysis of change from baseline in SBP showed that dapagliflozin reduced SBP during the study, from the timepoint of 14 days into the study to 36 months, with a mean difference between treatment groups ranging from -2.21 to -3.68 mmHg.

HbA1c

In the T2DM population, analysis of percent change from baseline in HbA1c from the timepoint of 14 days into the study until 16 months showed a greater reduction in HbA1c for dapagliflozin compared to placebo; the mean difference between treatment groups ranged from -0.05 to -0.24. There were no significant differences in HbA1c between dapagliflozin and placebo from the timepoint of 20 months to 36 months in the study.

Body weight

Analysis of change from baseline in body weight over time showed a greater reduction in weight for dapagliflozin compared to placebo, from the timepoint of 14 days into the study until 36 months. At 36 months, the mean change from baseline in weight was -1.73 kg in patients treated with dapagliflozin and -0.93 kg in patients treated with placebo, giving a difference between treatment groups of -0.80 (95% CI -1.47, -0.14)

Patient Reported Outcomes/Quality of Life

Two questionnaires were used to collect PRO data in the study, KDQOL™-36 and EQ-5D-5L. No significant differences in the above-mentioned scores were noted at baseline between the dapagliflozin and the placebo groups. At 12, 24 and 36 months, no clinically relevant changes compared to baseline were seen for either group.

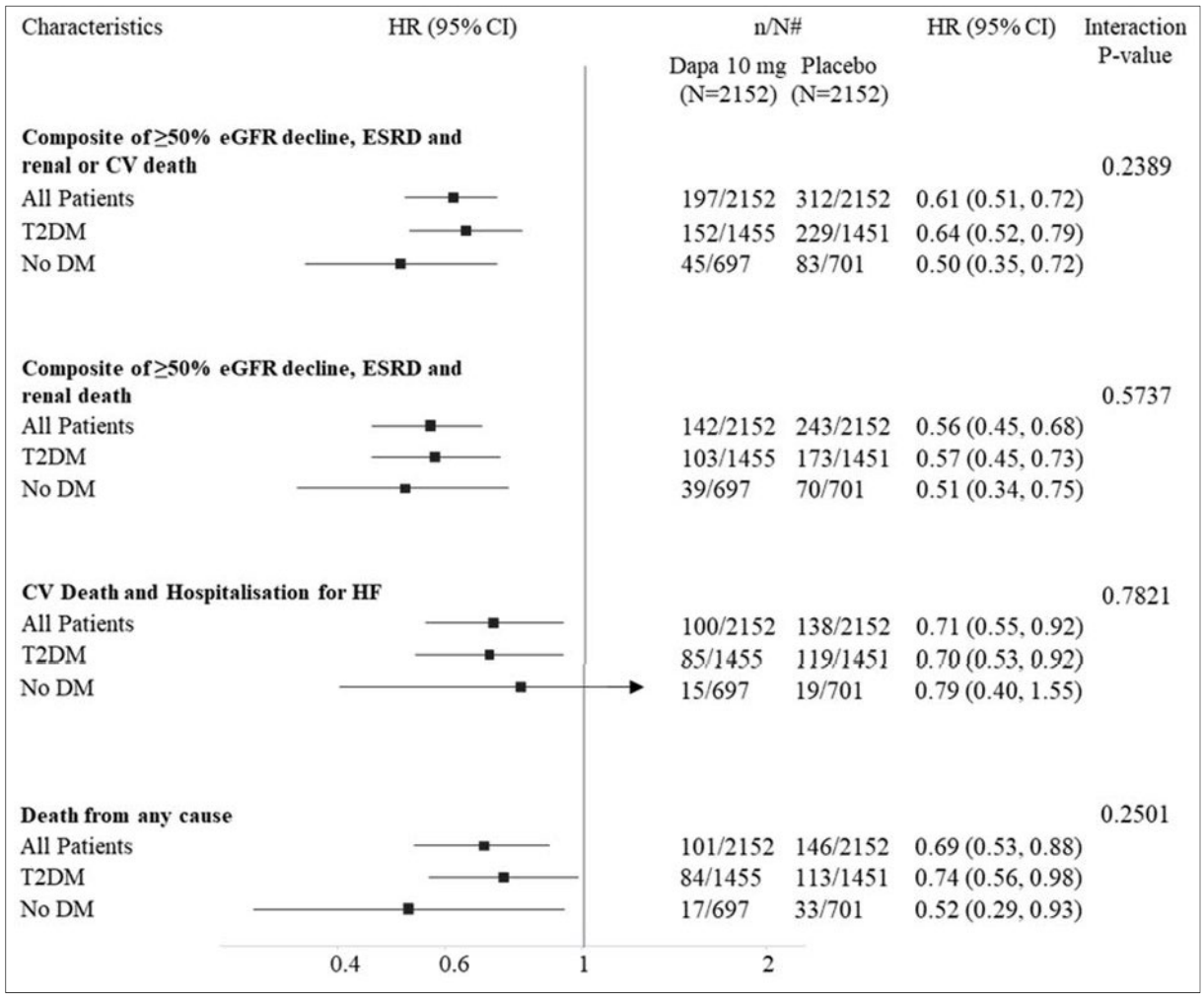
Ancillary analyses

Efficacy by Diabetes Status

Overview of Primary and Secondary Endpoints

Figure 13 summarizes the primary and secondary endpoints by diabetes status at baseline.

Figure 12: Forest Plot of the Primary and Secondary Endpoints by Baseline Diabetes Status (FAS)



Composite of ≥ 50% Sustained Decline in eGFR, ESRD, and Renal or CV Death

The reduction on the incidence of the primary endpoint was consistent in subgroups of patients with T2DM (HR 0.64 [95% CI 0.52, 0.79]) and without diabetes (HR 0.50 [95% CI 0.35, 0.72]) (Figure 13). The KM

curves of the primary endpoint for placebo and dapagliflozin groups began to separate early and continued to separate over the course of the study both in patients with T2DM (Figure 15) and without diabetes (Figure 14).

Figure 14: Kaplan-Meier Plot of the Composite of ⩾ 50% eGFR Decline, ESRD and Renal or CV death by T2DM status (FAS) – Subjects with T2DM

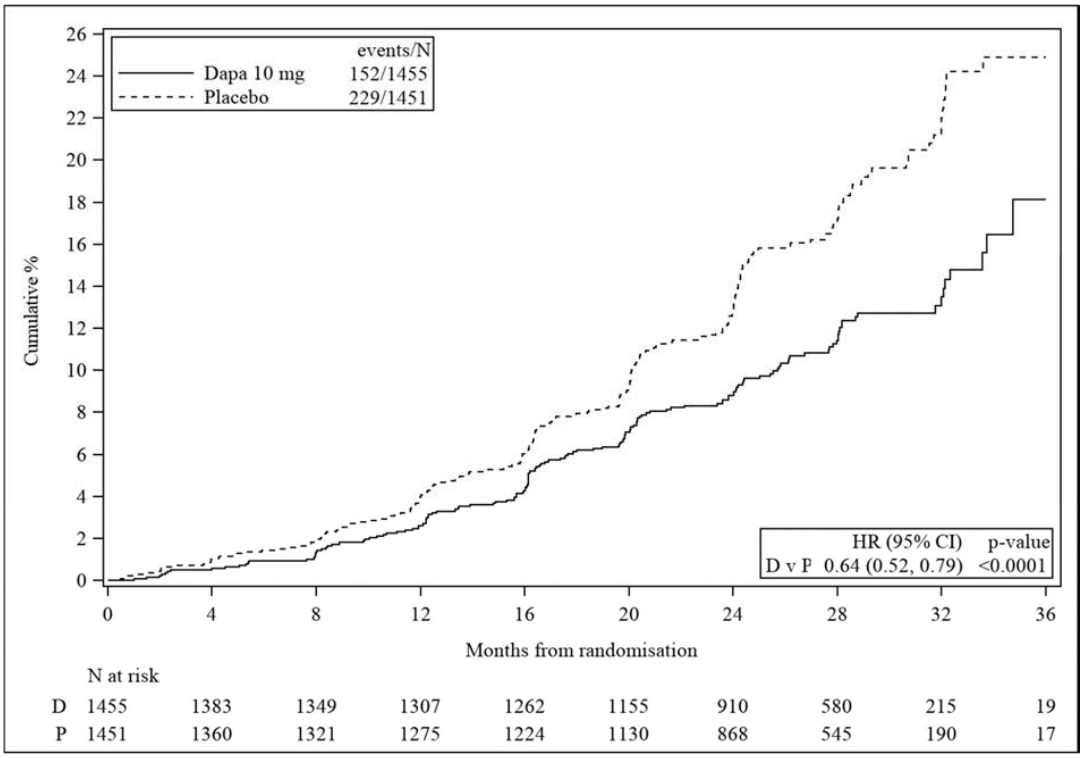
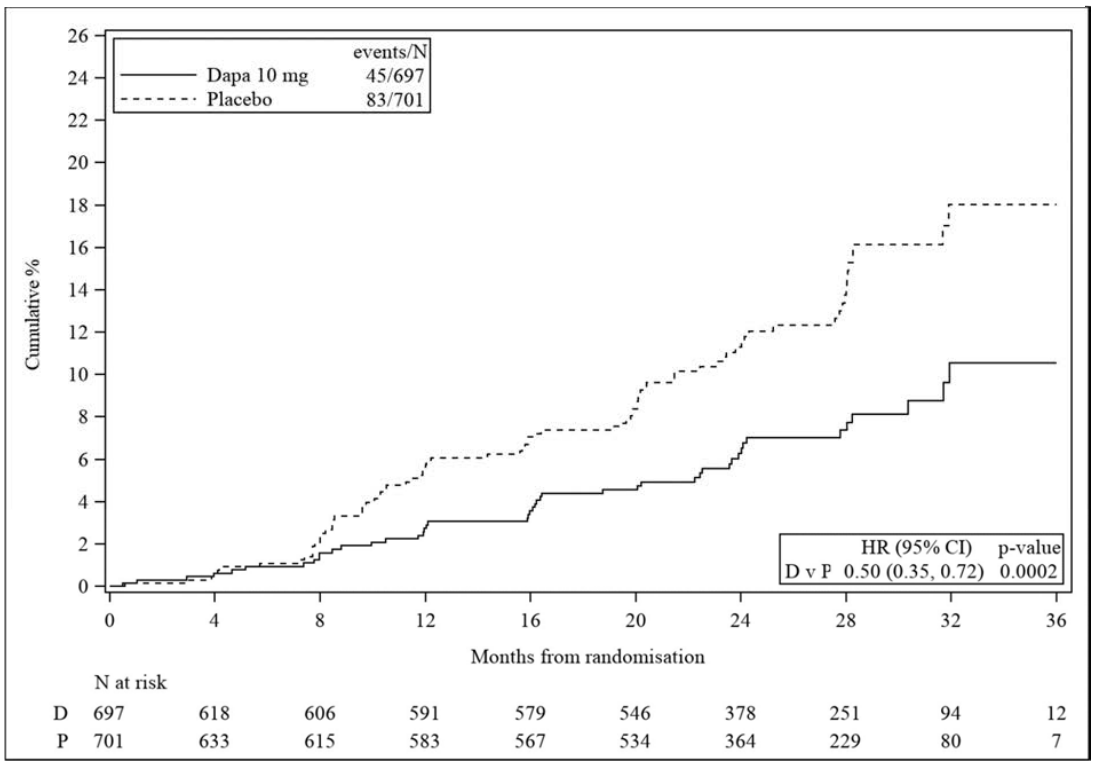


Figure 13: Kaplan-Meier Plot of the Composite of ⩾ 50% eGFR Decline, ESRD and Renal or CV death by T2DM status (FAS) – Subjects without Diabetes



All components of the composite (≥ 50% sustained decline in eGFR, ESRD, renal or CV death) contributed to the treatment effect both in patients with T2DM and without diabetes (Table 11).

Table 11: Time to First Event of the Composite of ≥ 50% eGFR Decline, ESRD, and Renal or CV death (including components) by T2DM status (FAS)

	Dapa 10 mg		Placebo			
Variable	**Subjects with events n (%)**	**Event rate**	**Subjects with events n (%)**	**Event rate**	**Hazard ratio**	**95% CI**
Subjects with T2DM	**(N = 1455)**		**(N = 1451)**			
Composite of ≥ 50% eGFR decline, ESRD, and renal or CV death	152 (10.4)	5.2	229 (15.8)	8.0	0.64	(0.52, 0.79)
≥ 50% decline in eGFR	79 (5.4)	2.7	140 (9.6)	4.9	0.55	(0.42, 0.72)
ESRD	77 (5.3)	2.6	109 (7.5)	3.7	0.69	(0.51, 0.92)
eGFR < 15 mL/min/1.73 m^2	57 (3.9)	1.9	77 (5.3)	2.6	0.73	(0.52, 1.03)
Chronic dialysis[a]	47 (3.2)	1.5	69 (4.8)	2.2	0.68	(0.47, 0.98)
Receiving renal transplant[a]	1 (<0.1)	0.0	3 (0.2)	0.1		
Renal death[a]	2 (0.1)	0.1	4 (0.3)	0.1		
CV death[a]	56 (3.8)	1.7	66 (4.5)	2.1	0.85	(0.59, 1.21)
Subjects without diabetes	**(N = 697)**		**(N = 701)**			
Composite of ≥ 50% eGFR decline, ESRD, and renal or CV death	45 (6.5)	3.4	83 (11.8)	6.3	0.50	(0.35, 0.72)
≥ 50% decline in eGFR	33 (4.7)	2.5	61 (8.7)	4.6	0.49	(0.32, 0.75)
ESRD	32 (4.6)	2.4	52 (7.4)	3.9	0.56	(0.36, 0.87)
eGFR < 15 mL/min/1.73 m^2	27 (3.9)	2.0	43 (6.1)	3.2	0.56	(0.35, 0.91)
Chronic dialysis[a]	21 (3.0)	1.5	30 (4.3)	2.1	0.62	(0.36, 1.09)
Receiving renal transplant[a]	2 (0.3)	0.1	5 (0.7)	0.3		
Renal death[a]	0	0	2 (0.3)	0.1		
CV death[a]	9 (1.3)	0.6	14 (2.0)	1.0	0.65	(0.28, 1.49)

According to the investigator's clinical judgement, the most likely aetiology of CKD was recorded at baseline. Subgroup analyses of aetiologies of CKD showed that dapagliflozin's treatment benefit observed on the primary endpoint was consistent across different aetiologies (Table 12).

Table 12: Time to First Event of the Composite of ≥ 50% eGFR Decline, ESRD, and Renal or CV death by CKD Etiologies (FAS)

	Dapa 10 mg (N = 2152)			Placebo (N = 2152)						
Subject characteristic Category	**Number of subjects**	**Subjects with event n(%)**	**Event rate**	**Number of subjects**	**Subjects with event n(%)**	**Event rate**	**Hazard ratio**	**95% CI**	**p-value**	**Interaction p-value**
CKD etiology										0.5289
Diabetic Nephropathy	1271	139 (10.9)	5.4	1239	207 (16.7)	8.5	0.63	(0.51, 0.78)	<0.0001	
Ischaemic/Hypertensive Nephropathy	324	24 (7.4)	3.7	363	35 (9.6)	4.9	0.75	(0.44, 1.26)	0.2754	
Chronic Glomerulonephritis	343	22 (6.4)	3.4	352	49 (13.9)	7.5	0.43	(0.26, 0.71)	0.0007	
Other[a] or unknown cause of CKD	214	12 (5.6)	2.9	198	21 (10.6)	5.5	0.58	(0.29, 1.19)	0.1345	

Composite of ≥ 50% Sustained Decline in eGFR, ESRD, and Renal Death

The benefit of dapagliflozin on the secondary endpoint renal composite without CV death was consistent between subgroups of patients with T2DM (HR 0.57 [95% CI 0.45, 0.73]) and without diabetes (HR 0.51 [95% CI 0.34, 0.75]) and results were consistent with those of the primary endpoint (Figure 13). For results on components of this secondary composite endpoint, see Table 11.

Composite of CV Death and Hospitalisation for Heart Failure

The benefit of dapagliflozin on the incidence of the composite of CV death and hospitalisation for HF was consistent in subgroups of patients with T2DM and without diabetes (Figure 13). The incidence of this composite was reduced by dapagliflozin in patients with T2DM (HR 0.70 [95% CI 0.53, 0.92]), and both components contributed to the overall effect (Table 9). In patients without diabetes, events of the composite of CV death and hospitalisation for HF were few but numerically reduced by dapagliflozin (15 in dapagliflozin, 19 in placebo) (HR 0.79 [95% CI 0.40, 1.55]) (Table 13).

Table 13: Time to First Event of the Composite of CV Death and Hospitalisation for HF (including components) by T2DM Status (FAS)

	Dapa 10 mg		Placebo			
Variable	**Subjects with events n (%)**	**Event rate**	**Subjects with events n (%)**	**Event rate**	**Hazard ratio**	**95% CI**
Subjects with T2DM	**(N = 1455)**		**(N = 1451)**			
Composite of CV death and hospitalisation for HF	85 (5.8)	2.7	119 (8.2)	3.8	0.70	(0.53, 0.92)
CV death[a]	56 (3.8)	1.7	66 (4.5)	2.1	0.85	(0.59, 1.21)
Hospitalisation for HF	31 (2.1)	1.0	64 (4.4)	2.1	0.47	(0.31, 0.73)
Subjects without diabetes	**(N = 697)**		**(N = 701)**			
Composite of CV death and hospitalisation for HF	15 (2.2)	1.0	19 (2.7)	1.3	0.79	(0.40, 1.55)
CV death[a]	9 (1.3)	0.6	14 (2.0)	1.0	0.65	(0.28, 1.49)
Hospitalisation for HF	6 (0.9)	0.4	7 (1.0)	0.5		

Death from Any Cause

The benefit of dapagliflozin on the incidence of the secondary endpoint all-cause mortality was consistent in subgroups of patients with T2DM (HR 0.74 [95% CI 0.56, 0.98]) and without diabetes (HR 0.52 [95% CI 0.29, 0.93]) (Figure 13). There were 197 deaths in the T2DM subgroup (84 in dapagliflozin, 113 in placebo), corresponding to event rates per 100 patient-years of 2.6 and 3.5, respectively. In the subgroup of patients without diabetes there were 50 deaths (17 in dapagliflozin, 33 in placebo), corresponding to event rates per 100 patient-years of 1.2 and 2.3, respectively.

Efficacy by Baseline and Demographic Characteristics

Composite of ≥ 50% Sustained Decline in eGFR, ESRD, and Renal or CV Death

The benefit of dapagliflozin on the primary endpoint was generally consistent across subgroups based on baseline demographic and renal variables, including age (≤ 65, > 65 years), eGFR (< 30, ≥ 30, < 45, ≥ 45 mL/min/1.73m2), and UACR (≤ 1000, > 1000 mg/g). A significant interaction p-value was observed for SBP subgroups (≤ 130 mmHg, > 130 mmHg), but both subgroups displayed a positive treatment effect (**Error! Reference source not found.**).

Composite of CV Death and Hospitalisation for Heart Failure

The benefit of dapagliflozin on the secondary endpoint composite CV death and hospitalisation for HF was generally consistent across subgroups based on demographic and baseline renal parameters, including age

(≤ 65, > 65 years), eGFR (< 30, ≥ 30, < 45, ≥ 45 mL/min/1.73m2), and UACR (≤ 1000, > 1000 mg/g). A significant interaction was detected on sex, however the HRs for males and females both indicated a positive treatment effect of dapagliflozin (**Error! Reference source not found.**).

Figure 15 Forest Plot of the Composite of ⩾ 50% eGFR Decline, ESRD, and Renal Death or CV Death by Subgroups (FAS)

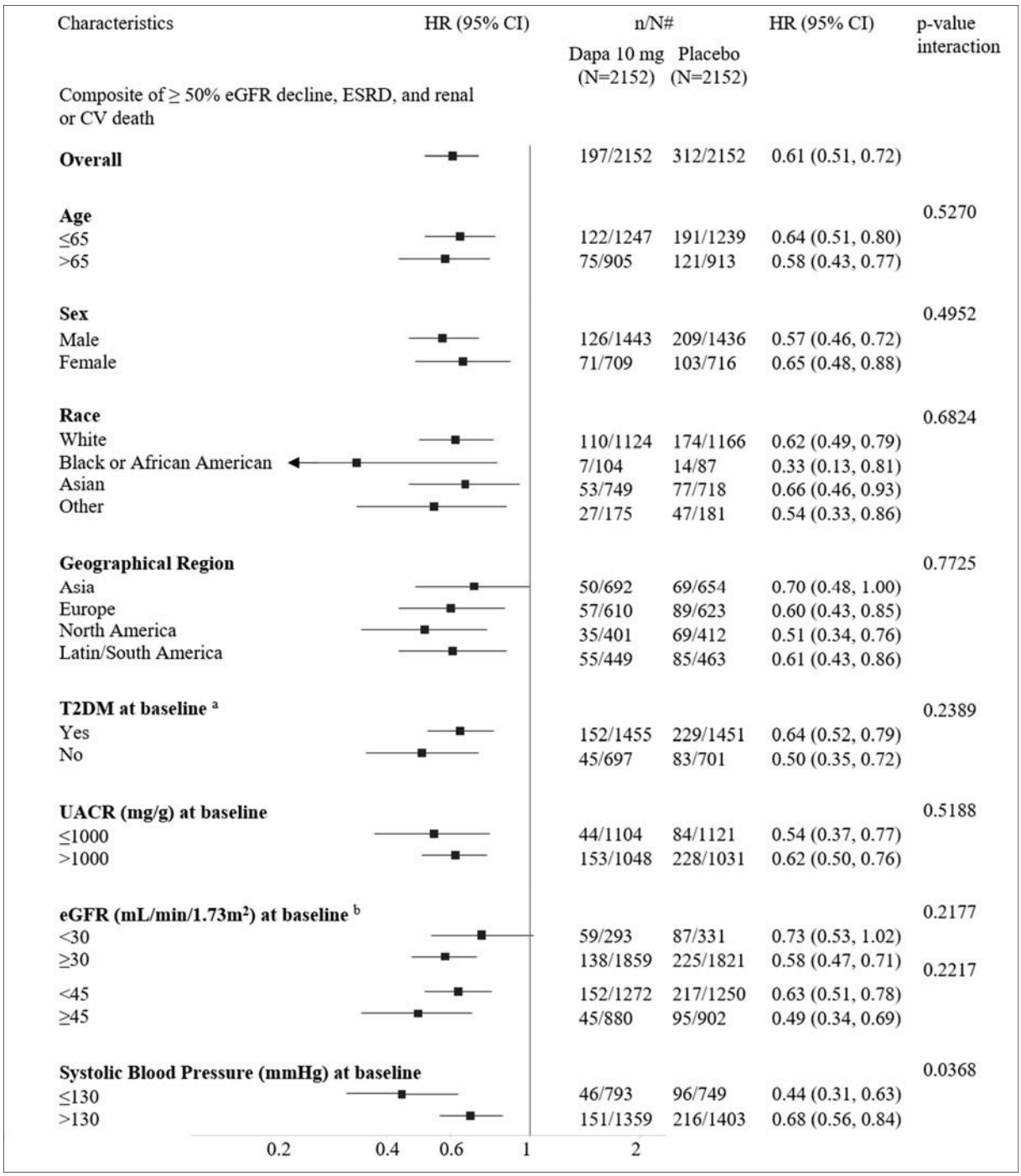
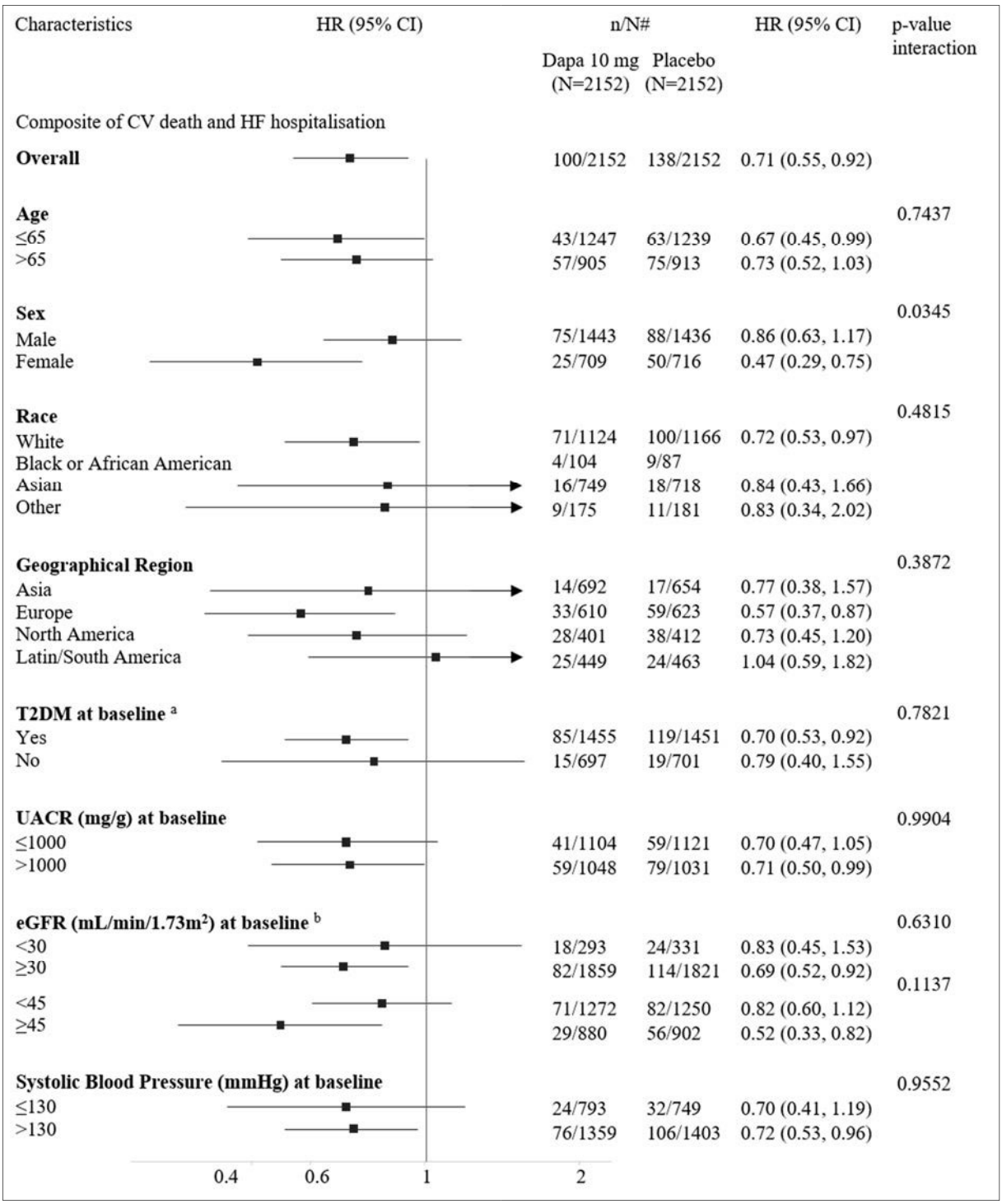


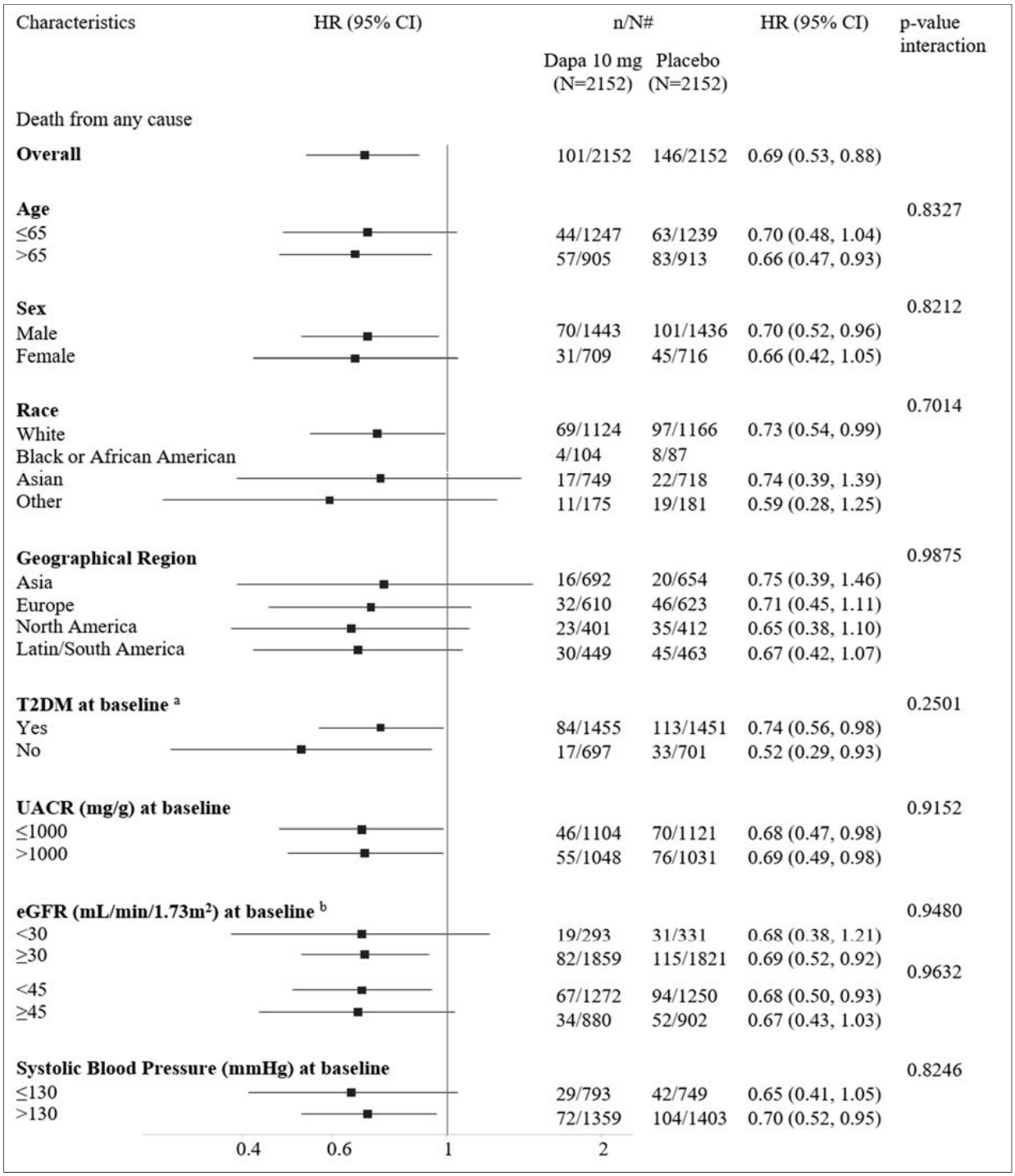
Figure 16 Forest Plot of the Composite of CV Death and Hospitalisation by Subgroups (FAS)



Death from Any causes

The benefit of dapagliflozin on the secondary endpoint all-cause death was consistent across subgroups based on demographic and baseline renal parameters, including age (≤ 65, > 65 years), eGFR (< 30, ≥ 30, < 45, ≥ 45 mL/min/1.73m2), and UACR (≤ 1000, > 1000 mg/g) (Figure 18)

Figure 17: Time to Death from Any Cause by Subgroups (FAS)



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 1. Summary of Efficacy for trial DAPA-CKD

Title: A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease			
Study identifier	Study code: D169AC00001 EudraCT Number: 2016-003896-24 NCT Number: NCT03036150		
Design	international, multicentre, event-driven, randomised, double-blind, parallel-group, placebo-controlled study, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to standard of care, to prevent the progression of chronic kidney disease (CKD) and renal or cardiovascular (CV) death.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Event-driven (The study was conducted between 02 February 2017 and 12 June 2020. not applicable not applicable
Hypothesis	Superiority This study was conducted to evaluate the effect of dapagliflozin on renal outcomes and CV mortality in patients with CKD. The rationale for the study was the growing body of evidence that sodium-glucose co-transporter 2 (SGLT2) inhibition is nephroprotective in patients with T2DM, and the available data suggesting that patients without T2DM would also benefit from SGLT2 inhibition.		
Treatments groups	Dapagliflozin 10 mg (Dapa)		2152 randomized and followed for a mean duration of 27.1 months. 2149 received at least 1 dose of double-blind study drug and were exposed for a mean duration of 24.6 months.
	Placebo		Placebo. Once daily. 2152 randomized and followed for a mean duration of 26.9 months. 2149 received at least 1 dose of double-blind study drug and were exposed for a mean duration of 24.1 months.
Endpoints and definitions	Primary endpoint	Composite of ≥ 50% eGFR decline, ESRD and renal or CV death	Time to the first occurrence of any of the components of this composite: 1. ≥ 50% sustained* decline in eGFR 2. Reaching ESRD - Sustained* eGFR <15 mL/min/1.73 m2 or, - Chronic* dialysis treatment or, - Receiving a renal transplant 3. CV death 4. Renal death
	Secondary endpoint (1)	Composite of ≥ 50% eGFR decline, ESRD and renal death	Time to the first occurrence of any of the components of this composite: 1. ≥ 50% sustained decline in eGFR 2. Reaching ESRD 3. Renal death

	Secondary endpoint (2)	Composite of CV death and hospitalisation for HF	Time to the first occurrence of either of the components of this composite: 1. CV death 2. Hospitalisation for heart failure
	Secondary endpoint (3)	Death from any cause	Time to death from any cause
Database lock	17 July 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat All patients who were randomised to study treatment were included in the FAS irrespective of their protocol adherence and continued participation in the study. <time point>		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapa
	Number of subject	2152	2152
	Primary Composite of ≥ 50% eGFR decline, ESRD and renal or CV death		
	Number of events	312	197
	Event rate per 100 patient-years	7.5	4.6
Effect estimate per comparison	Primary Composite of ≥ 50% eGFR decline, ESRD and renal or CV death	Comparison groups	Dapa vs Placebo
		Hazard Ratio	0.61
		95% confidence interval	(0.51, 0.72)
		P-value	< 0.0001
Descriptive statistics and estimate variability	Secondary Composite of ≥ 50% eGFR decline, ESRD and renal death		
	Number of events	243	142
	Event rate per 100 patient-years	5.8	3.3
Effect estimate per comparison	Secondary Composite of ≥ 50% eGFR decline, ESRD and renal death	Comparison groups	Dapa vs Placebo
		Hazard Ratio	0.56
		95% confidence interval	(0.45, 0.68)
		P-value	< 0.0001
Descriptive statistics and estimate variability	Secondary Composite of CV death and hospitalisation for HF		
	Number of events	138	100
	Event rate per 100 patient-years	3.0	2.2
Effect estimate per comparison	Secondary Composite of CV death and hospitalisation for HF	Comparison groups	Dapa vs Placebo
		Hazard Ratio	0.71
		95% confidence interval	(0.55, 0.92)
		P-value	

Descriptive statistics and estimate variability	Secondary Death from any cause Number of events Event rate per 100 patient-years	 146 3.1	 101 2.2
Effect estimate per comparison	Secondary Death from any cause	Comparison groups	Dapa vs Placebo
		Hazard Ratio	0.69
		95% confidence interval	(0.53, 0.88)
		P-value	

4.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The DAPA-CKD study was an international, multicentre, event-driven, randomized, double-blind, parallel-group, placebo-controlled study, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to standard of care, to prevent the progression of CKD and renal or CV death.

The study population consisted of adult patients with CKD (eGFR ≥ 25 and ≤ 75 mL/min/1.73 m^2) and evidence of increased albuminuria (urine albumin creatinine ratio [UACR] ≥ 200 and ≤ 5000 mg/g), with type 2 diabetes (T2DM) or without diabetes. In addition, patients had to be on stable, maximum-tolerated labelled daily dose, of ACE-I or ARB for at least 4 weeks before Visit 1, if not medically contraindicated.

Of note, only patients with overt albuminuria levels ≥200 mg/g have been included in the study. A lower inclusion limit of UACR 200 mg/g in the Dapa-CKD study was agreed within an EMA scientific advice, as a prognostic enrichment strategy to select patients at higher risk of experiencing a disease related-endpoint event and not due to any expectation that dapagliflozin would have less efficacy in patients without albuminuria.

Data from the DECLARE trial on patients with T2D, with and without albuminuria but without CKD is considered supportive data, but data on patients with T2D and CKD without albuminuria is rather limited, especially in patients with CKD categories 3-4. Additional data on the effect of dapagliflozin on the treatment of CKD on patients without diabetes and without albuminuria has not been provided. Treatment with dapagliflozin may provide a potential benefit for patients with CKD that has not yet developed albuminuria, but data in this patient group is scarce.

Addition descriptive analyses of the effect of UACR as a mediator of treatment effects on kidney outcomes shows that a substantial non-albumin-mediated treatment effect can be seen in the subgroup of patients with nondiabetic etiologies of CKD. Together with the knowledge of effect of the SGLT2 inhibitors on the pathophysiological mechanisms leading to CKD, it seems plausible that patients without albuminuria might benefit from treatment with dapagliflozin (albeit likely to a less extent). The Applicant was therefore requested to include in section 4.4 of the SmPC that there is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria. Patients with albuminuria may benefit more, as this information is of importance to the prescriber.

Patients with known polycystic kidney disease, glomerulonephritis with flares (lupus or ANCA-associated vasculitis), ongoing active renal inflammation or T1D were excluded. For patients with T2D, changes to diabetes treatment following recommendation by clinical guidelines were allowed, for all drugs but for those containing SGLT-2 inhibitor other than the IP, which were prohibited. CKD treatment as recommended by clinical guidelines, if not medically contraindicated, was mandatory.

The 10 mg dapagliflozin dose choice was based on efficacy/safety data in the T2D population as well as population with HFrEF. Furthermore, in a previous study in patients with CKD stage 3 (eGFR 30 to 60 mL/min/1.73 m^2) the dose was found to be well tolerated. Background medication in both study groups included available standard CKD treatment. Reduction of dapagliflozin to 5mg was temporally allowed, if clinically indicated.

The study was event-driven, with an anticipated duration was ca 45 months, when the predetermined number of primary endpoints (n=681) was predicted to have occurred. The sample size was calculated to 4000 patients in order to detect 681 events of the primary endpoint (≥ 50% sustained decline in eGFR, ESRD, CV death or renal death). The MAH took the decision to amend the study protocol to remove the planned interim analysis when 75% of endpoint events were reached. An independent DMC recommended the premature study stop based on positive efficacy results in an informal review when 408 primary endpoint events were observed. This was contemplated in the original study protocol. The study end date was set to 3 April 2020. The final database included 509 events, instead of the 681 primary endpoints events initially calculated.

Stratification factors were T2DM status and UACR. The number of randomized patients was monitored in order to ensure specific predefined size of the subgroups in respect to eGFR, tolerability to ACE-I/ARB and geographic location at the time of randomization.

Primary and secondary endpoints seem appropriate. Of note, the primary efficacy outcome is similar to the one used in the Credence trial, but with the inclusion of patient with and without type2 diabetes. Secondary efficacy outcomes include several CV endpoints, relevant to the population with CKD and high CV risk included. According to the applicant, the primary outcome was chosen based on the requirements as outlined in the CHMP *Guideline on clinical investigation of medicinal products to prevent development/slow progression of chronic renal insufficiency.*

All amendments were made after the start of patient recruitment. Of note, two new exploratory objectives were added on January the 22nd, 2020: *To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of the composite endpoint of chronic dialysis, renal death or receiving a renal transplant; To determine whether dapagliflozin compared with placebo will result in a reduction in the incidence of the composite endpoint of CV death, MI or stroke.*

None of the amendments is thought to significantly influence the interpretation of the efficacy and safety outcomes, except for the removal of the interim analysis. Additionally, there were few protocol deviations and equally distributed between the study groups.

In summary, the study design and study conduct are generally endorsed. The randomization and blinding procedures are considered acceptable.

Statistical methods applied are in general acceptable. Given the compelling efficacy results, the decision for early stop seems reasonable, however, without any consideration of its impact on evaluability of the safety data (particularly adverse events of special interest, e.g. related to lower limb amputation) and disregarding from the issues raised below.

The informal analyses by the DMC that triggered the early stop was based on 408 events of the composite primary endpoint, i.e. prior to the initially planned interim analysis that was to be performed when 75% of the primary events were adjudicated. According to the SAP version 1, there was one planned interim analysis, with the possibility of the DMC to do *subsequent* interim analysis if they deem necessary, and no efficacy analysis was mentioned to be performed by the DMC prior to the first planned interim analysis. It is acknowledged that the CSP stated that the study may be terminated early if either a clear beneficial or harmful effect of the study treatment is detected during the DMC review, but performing unplanned interim analysis is problematic in multiple aspects. According to the first SAP version, one-sided alpha level of 0.001

was to be assigned at the interim analysis and significance level for the final analysis would be determined by the Haybittle-Peto function based on the actual number and timing of interim analyses. Thus, if the current analysis would have been regarded as the planned interim analysis, then the hierarchical testing procedure for the primary and secondary endpoints should have been performed at one-sided significance level of 0.001. The circumstances around the early stop were clarified by the MAH on request. The DMC meeting minutes showed that the decision to perform an inferential efficacy analysis prior to the planned interim analysis was made by the DMC well in advance of amending the protocol (version 4). However, the decision to perform an early efficacy analysis was made based on descriptive statistics for the primary composite endpoint (unblinded data), which was not part of the safety review according to the DMC charter, and the rationale for the MAH's decision to remove the interim analysis in the protocol version 4 is unclear. The reason for the decision by the MAH to follow the recommendation by the DMC to stop the study early has not been addressed. The unplanned early stop has therefore implications on the interpretation of statistical significance of the primary and secondary endpoints, and the appropriate way of presentation of these endpoints in the SmPC.

Following the protocol version 4, and after the decision to prematurely stop the study, the MAH had updated the SAP by simply removing the interim analysis, and applying significance level of one sided 0.025 to test the primary and the secondary endpoints in the hierarchical procedure, with no handling of multiplicity caused by the informal analysis (one or multiple) by the DMC and the unplanned early stop, despite knowing that the study was terminated early. Also, the study has been described as an event-driven study with 681 primary endpoint events required for the primary analysis, while the current analysis comprises 509 events and as such, cannot be regarded as the final analysis with hypotheses tested on one-sided significance level of 0.025 as described in the SAP. The MAH approached this multiplicity issue retrospectively, in the CSR. In a retrospective evaluation of multiplicity, the MAH considered applying the stringent Haybittle-Peto boundary of 0.001 one-sided for the primary endpoint, while for the 3 secondary endpoints, the framework similar to Glimm et al 2010 was adopted to show that a two-sided alpha threshold of 0.03 would ensure strong control of FWER, accounting for 3 analyses: DMC informal analysis for the primary endpoint only, current analysis and planned final analysis. Without further in-dept assessment of the framework presented, the value of the multiplicity handling diminishes due to being presented retrospectively and due to the uncertainties around the informal statistical analyses performed by the DMC. It is expected that, at least, the initially planned Haybittle-Peto rule would have been applied in the hierarchical testing procedure, i.e. with the current analysis considered as interim, using one-sided significance level of 0.001 (i.e. 0.002 two-sided). In this respect, we may base the interpretation of the study results on a 0.002 threshold for p-values in the hierarchical procedure, which means that only the primary and the first secondary endpoint are considered as statistically significant when adjusting for multiplicity. Considering the MAH's clarification of the circumstances around the early stop, there was no doubt that the early efficacy analysis, performed prior to the planned interim analysis, was triggered primarily by the (unblinded) observed data.

Of note, two-sided p-values are presented in the CSR and the alpha threshold for statistical significance in the confirmatory testing was 0.05, while the SAP only mentions one-sided alpha of 0.025.

Regarding missing data, incomplete follow-up (due to any reason) of the primary endpoint accounted for approximately 6% of the total person time. The extent of incomplete follow-up was balanced between treatment groups and was overwhelmingly driven by missing eGFR samples (due to any reason, including COVID-19). Related to the Kaplan-Meier analysis of the primary and secondary endpoints, the numbers of censored observations due to different reasons were presented for each endpoint. For the primary endpoint and the secondary renal endpoint, the majority of events censored before study end date (approximately 19%) were due to missing eGFR sample after study end. Censoring prior to the primary analysis censoring date was well balanced between the treatment groups.

Efficacy data and additional analyses

The study was conducted at 405 sites across 21 countries, and patients were randomized at 386 sites. 28.6% of patients randomised in Europe. The COVID-19 pandemic is thought not to have meaningfully impacted the overall quality of the study and the interpretation of the results.

Demographics, baseline patient characteristics and medical history were generally balanced between treatment groups. Baseline medication use was representative of standard of care for CKD and CV disease. At baseline, 67.5% of patients in the study had T2DM, being diabetic nephropathy the most common cause of CKD (58.3%). 97.0% of patients were treated with ACE-I or ARB and 94% of patients with T2DM were treated with diabetes medications.

The full analysis set (FAS) includes all randomised patients assessed according to their randomised study drug assignment (2152 patients in in each treatment arm). 6 patients did not receive IP and were therefore excluded from the safety analysis set (SAS).

Compliance with the study drug was high and similar between treatment groups, almost 100%. Under COVID-19 pandemic, information regarding compliance was collected verbally if physical visits were not possible.

The study met its primary outcome, as dapagliflozin reduced the risk of the primary composite endpoint (≥ 50% sustained decline in eGFR, ESRD, and renal or CV death) compared to placebo. The primary composite event rate was 7,5 in the placebo arm and 4,6 in the dapagliflozin arm, yielding a hazard ration of 0.61 ($p<0.0001$). The KM curves of the primary endpoint for placebo and dapagliflozin groups began to separate early (4 months) and continued to separate over the course of the study. The number needed to treat per 27 months was 19.

All components of the primary composite favoured the dapagliflozin group; however, the treatment effect was mainly driven by the components ≥ 50% sustained decline in eGFR and ESRD. For the component renal death, only eight events were reported in total, six for placebo and two for dapagliflozin. The component CV death was numerically lower in the dapagliflozin arm.

Dapagliflozin reduced the risk of the secondary renal composite endpoint of ≥ 50% Sustained Decline in eGFR, ESRD, and Renal Death vs placebo, with a hazard ratio of 0.56 ($p<0.0001$). The KM curves began to separate early and continued to separate over the course of the study.

Dapagliflozin reduced the risk of the secondary CV composite endpoint of CV Death and Hospitalisation for Heart Failure, with a hazard ration of 0.7. The KM curves began to separate early and continued to separate over the course of the study. Of note, the number of events increased in the dapagliflozin group towards the end of the study, while it was kept constant in the placebo group.

The incidence of hospitalisation for HF was reduced in the dapagliflozin group (HR 0.51) vs placebo while the incidence of CV death as a single component was only numerically reduced.

Dapagliflozin reduced the risk of the secondary endpoint Death from Any Cause, with a hazard ratio of 0.7. The KM curves began to separate early and continued to separate over the course of the study. A reduction in both CV (mainly HF) and non-CV causes (mainly infections, malignancies, renal deaths) was seen.

Treatment with dapagliflozin was associated with a greater reduction in UACR. The difference between groups was clinically relevant and was maintained throughout the duration of the study.

Dapagliflozin reduced the incidence of time to first doubling of serum creatinine levels compared to placebo. The observed initial drop in eGFR in the dapagliflozin group as compared with placebo is consistent with the known mode of action of SGLT2 inhibitors. After the initial drop, the decline in eGFR was slower in the dapagliflozin group.

A minor reduction in HbA1c (-0.05 to -0.24 %) was observed in the T2DM population. Indeed, a significant change in HbA1c was not expected, as the glucose-lowering effect of dapagliflozin is eGFR dependent, thereby low in this population with reduced kidney function.

In line with previous observations, a minor reduction in body weight was observed after 36 months of treatment with dapagliflozin (-0.8 kg) as compared to placebo.

Dapagliflozin effect on the primary endpoint was independent of diabetes status at baseline. The KM curves began to separate earlier in the group with diabetes (4 months) vs is those without diabetes (8 months) and continue to separate throughout the rest of the study. The composite without CV death (≥ 50% Sustained Decline in eGFR, ESRD and Renal Death) was also consistent with the primary endpoint, irrespective of diabetes diagnose.

As expected, the event rate of the primary composite endpoint in patients with diabetes was higher (placebo 8.0 vs dapa 5.2) than those without diabetes (placebo 6.3 vs dapa 3.4). The hazard ratio was similar, independent of diabetes status (diabetes 0.6 vs w/o diabetes 0.5). All components of the composite contributed to the treatment effect, irrespective of diabetes status at baseline.

A similar reduction of the primary composite endpoint in the dapagliflozin group was seen independent of the aetiology of kidney disease. However, other causes of CKD such as inflammatory and immunological were excluded from the study.

The Applicant has further justified why ongoing or recent requirements of immunomodulating or cytotoxic therapies for primary and secondary renal diseases within 6 months of enrolment were actively excluded from the study (for practical and safety reasons, as this patients often require intense and sometimes prolonged courses of anti-inflammatory and immunosuppressive therapy or other immunotherapy that could bias the study results). Besides, the Applicant elaborates on the fact that treatment with SGLT2 inhibitors in PKD patients lacks strong rationale, as dapagliflozin has not been shown to affect cyst growth.

Additional analyses of the primary endpoint by investigator judged CKD aetiology points towards a consistent treatment benefits across all included aetiologies, including chronic glomerulonephritis. Even though no firm conclusion can be drawn from smaller subgroup analyses due to the low number of patients, a numerical benefit in favour of dapagliflozin can be seen in most subgroups.

The reason for not including patients with active inflammatory and immunosuppressive treatments in this clinical trial is accepted, so is the exclusion of patients with PKD. The fact that the pathophysiology of CKD in these aetiologies share the same mechanism, namely glomerular hyperfiltration, makes dapagliflozin a plausible drug candidate, even if data from the Dapa-CKD study concerning these aetiologies is very limited.

The exclusion of patients with T1D is acknowledged and the proposed addition of text to SmPC section 4.4 is accepted.

Of note, roughly 200 patients with diabetes in each treatment group were not judged to have diabetic nephropathy as the main cause of their kidney disease.

The Applicant has reviewed data for the primary and secondary endpoints in the type2 diabetes patient population according to the adjudicated cause of their CKD aetiology. The fact that there were few events in the non-DKD group for the all endpoints limits the interpretation of the data. The treatment effect of dapagliflozin seems to be consistent between the CKD aetiology categories diabetic and non-diabetic nephropathy for the primary endpoint and all secondary endpoints. Furthermore, there is no sign of negative effect of dapagliflozin in the non-diabetic nephropathy population.

The incidence of the secondary outcome composite CV Death and Hospitalisation for Heart Failure was reduced in patients with diabetes (HR 0,70) as well as in patients without diabetes (HR 0,79). In patients with diabetes, the effect was driven by the component hospitalization for HF.

The reduction of risk as documented by the primary composite endpoint was similar across subgroups based on baseline demographic and renal variables, including age, eGFR and UACR. However, patients in the lower eGFR categories (<30 vs ≥30 and < 45 vs ≥ 45) seem to have less effect, as the HR was higher in patients with lower eGFR. No further results have been provided in the different eGFR strata (1-5).

Further analyses of the primary and secondary endpoints by eGFR strata show that the effect of dapagliflozin was consistent across all eGFR strata, including in patients with eGFR < 30 mL/min/1.73 m^2 (HR 0.73 [95% CI 0.53 to 1.02]).

Additional analyses on the components of the primary endpoint by baseline eGFR subgroup (< 30, ≥ 30, < 45, and ≥ 45 mL/min/1.73 m^2) show a numerical reductions of ESRD (HR 0.72 [95% CI 0.50 to 1.04]) and its subcomponents (eGFR < 15 mL/min/1.73 m^2 and chronic dialysis) in patients with eGFR < 30 mL/min/1.73 m^2. Of note, the confidence intervals in the analyses of the group with eGFR < 30 mL/min/1.73 m^2 are wider than those with ≥30 mL/min/1.73 m^2, while the upper confidence interval was greater than 1 in all subgroups, adding uncertainty to the finding.

Concerning secondary endpoints, reductions in all 3 secondary endpoints were observed in patients with eGFR < 30 mL/min/1.73 m^2: the renal endpoint (HR 0.71 [95% CI 0.49 to 1.02]), CV death and hospitalisation for HF (HR 0.83 [95% CI 0.45 to 1.53]), and all-cause mortality (HR 0.68 [95% CI 0.38 to 1.21]).

Patients in the lower systolic blood pressure category (<130 mmHg) had a higher reduction of the primary endpoint, vs those with higher SBP (>130 mmHg). It could be that patients with lower systolic blood pressure are subject to a more aggressive pharmacological treatment for their heart and kidney disease. The applicant has conducted additional analyses on background anti-hypertensive medication at baseline. Of note, several main categories of CKD and CV medications were less frequently used in the patients with lower SBP. Additional analyses on the primary endpoint shows that the effect of dapagliflozin was generally consistent across categories of baseline CKD or CV medication.

The reduction of the secondary endpoint CV death and hospitalization for HF was similar across demographic and baseline renal parameters. Of note, female patients had a significant reduction of the HR as compared to male. Furthermore, the effect seems to be more pronounced in patients with eGFR ≥45 than those with eGFR <45, even though the interaction was not significant.

The Applicant has provided further analyses of the secondary composite endpoint of CV death and hospitalisation for HF by baseline eGFR strata. The Applicant has also provided data on other secondary composite endpoints by eGFR strata. Even though no firm conclusion can be drawn from smaller subgroup analyses due to the low number of events, a numerical benefit in favour of dapagliflozin can be seen in all subgroups. These indicates a consistent efficacy across all eGFR levels and provides no indication of a trend towards reduced efficacy with decreased renal function.

The reduction in death from any cause was similar across demographic and baseline renal parameters.

4.4.3. Conclusions on the clinical efficacy

A positive treatment effect of dapagliflozin on the primary composite endpoint (≥ 50% eGFR decline, ESRD and renal or CV death) was shown, irrespective of diabetes status at baseline. The effect was mainly driven by the two renal components, ≥ 50% eGFR decline and ESRD. Dapagliflozin was superior to placebo for the reduction of the renal and CV secondary endpoints as well as all-cause mortality. The effects of dapagliflozin on the primary and secondary endpoints were generally consistent across the analysed subgroups, including diabetes status, eGFR and UACR level at baseline.

Of note, roughly 200 patients with diabetes in each treatment group were not judged to have diabetic nephropathy as the main cause of their kidney disease. Treatment effect of dapagliflozin seems to be consistent between the CKD aetiology categories diabetic and non-diabetic nephropathy for the primary endpoint and all secondary endpoints and no sign of negative effect of dapagliflozin has been reported in the non-diabetic nephropathy population.

Further to this, only patients with overt albuminuria levels ≥ 200 mg/g have been included in the study. Treatment with dapagliflozin may provide a potential benefit for patients with CKD that has not yet developed albuminuria, but clinical data in this patient group is scarce. From a mechanistic point of view, it seems reasonable to believe that the effect of SGLT2 inhibitors in the development and progression of CKD is not only dependent on the reduction of albuminuria. This is supported by additional analyses showing that a substantial non-albumin-mediated treatment effect can be seen in the subgroup of patients with nondiabetic etiologies of CKD. However, evidence is higher for those patients with high levels of albuminuria, which is reflected in the SmPC.

A similar reduction of the primary composite endpoint in the dapagliflozin group was seen independent of the aetiology of kidney disease. However, other causes of CKD such as T1DM, inflammatory and immunological conditions were excluded from the study. Additional analyses of the primary endpoint by CKD aetiology shows a consistent treatment benefits across all included aetiologies, including chronic glomerulonephritis.

The fact that the pathophysiology of CKD in these aetiologies share the same mechanism, namely glomerular hyperfiltration, makes dapagliflozin a plausible drug candidate, even if data from the Dapa-CKD study concerning these aetiologies is very limited. The exclusion of patients with T1D is acknowledged and covered in SmPC section 4.4.

The reduction of risk as documented by the primary composite endpoint was similar across subgroups based on baseline demographic and renal variables, including age, eGFR and UACR. However, patients in the lower eGFR categories (<30 vs >30 and < 45 vs > 45) seem to have less effect, as the HR was higher in patients with lower eGFR. Further analyses of the primary and secondary endpoints by eGFR strata show that the effect of dapagliflozin was consistent across all eGFR strata, including in patients with eGFR < 30 mL/min/1.73 m^2.

Patients in the lower systolic blood pressure category (<130 mmHg) had a higher reduction of the primary endpoint vs those with higher SBP (>130 mmHg) but additional analyses on background of anti-hypertensive medication at baseline show that several main categories of CKD and CV medications were less frequently used in the patients with lower SBP. Additional analyses on the primary endpoint shows that the effect of dapagliflozin was generally consistent across categories of baseline CKD or CV medication.

The reduction of the secondary endpoint CV death and hospitalization for HF was similar across demographic and baseline renal parameters but seems to be more pronounced in patients with eGFR >45 than those with eGFR <45, even though the interaction was not significant. Even though no firm conclusion can be drawn from smaller subgroup analyses due to the low number of events, a numerical benefit in favour of dapagliflozin can be seen in all subgroups. These indicates a consistent efficacy across all eGFR levels and provides no indication of a trend towards reduced efficacy with decreased renal function.

Although the benefit of dapagliflozin on the primary endpoint and secondary endpoint composite CV death and hospitalisation for HF was generally consistent across subgroups based on demographic and baseline renal parameters (eGFR (< 30, ≥ 30, < 45, ≥ 45 mL/min/1.73m2)), due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 mL/min. This is reflected in section 4.2 of the SmPC. If GFR falls below 45 mL/min, additional glucose lowering treatment should be considered in patients with diabetes mellitus if further glycaemic control is needed. This is also appropriately reflected in the SmPC.

4.5. Clinical safety

Introduction

The current safety evaluation is based on data from the completed DAPA-CKD study.

The target population had CKD (eGFR ≥25 and ≤75 mL/min/1.73 m^2) with albuminuria (UACR ≥200 and ≤5000 mg/g). The study population included both patients with T2DM and patients without diabetes, and patients were stratified based on T2DM status and UACR at baseline (UACR >1000 and ≤1000 mg/g).

All summaries of AEs, safety laboratory data, and vital signs described below are presented for the on-treatment period, which includes AEs with an onset date on or after date of first dose and up to and including 30 days following last dose of study drug.

Additional presentations include all events with onset on or after first dose of study drug regardless of whether patients were on study treatment or not at the time of the event, the on- and off-treatment period. With regard to AEs of special interest, on- and off- treatment (labelled simply as "SAS") is considered the primary analysis approach for fractures and amputations, whereas the on-treatment period (labelled as "on-treatment (SAS)") is the primary analysis approach for other AEs of special interest.

Patient exposure

The DAPA-CKD SAS included 4,298 patients, 2,149 on dapagliflozin 10 mg and 2,149 on placebo. About 70% of the study population were subjects with T2DM (1,453 and 1,450 subjects for dapagliflozin and placebo, respectively).

Duration of exposure

The duration of exposure to study drug ranged from 0 to 39.0 months. In total, there were 4,448 patient-years of exposure to dapagliflozin in the study. The median duration of exposure to study drug was balanced between treatment groups: 27.3 months in the dapagliflozin treatment group and 27.0 months in the placebo group.

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

Characteristic	Statistic	Dapa 10 mg (N=2149)	Placebo (N=2149)
Duration of exposure (months)[a]	n	2149	2149
	Mean	24.8	24.3
	SD	9.4	9.6
	Minimum	0.0	0.0
	1st quartile	22.3	21.7
	Median	27.3	27.0
	3rd quartile	31.2	31.1
	Maximum	39.0	38.8
	Total treatment years	4448	4359
Cumulative exposure over time, n(%)[b]	≥ 1 day	2149 (100.0)	2149 (100.0)
	≥ 1 month	2121 (98.7)	2120 (98.7)
	≥ 6 months	1946 (90.6)	1932 (89.9)
	≥ 12 months	1865 (86.8)	1829 (85.1)
	≥ 18 months	1773 (82.5)	1745 (81.2)
	≥ 24 months	1423 (66.2)	1364 (63.5)
	≥ 28 months	992 (46.2)	945 (44.0)
	≥ 32 months	445 (20.7)	411 (19.1)
	≥ 36 months	80 (3.7)	70 (3.3)

Study drug 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 by the protocol.

There were 90 (4.2%) patients with dose reductions in the dapagliflozin group and 61 (2.8%) in the placebo group. Of these patients, 67 (3.1%) in the dapagliflozin group and 48 (2.2%) in the placebo group did not return to the 10 mg dose of dapagliflozin or matching placebo.

The most frequent reason for dose reduction was AE: 48 (2.2%) patients in the dapagliflozin treatment group and 35 (1.6%) patients in the placebo group; SAEs that led to dose reduction were observed in 4 (0.2%) patients in the dapagliflozin treatment group and 3 (0.1%) patients in the placebo group. The most common AEs that led to dose reduction of study drug were chronic kidney disease and hypovolaemia in the dapagliflozin group (5 [0.2%]) patients for both PTs), and renal impairment (9 [0.4%] patients) in the placebo group.

Study drug interruption

There were 378 (17.6%) patients with dose interruptions in the dapagliflozin group and 380 (17.7%) in the placebo group. Most patients had only 1 period of interruption. The median number of days per interruption was 14 days in the dapagliflozin treatment group and 9 days in the placebo group. The most common reason for interruption of study drug was AE, reported for 265 (12.3%) patients in the dapagliflozin treatment group and 269 (12.5%) patients in the placebo group. The most frequently reported AE, by PT, that led to interruption of study drug was urinary tract infection for dapagliflozin with 15 (0.7%) patients reporting this term (compared to 8 [0.4%] in the placebo group), and acute kidney injury for placebo with 18 (0.8%) patients reporting this term (compared to 14 [0.7%] in the dapagliflozin group).

Demographic and baseline characteristics

DAPA-CKD included patients with CKD (with an eGFR of ≥ 25 and ≤ 75mL/min/1.73 m^2 and UACR ≥ 200 and ≤ 5000mg/g), either with T2DM or without diabetes, receiving dapagliflozin or placebo on top of standard of care.

Adverse events

The safety and tolerability of dapagliflozin were evaluated based on SAEs, DAEs, changes in clinical chemistry/haematology parameters, and AEs of special interest. AEs were only to be recorded if they qualified as SAEs, or if the AE was the reason for permanent discontinuation from IP, IP interruption, or dose reduction, or if the AE qualified as an AE of special interest, or if a potential endpoint fulfilled the AE criteria.

A summary of AEs in any category is presented in **Table *15***.

Table 15 Number of subjects with adverse events in any category

	Number (%) of subjects	
	Dapa 10 mg (N = 2149)	**Placebo (N = 2149)**
AE category		

Any AE with outcome = death (on-treatment)	67 (3.1)	85 (4.0)
Any AE with outcome = death (on- and off-treatment)	106 (4.9)	159 (7.4)
Any SAE, including events with outcome = death (on-treatment)	594 (27.6)	674 (31.4)
Any SAE, including events with outcome = death (on- and off- treatment)	633 (29.5)	729 (33.9)
Any AE leading to discontinuation of IP	118 (5.5)	123 (5.7)
Any AE leading to dose interruption	272 (12.7)	268 (12.5)
Any AE leading to dose reduction	39 (1.8)	31 (1.4)
Any AE possibly related to IP	275 (12.8)	222 (10.3)
Any definite or probable diabetic ketoacidosis	0	2 (0.1)
Any major hypoglycaemic event	14 (0.7)	28 (1.3)
Any event of symptoms of volume depletion	120 (5.6)	84 (3.9)
Any fracture	85 (4.0)	69 (3.2)
Any renal AE	144 (6.7)	169 (7.9)
Any amputation	35 (1.6)	39 (1.8)

Serious adverse event and deaths

Deaths

During the on-treatment period, 67 (3.1%) patients in the dapagliflozin group and 85 (4.0%) in the placebo group died.

During the on- and off-treatment period, 106 (4.9%) patients in the dapagliflozin group and 159 (7.4%) in the placebo group died. In both treatment groups, most deaths occurred in the SOC of cardiac disorders. The most commonly reported AEs with an outcome of death by PT were death, acute myocardial infarction, myocardial infarction, and septic shock in the dapagliflozin group and death, acute myocardial infarction, pneumonia, and septic shock in the placebo group.

Serious adverse events

On treatment, there were fewer patients with SAEs in the dapagliflozin treatment group than in the placebo group: 594 (27.6%) patients and 674 (31.4%) patients, respectively. The 3 most commonly reported SAEs by PT were: acute kidney injury, pneumonia, and cardiac failure in the dapagliflozin group and pneumonia, cardiac failure, and acute kidney injury in the placebo group (**Table *16***).

Table 16 Number of Subjects with Serious Adverse Events (Frequency ≥ 0.5% in either treatment group) by Preferred Term - On Treatment (SAS)

	Number (%) of subjects

	Dapa 10 mg (N=2149)	Placebo (N=2149)
Preferred term		
Subjects with any SAE	594 (27.6)	674 (31.4)
Acute kidney injury	36 (1.7)	44 (2.0)
Pneumonia	36 (1.7)	58 (2.7)
Cardiac failure	35 (1.6)	48 (2.2)
Acute myocardial infarction	28 (1.3)	38 (1.8)
End stage renal disease	23 (1.1)	29 (1.3)
Ischaemic stroke	21 (1.0)	22 (1.0)
Urinary tract infection	20 (0.9)	13 (0.6)
Chronic kidney disease	15 (0.7)	27 (1.3)
Cellulitis	14 (0.7)	15 (0.7)
Angina unstable	12 (0.6)	22 (1.0)
Renal impairment	12 (0.6)	13 (0.6)
Transient ischaemic attack	11 (0.5)	8 (0.4)
Cardiac failure congestive	10 (0.5)	16 (0.7)
Cerebrovascular accident	10 (0.5)	8 (0.4)
Myocardial infarction	10 (0.5)	5 (0.2)
Osteomyelitis	10 (0.5)	10 (0.5)
Prostate cancer	10 (0.5)	5 (0.2)
Hypoglycaemia	9 0.4)	17 (0.8)
Sepsis	9 (0.4)	14 (0.7)
Atrial fibrillation	6 (0.3)	17 (0.8)
Death	6 (0.3)	11 (0.5)
Hyperkalaemia	6 (0.3)	11 (0.5)
Hyperglycaemia	5 (0.2)	15 (0.7)

The results for the on- and off- treatment period was similar to those for the on-treatment period, with fewer patients with SAEs in the dapagliflozin treatment group than in the placebo group: 633 (29.5%) patients and 729 (33.9%) patients, respectively.

Results from subgroup analyses, see section Special population.

Adverse events of special interest

Adverse events of symptoms of volume depletion

On treatment, there were 120 (5.6%) patients in the dapagliflozin group and 84 (3.9%) in the placebo group with any AE of symptoms of volume depletion, corresponding to event rates of 2.68 and 1.91 events per 100 patient-years, respectively (**Table *17***). Serious AEs of symptoms of volume depletion were reported at a similar rate in the dapagliflozin treatment group and the placebo group: 16 (0.7%) and 15 (0.7%) patients, respectively. Few patients discontinued study drug due to AEs of symptoms of volume depletion; 4 (0.2%) in the dapagliflozin group and 1 (0.0%) in the placebo group.

The most commonly reported AEs of symptoms of volume depletion, by PT, were hypotension reported by 47 (2.2%) patients in the dapagliflozin group and by 28 (1.3%) in the placebo group, followed by hypovolaemia with 37 (1.7%) in the dapagliflozin group and 21 (1.0%) in the placebo group. All other events were reported by less than 1.0% of patients in any treatment group (**Table *18***). Most reported events were mild in intensity; 7 patients in the dapagliflozin group and 6 in the placebo group had an event of severe intensity.

Table 17 Summary of Adverse Events of Symptoms of Volume Depletion - On Treatment (SAS)

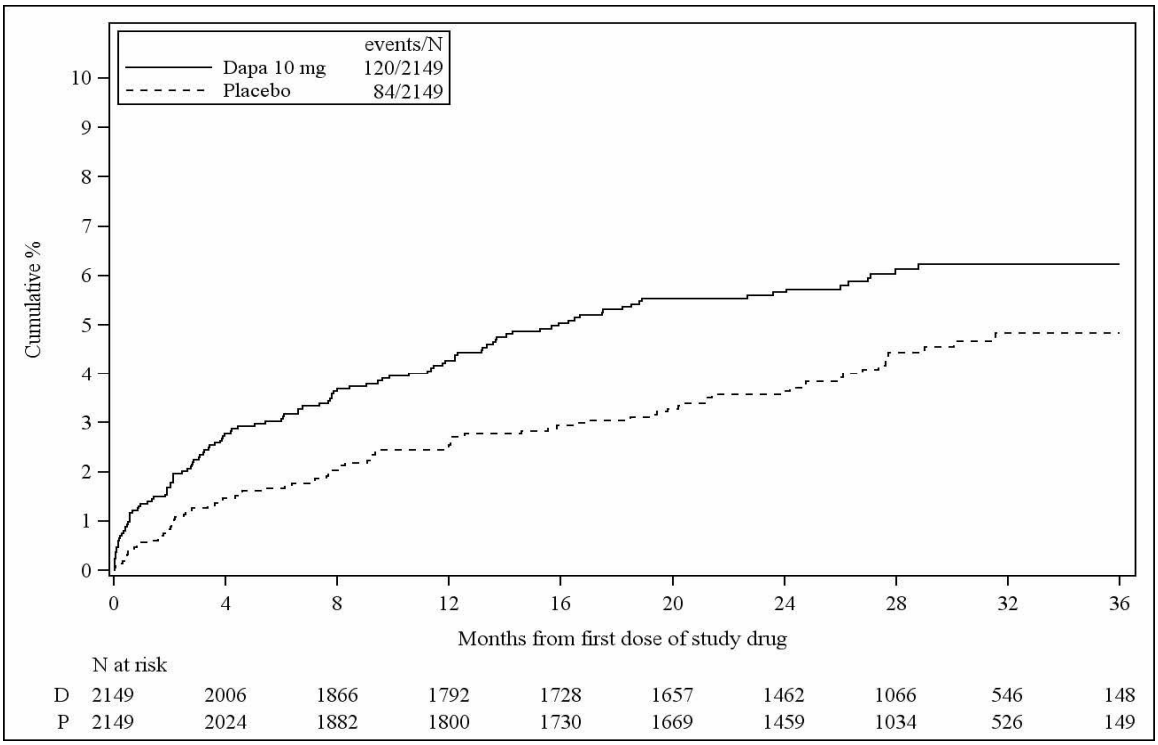
	Number (%) of subjects[a]	
AE category	**Dapa 10 mg (N=2149)**	**Placebo (N=2149)**
Subjects with any AE of symptoms of volume depletion	120 (5.6)	84 (3.9)
Event rate per 100 subject years	2.68	1.91
Any SAE	16 (0.7)	15 (0.7)
With outcome death	0	0
SAE excluding death	16 (0.7)	15 (0.7)
Any DAE	4 (0.2)	1 (0.0)
Any SAE leading to discontinuation of IP	2 (0.1)	0
Any AE leading to dose reduction	11 (0.5)	5 (0.2)
Any AE leading to interruption	12 (0.6)	6 (0.3)
Maximum intensity		
Mild	77 (3.6)	53 (2.5)
Moderate	45 (2.1)	25 (1.2)
Severe	7 (0.3)	6 (0.3)
Any AE possibly related to IP	54 (2.5)	30 (1.4)

Table 18 Adverse Events of Symptoms of Volume Depletion by Preferred Term – On Treatment (SAS)

	Number (%) of subjects	
	Dapa 10 mg (N=2149)	**Placebo (N=2149)**
Preferred term		
Subjects with any AE of symptoms of volume depletion [b]	120 (5.6)	84 (3.9)
Hypotension	47 (2.2)	28 (1.3)
Hypovolaemia	37 (1.7)	21 (1.0)
Dehydration	17 (0.8)	12 (0.6)
Syncope	12 (0.6)	10 (0.5)
Orthostatic hypotension	11 (0.5)	10 (0.5)
Blood pressure decreased	2 (0.1)	3 (0.1)
Hypovolaemic shock	1 (0.0)	0
Urine flow decreased	1 (0.0)	0
Urine output decreased	1 (0.0)	0

In a Kaplan-Meier plot of symptoms of volume depletion, the curves for the placebo and dapagliflozin groups diverged very early in the study and then did not separate further over the course of the study (**Figure *18***).

Figure 18 Kaplan-Meier Plot of Adverse Events of Symptoms of Volume Depletion – On Treatment (SAS)



Renal adverse events

On treatment, there were 144 (6.7%) patients with any renal AE in the dapagliflozin group and 169 (7.9%) in the placebo group, corresponding to event rates of 3.21 and 3.85 events per 100 patient-years, respectively (**Table *19***).

There were 54 (2.5%) patients with renal SAEs in the dapagliflozin treatment group compared with 69 (3.2%) in the placebo group. The number of patients with renal DAEs was low: 16 (0.7%) patients in the dapagliflozin group and 20 (0.9%) in the placebo group. In the dapagliflozin treatment group, 37 patients reported events of severe intensity compared to 47 patients in the placebo group.

Table 19 Summary of Renal Adverse Events - On Treatment (SAS)

	Number (%) of subjects	
	Dapa 10 mg (N=2149)	**Placebo (N=2149)**
Subjects with any renal AE	144 (6.7)	169 (7.9)
Event rate per 100 subject years	3.21	3.85
Any SAE	54 (2.5)	69 (3.2)
With outcome death	1 (0.0)	1 (0.0)
SAE excluding death	52 (2.4)	68 (3.2)
Any DAE	16 (0.7)	20 (0.9)

Any SAE leading to discontinuation of IP	6 (0.3)	8 (0.4)
Any AE leading to dose reduction	6 (0.3)	11 (0.5)
Any AE leading to interruption	25 (1.2)	28 (1.3)
Maximum intensity		
Mild	44 (2.0)	40 (1.9)
Moderate	72 (3.4)	93 (4.3)
Severe	37 (1.7)	47 (2.2)
Any AE possibly related to IP	35 (1.6)	27 (1.3)

Acute kidney injury was the most commonly reported renal AE; (74 [3.4%] patients in the dapagliflozin group compared to 81 [3.8%] in the placebo group), followed by renal impairment (58 [2.7%] patients in the dapagliflozin group compared to 71 [3.3%] in the placebo group) (**Table *20***).

Table 20 Renal Adverse Events by Preferred Term - On Treatment (SAS)

	Number (%) of subjects	
	Dapa 10 mg (N=2149)	**Placebo (N=2149)**
Preferred term		
Subjects with a renal AE	144 (6.7)	169 (7.9)
Acute kidney injury	74 (3.4)	81 (3.8)
Renal impairment	58 (2.7)	71 (3.3)
Renal failure	11 (0.5)	14 (0.7)
Nephropathy toxic	3 (0.1)	4 (0.2)
Prerenal failure	1 (0.0)	3 (0.1)
Azotaemia	0	1 (0.0)

Diabetes ketoacidosis

On treatment, 22 (1.0%) patients in the dapagliflozin treatment group and 20 (0.9%) patients in the placebo treatment group had a potential DKA event that was sent for central independent adjudication. Two patients in the placebo treatment group had events adjudicated as definite or probable DKA compared to none in the dapagliflozin group. Both events were adjudicated as definite (i.e., none-probable) and neither of them had a fatal outcome. No event of DKA was reported for patients without diabetes.

Major hypoglycaemic events

On treatment, there were 14 patients (0.7%) with major hypoglycaemic events in the dapagliflozin group and 28 (1.3%) in the placebo group, corresponding to event rates of 0.31 and 0.64 events per 100 patient-years, respectively. No major hypoglycaemic events were reported for patients without diabetes.

All patients with major hypoglycaemic events in both treatment groups were using sulfonylureas or insulin, or a combination, at the time of event, except for 1 patient in the dapagliflozin group and 3 patients in the placebo group.

Table 21 Summary of major hypoglycaemic events - On Treatment (SAS)

	Number (%) of subjects	
	Dapa 10 mg (N=2149)	**Placebo (N=2149)**
Preferred term		
Subjects with any major hypoglycaemic event	14 (0.7)	28 (1.3)
Event rate per 100 subject years	0.31	0.64
Any SAE	6 (0.3)	14 (0.7)
With outcome death	0	0
SAE excluding death	6 (0.3)	14 (0.7)
Any DAE	0	1 (0.0)
Any SAE leading to discontinuation of IP	0	1 (0.0)
Any AE leading to dose reduction	0	1 (0.0)
Any AE leading to interruption	2 (0.1)	2 (0.1)
Maximum intensity		
Mild	4 (0.2)	5 (0.2)
Moderate	4 (0.2)	11 (0.5)
Severe	8 (0.4)	13 (0.6)
Any AE possibly related to IP	2 (0.1)	6 (0.3)

Fractures

AEs of fracture were analysed primarily for the on- and off-treatment period (from first day of treatment until last visit).

There were 85 (4.0%) patients with any AE of fracture in the dapagliflozin treatment group as compared to 69 (3.2%) in the placebo group, corresponding to event rates of 1.75 and 1.43 events per 100 patient-years, respectively (**Table *22***.)

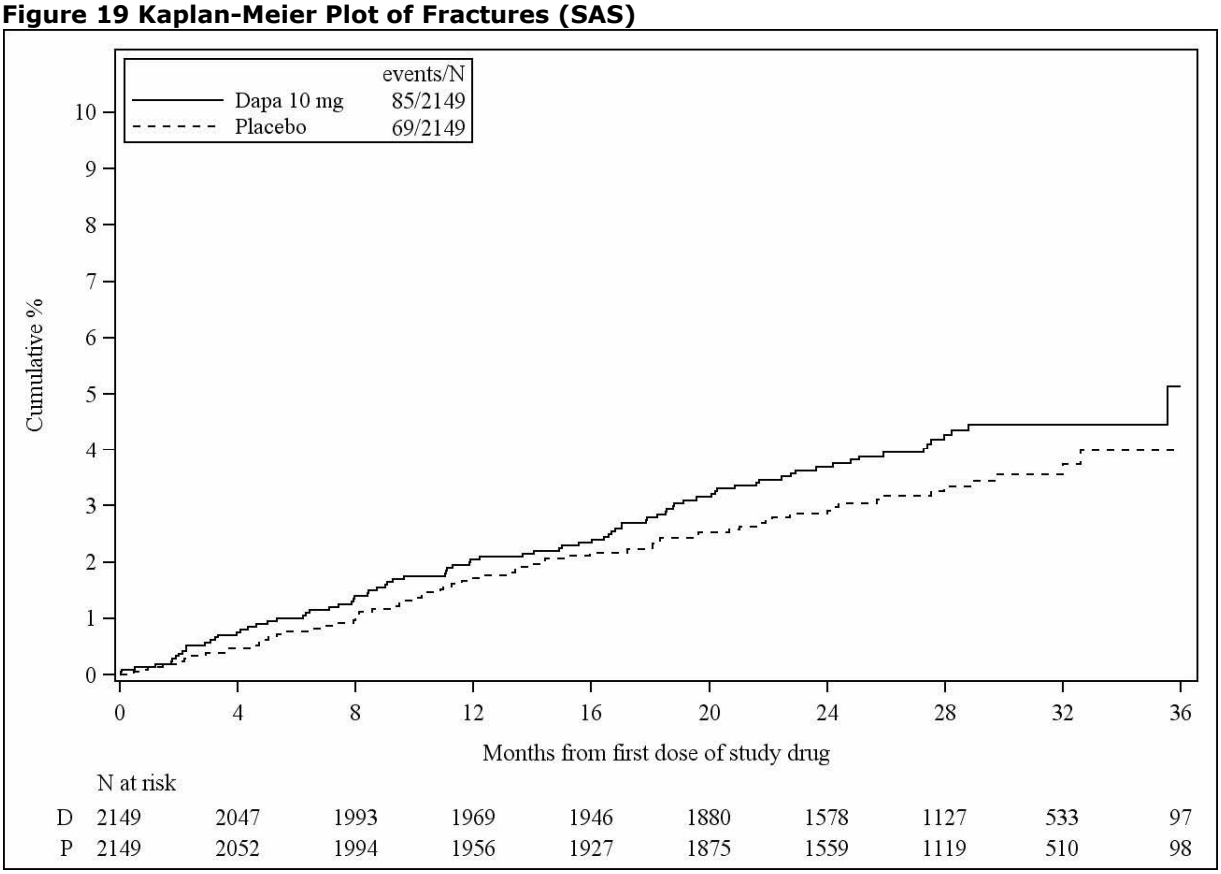
Table 22 Summary of Adverse Events of Fracture (SAS)

	Number (%) of subjects

	Dapa 10 mg (N=2149)	Placebo (N=2149)
AE category		
Subjects with any AE of fracture	85 (4.0)	69 (3.2)
Event rate per 100 subject years	1.75	1.43
Any SAE	40 (1.9)	28 (1.3)
With outcome death	0	0
SAE excluding death	40 (1.9)	28 (1.3)
Any DAE	0	1 (0.0)
Any SAE leading to discontinuation of IP	0	1 (0.0)
Any AE leading to dose reduction	0	1 (0.0)
Any AE leading to interruption	10 (0.5)	4 (0.2)
Maximum intensity		
Mild	24 (1.1)	18 (0.8)
Moderate	49 (2.3)	43 (2.0)
Severe	15 (0.7)	11 (0.5)
Any AE possibly related to IP	4 (0.2)	3 (0.1)

In a Kaplan-Meier plot for AEs of fractures, the curves show a similar pattern for both treatment groups, with incidence rates remaining similar over time throughout the whole study period (**Figure 19**).

Figure 19 Kaplan-Meier Plot of Fractures (SAS)



The most commonly reported PTs (in both groups combined) were rib fracture, foot fracture and humerus fracture (**Table 23**).

PTs identified as describing fractures at sites commonly associated with osteoporosis were femur fracture, femoral neck fracture, hip fracture, spinal fracture, spinal compression fracture, lumbar vertebral fracture, thoracic vertebral fracture, wrist fracture and radius fracture.

Table 23 Adverse Events of Fracture by Preferred Term (SAS)

	Number (%) of subjects	
	Dapa 10 mg (N=2149)	**Placebo (N=2149)**
Preferred term		
Subjects with any AE of fracture	85 (4.0)	69 (3.2)
Rib fracture	12 (0.6)	8 (0.4)
Foot fracture	11 (0.5)	7 (0.3)
Humerus fracture	9 (0.4)	6 (0.3)
Femur fracture	8 (0.4)	4 (0.2)
Tibia fracture	6 (0.3)	2 (0.1)
Ankle fracture	5 (0.2)	3 (0.1)
Lower limb fracture	5 (0.2)	0

Radius fracture	4 (0.2)	3 (0.1)
Spinal fracture	4 (0.2)	1 (0.0)
Upper limb fracture	4 (0.2)	4 (0.2)
Hand fracture	3 (0.1)	8 (0.4)
Patella fracture	3 (0.1)	2 (0.1)
Spinal compression fracture	3 (0.1)	5 (0.2)
Wrist fracture	3 (0.1)	4 (0.2)
Cervical vertebral fracture	2 (0.1)	1 (0.0)
Facial bones fracture	2 (0.1)	1 (0.0)
Femoral neck fracture	2 (0.1)	3 (0.1)
Hip fracture	2 (0.1)	2 (0.1)
Multiple fractures	2 (0.1)	2 (0.1)
Scapula fracture	2 (0.1)	0
Clavicle fracture	1 (0.0)	0
Costal cartilage fracture	1 (0.0)	0
Fibula fracture	1 (0.0)	0
Limb traumatic amputation	1 (0.0)	0
Lumbar vertebral fracture	1 (0.0)	0
Pelvic fracture	1 (0.0)	0
Bone fissure	0	1 (0.0)
Forearm fracture	0	1 (0.0)
Fracture nonunion	0	2 (0.1)
Stress fracture	0	1 (0.0)
Thoracic vertebral fracture	0	1 (0.0)
Traumatic fracture	0	1 (0.0)

Table 24 shows a summary of fractures by subgroups (age ≤ 65, > 65 years; male, female; baseline eGFR < 30, < 45, ≥ 45 mL/min/1.73 m^2; and diabetes status).

Table 24 Summary of Adverse Events of Fracture by Subgroups (SAS)

Subgroup	**Dapa 10 mg (N=2149)**	**Placebo (N=2149)**

Subject characteristic Category	Number of subjects	Subjects with any AE of fracture n (%)	Number of subjects	Subjects with any AE of fracture n (%)
All patients	2149	85 (4.0)	2149	69 (3.2)
Age (years)				
≤ 65 years	1246	44 (3.5)	1238	25 (2.0)
> 65 years	903	41 (4.5)	911	44 (4.8)
Sex				
Male	1440	48 (3.3)	1433	35 (2.4)
Female	709	37 (5.2)	716	34 (4.7)
Female >55 years	525	30 (5.7)	528	32 (6.1)
Baseline eGFR (mL/min/1.73m^2)				
< 30	293	11 (3.8)	331	15 (4.5)
< 45	1270	60 (4.7)	1248	43 (3.4)
≥ 45	879	25 (2.8)	901	26 (2.9)
By diabetes status				
Patients with T2DM	1453	65 (4.5)	1450	51 (3.5)
Patients without T2DM	696	20 (2.9)	699	18 (2.6)

The identified subjects with events indicative of osteoporosis are presented by PT and treatment group in **Table *25***. Among the 154 patients with at least one fracture during the study (85 [4.0%) in the dapagliflozin group and 69 [3.2%] in the placebo group), osteoporosis was reported in the medical history at the start of the study for 7 patients in the dapagliflozin group and 9 patients in the placebo group. Of these, 2 patients in the dapagliflozin group and 5 in the placebo group reported fractures at sites commonly associated with osteoporosis.

Table 25 Adverse Events of Fractures Indicative of Osteoporosis by Preferred Term (SAS)

	Number (%) of subjects [a]	
	Dapa 10 mg (N = 2149)	**Placebo (N = 2149)**
Preferred term		
Subjects with any AE of fracture indicative of osteoporosis	26 (1.2)	23 (1.1)

[b]		
Femur fracture (all)	8 (0.4)	4 (0.2)
Femur fracture reported at inter- or pertrochanteric area	*1 (0.0)*	*3 (0.1)*
Radius fracture	4 (0.2)	3 (0.1)
Spinal fracture	4 (0.2)	1 (0.0)
Spinal compression fracture	3 (0.1)	5 (0.2)
Wrist fracture	3 (0.1)	4 (0.2)
Femoral neck fracture	2 (0.1)	3 (0.1)
Hip fracture	2 (0.1)	2 (0.1)
Lumbar vertebral fracture	1 (0.0)	0
Thoracic vertebral fracture	0	1 (0.0)

High-energy and Low-energy Fractures

In total, there were 98 fractures reported in the dapagliflozin group (51 AEs and 47 SAEs) and 76 reported in the placebo group (43 AES and 33 SAEs). In the dapagliflozin group, 43 (44%) had information on energy level with 16 (16%) due to high-energy trauma and 27 (28%) due to low-energy trauma. In the placebo group, 26 (34%) had information on energy level with 9 (12%) due to high-energy trauma and 17 (22%) due to low-energy trauma. For the remaining fractures, information on trauma is either unavailable or unclear.

Among patients with fractures at sites commonly associated with osteoporosis, information indicating low-energy trauma was reported for 13 fractures in the dapagliflozin group (5 femur, 2 radius, 2 spinal, 2 femoral neck, 1 hip, 1 spinal compression) and for 10 fractures in the placebo group (4 femur, 2 femoral neck, 1 hip, 1 wrist, 1 radius, 1 spinal). High-energy trauma was reported for 3 fractures in the dapagliflozin group: motorcycle accident (spinal fracture); traffic accident (spinal compression fracture); and falling down stairs (femur fracture), and for 2 fractures in the placebo group: fall on stairs (hip fracture) and road trauma (femoral neck fracture).

Fractures related to volume depletion

Volume depletion events could also potentially increase the risk of falls, and thereby fractures. The possibility that events of volume depletion led to a secondary increase in the risk of fractures was evaluated by investigating whether patients with a fracture had any reported symptoms of volume depletion within 3 days prior to, or on, the day of onset of the fracture. No such pattern was seen. There were only 2 such patients, both in the dapagliflozin group: 1 with reported hypotension and 1 with reported hypovolaemia, in both cases on the same day as the onset of the fracture. The patient with hypovolaemia had stopped treatment with dapagliflozin on the day before the event (this was the patient's own decision, after 863 days on IP).

Amputations

AEs of amputations were analysed primarily for the on- and off-treatment period (from first day of treatment until last visit).

The number of patients who underwent at least 1 amputation (excluding trauma) was similar in both treatment groups; 35 (1.6%) and 39 (1.8%) patients in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 0.72 and 0.81 events per 100 patient-years, respectively. More than 1 amputation was reported by 12 patients in the dapagliflozin group and 11 patients in the placebo group, of which 1 and 3 patients reported >3 amputations in the dapagliflozin and placebo group, respectively (**Table 26**). Only one patient without diabetes (in the placebo group) reported a non-traumatic amputation.

There were numerically fewer patients with major amputations (below knee and above knee) in the dapagliflozin group (13 patients) than in the placebo group (20 patients).

The great majority of amputations were surgical amputations, and traumatic and non-surgical amputations were only reported by isolated patients. Most patients with surgical amputations had 1 amputation; all apart from one were lower limb amputations.

Table 26 Amputation by Type of Event and Location (SAS)

	Number (%) of subjects [a]	
	Dapa 10 mg (N=2149)	**Placebo (N=2149)**
Category		
Subjects with at least one amputation [b]	36 (1.7)	39 (1.8)
1 amputation	24 (1.1)	28 (1.3)
2 amputations	9 (0.4)	4 (0.2)
3 amputations	2 (0.1)	4 (0.2)
> 3 amputations	1 (0.0)	3 (0.1)
Type of event		
Trauma by accident	1 (0.0)	0
Surgical amputation	34 (1.6)	38 (1.8)
Spontaneous/non-surgical amputation	1 (0.0)	1 (0.0)
Anatomic localisation		
Lower limb amputation	35 (1.6)	39 (1.8)
Big toe	9 (0.4)	11 (0.5)
Index toe	6 (0.3)	4 (0.2)
Middle toe	7 (0.3)	3 (0.1)
Fourth toe	5 (0.2)	6 (0.3)
Little toe	4 (0.2)	4 (0.2)
Trans metatarsal	0	5 (0.2)

Foot	0	1 (0.0)
Below knee	7 (0.3)	8 (0.4)
Above knee	6 (0.3)	12 (0.6)
Other	6 (0.3)	9 (0.4)
Upper limb amputation	1 (0.0)	0
Thumb	0	0
Index finger	0	0
Middle finger	0	0
Ring finger	0	0
Little finger	0	0
Hand	0	0
Below elbow	0	0
Above elbow	0	0
Missing	1 (0.0)	0

The most common condition that triggered amputation was infection, occurring in 30 (1.4%) patients in the dapagliflozin treatment group and 32 (1.5%) in the placebo treatment group. Neuropathy was the most commonly reported contributing factor (0.6% of patients in both treatment groups).

The incidence of amputations for dapagliflozin and placebo was 1.8% vs 2.3% in subjects ≤65 years and 1.4% vs 1.1% for subjects >65 years. The incidence of amputations for dapagliflozin and placebo was 1.0% vs 1.2% in subjects with baseline eGFR <30 mL/min/1.73 m^2; 1.3% vs 1.2% in subjects with eGFR <45 mL/min/1.73 m^2 and 2.0% vs 2.7% in subjects with eGFR ≥ 45 mL/min/1.73 m^2 (source: Table 14.3.11.5).

Events Leading to a Risk for Lower Limb Amputation ("Preceding Events")

AEs of "preceding events", based on a pre-specified list of terms defined by the EMA PRAC, were analysed for the on- and off-treatment period (from first day of treatment until last visit).

The number of patients with "preceding events" was 220 (10.2%) patients in the dapagliflozin treatment group and 200 (9.3%) patients in the placebo group, corresponding to event rates of 4.53 and 4.15 patients with events per 100 patient-years, respectively (**Table *27***, **Table 28**). Of these patients, 18 in the dapagliflozin treatment group, and 23 in the placebo group had subsequent amputations.

The proportion of patients with preceding events in the subgroup of patients with eGFR <30 mL/min/1.73 m^2 was consistent with the overall population (**Table *29***). In this subgroup, no patient in the dapagliflozin treatment group and 2 patients in the placebo group had subsequent amputations.

Table 27 Summary of adverse events related to risk for lower limb amputation (SAS)

AE category	Number (%) of subjects[a] Dapa 10 mg (N=2149)	Placebo (N=2149)
Subjects with any AE related to risk for lower limb amputation[b]	220 (10.2)	200 (9.3)
Event rate per 100 subject years	4.53	4.15
Any SAE	76 (3.5)	83 (3.9)
With outcome death	1 (0.0)	0
SAE excluding death	75 (3.5)	83 (3.9)
Any DAE	7 (0.3)	4 (0.2)
Any SAE leading to discontinuation of IP	4 (0.2)	3 (0.1)
Any AE leading to dose reduction	6 (0.3)	2 (0.1)
Any AE leading to interruption	30 (1.4)	24 (1.1)
Maximum intensity[c]		
Mild	117 (5.4)	94 (4.4)
Moderate	98 (4.6)	99 (4.6)
Severe	35 (1.6)	35 (1.6)
AE related to risk for lower limb amputation and subsequent amputation[d]	18 (0.8)	23 (1.1)
Any AE possibly related to IP[e]	31 (1.4)	14 (0.7)

Table 28 Adverse events related to risk for lower limb amputation by PRAC categories and preferred term (SAS)

PRAC category[b] / preferred term	Number (%) of subjects[a] Dapa 10 mg (N=2149)	Placebo (N=2149)
Subjects with AE related to risk for lower limb amputation[c]	220 (10.2)	200 (9.3)
Diabetic foot related AEs	100 (4.7)	113 (5.3)
Cellulitis	30 (1.4)	37 (1.7)
Skin ulcer	27 (1.3)	35 (1.6)
Diabetic foot	14 (0.7)	15 (0.7)
Osteomyelitis	13 (0.6)	13 (0.6)
Localised infection	9 (0.4)	11 (0.5)
Gangrene	7 (0.3)	3 (0.1)
Diabetic foot infection	5 (0.2)	6 (0.3)
Extremity necrosis	3 (0.1)	2 (0.1)
Infected skin ulcer	3 (0.1)	3 (0.1)
Neuropathic ulcer	3 (0.1)	3 (0.1)
Diabetic gangrene	2 (0.1)	2 (0.1)
Diabetic ulcer	2 (0.1)	1 (0.0)
Ischaemic skin ulcer	2 (0.1)	0
Postoperative wound infection	2 (0.1)	5 (0.2)
Dry gangrene	1 (0.0)	1 (0.0)

Osteomyelitis acute	1 (0.0)	1 (0.0)
Osteomyelitis chronic	1 (0.0)	0
Osteonecrosis	1 (0.0)	2 (0.1)
Soft tissue infection	1 (0.0)	1 (0.0)
Cellulitis gangrenous	0	1 (0.0)
Osteitis	0	1 (0.0)
Skin erosion	0	2 (0.1)
Nervous System Disorders	29 (1.3)	29 (1.3)
Diabetic neuropathy	13 (0.6)	14 (0.7)
Neuropathy peripheral	6 (0.3)	7 (0.3)
Paraesthesia	6 (0.3)	3 (0.1)
Hypoaesthesia	4 (0.2)	4 (0.2)
Peripheral sensory neuropathy	0	1 (0.0)
Vascular AEs	33 (1.5)	35 (1.6)
Peripheral arterial occlusive disease	14 (0.7)	17 (0.8)
Intermittent claudication	5 (0.2)	2 (0.1)
Peripheral ischaemia	5 (0.2)	9 (0.4)
Arteriosclerosis	3 (0.1)	1 (0.0)
Peripheral artery stenosis	3 (0.1)	2 (0.1)
Peripheral vascular disorder	3 (0.1)	1 (0.0)
Angiopathy	1 (0.0)	1 (0.0)
Iliac artery stenosis	1 (0.0)	1 (0.0)
Peripheral artery thrombosis	1 (0.0)	0
Arterial occlusive disease	0	2 (0.1)
Diabetic vascular disorder	0	1 (0.0)
Peripheral artery occlusion	0	1 (0.0)
Volume depletion	55 (2.6)	36 (1.7)
Hypovolaemia	37 (1.7)	22 (1.0)
Dehydration	18 (0.8)	14 (0.7)
Wound/Infection	18 (0.8)	13 (0.6)
Skin infection	5 (0.2)	2 (0.1)
Wound	4 (0.2)	3 (0.1)
Wound infection	3 (0.1)	0
Abscess limb	2 (0.1)	3 (0.1)
Impaired healing	2 (0.1)	3 (0.1)
Skin wound	1 (0.0)	2 (0.1)
Subcutaneous abscess	1 (0.0)	0

Table 29 Summary of adverse events related to risk for lower limb amputation in subjects with baseline eGFR < 30 (ml/min/1.73 m^2) (SAS)

	Baseline eGFR <30 Number (%) of subjects[a]	
AE category	Dapa 10 mg (N=293)	Placebo (N=331)
Subjects with any AE related to risk for lower limb amputation[b]	29 (9.9)	30 (9.1)
Event rate per 100 subject years	4.48	4.23
Any SAE	9 (3.1)	9 (2.7)
With outcome death	0	0
SAE excluding death	9 (3.1)	9 (2.7)
Any DAE	0	0
Any SAE leading to discontinuation of IP	0	0
Any AE leading to dose reduction	0	0
Any AE leading to interruption	4 (1.4)	1 (0.3)
Maximum intensity[c]		
Mild	16 (5.5)	14 (4.2)
Moderate	12 (4.1)	14 (4.2)
Severe	3 (1.0)	5 (1.5)

AE related to risk for lower limb amputation and subsequent amputation[d]	0	2 (0.6)
Any AE possibly related to IP[e]	1 (0.3)	3 (0.9)

Additional Safety Analyses

Fournier's Gangrene

A total of 6 cases (3 from each treatment group) indicating potential Fournier's gangrene were identified for blinded medical assessment by the Sponsor (**Table *30***). One of these events was assessed as Fournier's gangrene (an event reported as anal abscess in the placebo group).

Table 30 AE's indicating genital area infections or necrotizing fasciitis (SAS)

	Number (%) of subjects[a]	
Preferred term	Dapa 10 mg (N=2149)	Placebo (N=2149)
Subjects with any AE indicating genital area infections or necrotizing fasciitis[b]	3 (0.1)	3 (0.1)
Fournier's gangrene	1 (0.0)	0
Necrotising fasciitis	1 (0.0)	0
Vulval cellulitis	1 (0.0)	0
Anal abscess	0	3 (0.1)

Genital infections

During the on-treatment period, SAEs and DAEs of genital infections were rare. Only 3 patients had an SAE of genital infection, all in the dapagliflozin group. The reported events were balanoposthitis, urogenital infection bacterial, and vulval cellulitis. Three patients, also in the dapagliflozin treatment group, had a DAE of genital infection.

Urinary tract infections

SAEs of UTI were more frequent in the dapagliflozin group (29 [1.3%]) compared with the placebo group (18 [0.8%]). By far the most frequently reported SAE by PT was urinary tract infection in both treatment groups, with 20 (0.9%) patients reporting this PT in the dapagliflozin group and 13 (0.6%) in the placebo group (**Table 31**). DAEs of UTI were reported for 8 (0.4%) patients in the dapagliflozin group and 3 (0.1%) patients in the placebo group. The PT urinary tract infection was also the single most reported DAE in both treatment groups with 7 (0.3%) patients in the dapagliflozin group and 3 (0.1%) patients in the placebo group (**Table 32**).

Table 31 Number of subjects with SAEs of urinary tract infection by T2DM status by preferred term - on treatment (SAS) T2DM

	Number (%) of subjects[a]	
Preferred term	Dapa 10 mg (N=2149)	Placebo (N=2149)
Subjects with any SAE of UTI[b]	29 (1.3)	18 (0.8)
Urinary tract infection	20 (0.9)	13 (0.6)
Pyelonephritis acute	5 (0.2)	1 (0.0)
Cystitis	1 (0.0)	2 (0.1)
Escherichia urinary tract infection	1 (0.0)	0
Pyelonephritis	1 (0.0)	2 (0.1)
Pyonephrosis	1 (0.0)	0
Urinary tract infection bacterial	1 (0.0)	0
Urogenital infection bacterial	1 (0.0)	0

Table 32 Number of subjects with DAEs of urinary tract infection by preferred term (SAS)

Preferred term	Number (%) of subjects[a] Dapa 10 mg (N=2149)	Placebo (N=2149)
Subjects with any DAE of UTI[b]	8 (0.4)	3 (0.1)
Urinary tract infection	7 (0.3)	3 (0.1)
Urogenital infection bacterial	1 (0.0)	0

Laboratory findings

Haematology

An increase in haemoglobin was observed in the dapagliflozin group compared to placebo (mean change from baseline to last treatment value was 3.9 g/L in the dapagliflozin group and -3.2 g/L in the placebo group).

Table 33 Haematology and clinical chemistry laboratory variables over time in SI units - on treatment (SAS)

Laboratory variable (unit)	Group	Time point	Result n	Result Mean	Result SD	Result Q1	Result Median	Result Q3	Change from baseline n	Change from baseline Mean	Change from baseline SD	Change from baseline Q1	Change from baseline Median	Change from baseline Q3
Hemoglobin (g/L)	Dapa 10 mg (N=2149)	Baseline	2137	128.6	18.1	116.0	129.0	141.0	2137					
		Last on treatment value	1547	133.6	20.3	120.0	134.0	148.0	1537	3.9	14.0	-4.0	5.0	12.0
	Placebo (N=2149)	Baseline	2135	127.9	18.0	116.0	127.0	140.0	2135					
		Last on treatment value	1515	125.5	19.1	112.0	125.0	139.0	1504	-3.2	13.7	-11.0	-3.0	5.0
Hematocrit [ratio]	Dapa 10 mg (N=2149)	Baseline	2144	0.39	0.06	0.35	0.39	0.43	2144					
		14 days	2023	0.39	0.05	0.36	0.39	0.43	2019	0.01	0.03	-0.01	0.00	0.02
		2 Months	2004	0.40	0.06	0.36	0.40	0.44	2000	0.01	0.03	0.00	0.01	0.03
		4 Months	1982	0.41	0.06	0.37	0.41	0.45	1978	0.02	0.04	0.00	0.02	0.04
		8 Months	1862	0.41	0.06	0.37	0.41	0.45	1859	0.02	0.04	0.00	0.02	0.05
		12 Months	1792	0.41	0.06	0.37	0.41	0.45	1788	0.02	0.04	0.00	0.02	0.05
		16 Months	1756	0.41	0.06	0.37	0.42	0.46	1752	0.02	0.04	0.00	0.02	0.05
		20 Months	1670	0.42	0.06	0.37	0.42	0.46	1666	0.02	0.04	0.00	0.02	0.05
		24 Months	1481	0.42	0.06	0.37	0.42	0.46	1478	0.02	0.04	0.00	0.03	0.05
		28 Months	1028	0.41	0.06	0.37	0.41	0.45	1025	0.02	0.04	-0.01	0.02	0.05
		32 Months	570	0.41	0.06	0.37	0.42	0.45	568	0.02	0.05	-0.01	0.02	0.04
		36 Months	203	0.41	0.06	0.38	0.41	0.46	202	0.02	0.05	0.00	0.02	0.05
		Last on treatment value	2137	0.41	0.06	0.36	0.41	0.45	2126	0.02	0.04	-0.01	0.02	0.04
	Placebo (N=2149)	Baseline	2142	0.39	0.05	0.35	0.39	0.43	2142					
		14 days	2061	0.39	0.05	0.35	0.38	0.42	2055	-0.00	0.03	-0.02	0.00	0.01
	Placebo (N=2149)	2 Months	2002	0.39	0.05	0.35	0.39	0.42	1997	-0.00	0.03	-0.02	0.00	0.02
		4 Months	1973	0.39	0.05	0.35	0.39	0.43	1968	0.00	0.03	-0.02	0.00	0.02
		8 Months	1839	0.39	0.05	0.35	0.39	0.43	1835	0.00	0.03	-0.02	0.00	0.02
		12 Months	1757	0.39	0.05	0.35	0.39	0.43	1754	-0.00	0.04	-0.02	0.00	0.02
		16 Months	1715	0.39	0.05	0.35	0.39	0.42	1712	-0.00	0.04	-0.02	0.00	0.02
		20 Months	1629	0.39	0.05	0.35	0.39	0.42	1625	-0.00	0.04	-0.03	0.00	0.02
		24 Months	1446	0.39	0.05	0.35	0.39	0.42	1442	-0.00	0.04	-0.03	0.00	0.02
		28 Months	970	0.39	0.05	0.35	0.38	0.42	969	-0.01	0.04	-0.03	0.00	0.02
		32 Months	524	0.38	0.05	0.35	0.38	0.42	524	-0.01	0.04	-0.03	-0.00	0.02
		36 Months	191	0.38	0.05	0.35	0.38	0.42	191	-0.00	0.05	-0.03	0.00	0.02
		Last on treatment value	2147	0.38	0.06	0.34	0.38	0.42	2131	-0.01	0.04	-0.03	-0.01	0.02

Clinical Chemistry

Creatinine/ eGFR

There was an initial increase in mean serum creatinine, which was more pronounced in the dapagliflozin treatment group than in the placebo group. However, the difference disappeared over the course of the study and from 12 months and throughout the remainder of the study, the mean change from baseline was larger in the placebo group.

In line with the findings for serum creatinine, there was an initial decrease in mean eGFR which was small but more pronounced in the dapagliflozin group than in the placebo group; however the difference between treatment groups changed over time and at 16 months and up to 32 months the decrease was larger in the placebo group.

Table 34 Haematology and clinical chemistry laboratory variables over time in SI units - on treatment (SAS)

			Result						Change from baseline					
Laboratory variable (unit)	Group	Time point	n	Mean	SD	Q1	Median	Q3	n	Mean	SD	Q1	Median	Q3
eGFR (mL/min/1.73 m2)	Dapa 10 mg (N=2149)	Baseline	2149	43.2	12.3	33.0	41.0	52.0	2149					
		14 days	2081	39.3	13.2	29.0	37.0	47.0	2081	-4.0	6.7	-7.0	-4.0	-1.0
		2 Months	2040	40.0	13.9	29.0	38.0	48.5	2040	-3.4	7.3	-7.0	-4.0	0.0
		4 Months	2025	40.3	13.8	30.0	38.0	49.0	2025	-3.1	7.4	-7.0	-4.0	0.0
		8 Months	1903	39.7	14.5	29.0	37.0	48.0	1903	-3.7	8.7	-8.0	-4.0	0.0
		12 Months	1837	39.2	14.8	28.0	37.0	48.0	1837	-4.3	8.8	-9.0	-5.0	-1.0
		16 Months	1790	38.5	14.7	28.0	36.0	47.0	1790	-5.1	9.8	-10.0	-5.0	-1.0
		20 Months	1716	38.2	14.8	27.0	36.0	46.0	1716	-5.6	9.7	-10.0	-6.0	-1.0
		24 Months	1542	37.9	15.2	27.0	36.0	47.0	1542	-6.3	9.9	-12.0	-7.0	-2.0
		28 Months	1106	37.7	15.8	26.0	35.0	47.0	1106	-7.4	10.3	-13.0	-7.0	-3.0
		32 Months	652	39.2	16.3	27.0	37.0	49.0	652	-8.2	10.9	-14.0	-8.0	-3.0
eGFR (mL/min/1.73 m2)	Dapa 10 mg (N=2149)	36 Months	217	38.6	15.5	27.0	37.0	49.0	217	-9.0	9.8	-15.0	-8.0	-3.0
		Last on treatment value	2141	36.2	14.9	26.0	35.0	45.0	2134	-7.1	10.7	-13.0	-7.0	-2.0
	Placebo (N=2149)	Baseline	2149	43.0	12.4	33.0	42.0	51.0	2149					
		14 days	2087	42.2	13.8	32.0	40.0	51.0	2087	-0.8	6.8	-4.0	-1.0	2.0
		2 Months	2041	41.9	14.2	31.0	40.0	50.0	2041	-1.2	7.5	-5.0	-1.0	2.0
		4 Months	2016	41.6	14.3	31.0	40.0	50.0	2016	-1.6	7.9	-5.0	-2.0	2.0
		8 Months	1874	40.8	15.0	30.0	39.0	50.0	1874	-2.6	9.0	-7.0	-3.0	1.0
		12 Months	1803	39.4	15.1	28.0	37.0	49.0	1803	-4.0	9.3	-8.0	-4.0	0.0
		16 Months	1757	38.1	14.7	27.0	36.0	47.0	1757	-5.4	9.5	-10.0	-5.0	-1.0
		20 Months	1680	37.5	15.0	26.0	35.5	47.0	1680	-6.3	10.1	-11.0	-6.0	-1.0
		24 Months	1502	36.6	15.4	25.0	35.0	46.0	1502	-7.3	10.5	-13.0	-7.0	-2.0
		28 Months	1056	36.6	16.2	24.0	35.0	46.0	1056	-8.6	11.3	-14.0	-8.0	-3.0
		32 Months	589	37.4	16.5	26.0	34.0	48.0	589	-9.3	11.9	-15.0	-9.0	-3.0
		36 Months	210	38.2	17.2	26.0	36.5	47.0	210	-8.7	12.7	-15.0	-9.0	-3.0
		Last on treatment value	2148	35.3	15.6	24.0	33.0	45.0	2138	-7.8	11.6	-14.0	-7.0	-2.0

Marked laboratory abnormalities

There were more patients with a marked abnormality of increased haematocrit in the dapagliflozin treatment group than in the placebo group.

There were fewer patients with marked abnormalities of ALP, ALT, AST, total bilirubin and creatinine increase in the dapagliflozin treatment group. There were also fewer patients with marked abnormalities of hyperkalaemia, hyponatraemia, and hypernatremia in the dapagliflozin treatment group. With regard to hyperkalaemia, 206 (9.6%) of the patients in the dapagliflozin group and 229 (10.7%) of the patients in the placebo group had at least one measurement of serum-potassium ≥ 6.0 mmol/L on treatment.

Table 35 Marked laboratory abnormalities - on treatment (SAS) – ALT, AST and bilirubin

	Number (%) of subjects[a]	
	Dapa 10 mg (N=2149)	Placebo (N=2149)
ALT (µkat/L) [a]		
Number of subjects with any on-treatment value	1656	1612
>3x ULN	3 (0.2)	5 (0.3)
>5x ULN	2 (0.1)	3 (0.2)
>10x ULN	0	1 (0.1)
>20x ULN	0	0
AST (µkat/L) [a]		
Number of subjects with any on-treatment value	1649	1607
>3x ULN	5 (0.3)	6 (0.4)
>5x ULN	1 (0.1)	3 (0.2)
>10x ULN	0	0
>20x ULN	0	0
AST or ALT (µkat/L) [a]		
Number of subjects with any on-treatment value	1656	1613
>3x ULN	6 (0.4)	6 (0.4)
>5x ULN	2 (0.1)	4 (0.2)
>10x ULN	0	1 (0.1)
>20x ULN	0	0
Bilirubin (µmol/L) [a]		
Number of subjects with any on-treatment value	1657	1615
>1.5x ULN	0	8 (0.5)
>2x ULN	0	2 (0.1)
AST or ALT > 3x ULN and Bilirubin > 1.5x ULN within 14 days after ALT/AST elevation	0	1 (0.0)
AST or ALT > 3x ULN and Bilirubin > 2x ULN within 14 days after ALT/AST elevation	0	1 (0.0)
AST or ALT > 3x ULN and Bilirubin > 2x ULN and no ALP>2x ULN within 14 days after ALT/AST elevation	0	0

Vital Signs and Body Weight

Body weight

There was a decrease in body weight in the dapagliflozin treatment group compared to the placebo treatment group (mean change from baseline to month 36 was -1.9 kg in the dapagliflozin treatment group and -1.0 kg in the placebo group).

				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 10 mg (N=2149)	Baseline	2148	81.5	20.1	67.0	79.0	93.8	2148					
			14 days	2088	81.2	20.0	67.0	78.7	93.1	2088	-0.4	1.8	-1.0	-0.3	0.2
			2 Months	2043	80.9	20.0	67.0	78.4	92.7	2043	-0.7	2.6	-1.8	-0.5	0.3
			4 Months	2029	80.7	19.8	66.9	78.3	92.5	2029	-1.0	3.3	-2.1	-0.7	0.5
			8 Months	1909	81.0	19.9	66.7	78.5	93.4	1909	-1.0	3.8	-2.6	-0.9	0.9
			12 Months	1839	81.0	20.0	67.0	78.6	93.4	1839	-1.2	4.3	-3.0	-1.0	1.0
			16 Months	1789	80.9	19.9	67.0	78.4	93.0	1789	-1.2	4.6	-3.3	-1.0	1.0
			20 Months	1719	81.0	19.7	67.0	78.6	92.8	1719	-1.0	5.0	-3.0	-1.0	1.5
			24 Months	1554	81.1	19.6	67.0	78.9	93.0	1554	-1.1	5.3	-3.5	-1.0	1.6
			28 Months	1121	82.1	19.8	68.0	79.6	94.3	1121	-1.2	6.1	-3.9	-1.0	1.7
			32 Months	653	83.3	19.9	69.2	81.0	95.3	653	-1.1	6.2	-3.7	-1.0	1.6
			36 Months	212	84.5	20.0	70.3	82.9	97.9	212	-1.9	6.6	-4.5	-1.6	1.6
		Placebo (N=2149)	Baseline	2148	82.0	20.9	67.0	79.9	94.3	2148					
			14 days	2092	82.2	21.0	67.0	80.0	94.7	2092	0.0	1.4	-0.6	0.0	0.6
			2 Months	2044	82.4	21.1	67.4	79.9	94.8	2044	0.0	2.1	-1.0	0.0	1.0
			4 Months	2018	82.4	21.0	67.4	79.8	95.0	2018	0.1	2.9	-1.1	0.0	1.5
			8 Months	1874	83.0	21.1	67.8	80.8	95.2	1874	-0.0	3.9	-1.6	0.0	2.0

Placebo (N=2149)	12 Months	1809	82.9	21.0	68.0	81.0	95.2	1809	-0.1	4.4	-2.0	0.0	1.9
	16 Months	1758	82.7	20.8	68.0	81.0	95.0	1758	-0.2	4.9	-2.3	0.0	2.0
	20 Months	1680	82.8	20.6	68.0	80.9	95.0	1680	-0.1	5.2	-2.4	0.0	2.4
	24 Months	1514	82.7	20.4	68.0	80.6	94.5	1514	-0.2	5.7	-2.6	0.0	2.5
	28 Months	1069	83.6	20.3	69.7	81.8	95.1	1069	-0.2	5.9	-2.9	0.0	2.7
	32 Months	593	83.8	19.8	70.0	82.0	94.6	593	-0.3	6.7	-3.0	0.0	3.0
	36 Months	200	84.3	20.8	69.1	82.0	93.9	200	-1.0	6.8	-4.2	-0.3	2.3

Blood pressure

Systolic BP decreased in the dapagliflozin treatment group compared with the placebo group over time: mean change from baseline to Month 36 was -2.2 mmHg in the dapagliflozin treatment group and 3.3 mmHg in the placebo group. There were no clinically relevant changes in diastolic BP or pulse rate in either treatment group.

Table 36 Vital signs variables over time - on treatment (SAS) – SBP and DBP

				Result						Change from baseline					
Vital signs variable	SI-unit	Group	Time point	n	Mean	SD	Q1	Median	Q3	n	Mean	SD	Q1	Median	Q3
Systolic Blood Pressure	mmHg	Dapa 10 mg (N=2149)	Baseline	2149	136.7	17.5	125.3	135.7	147.0	2149					
			14 days	2092	132.2	16.8	120.7	131.0	141.7	2092	-4.6	14.6	-12.7	-3.7	3.7
			2 Months	2048	132.5	17.1	121.0	131.7	142.0	2048	-4.4	16.1	-13.3	-3.3	5.0
			4 Months	2034	133.3	17.5	121.3	132.0	143.0	2034	-3.5	16.5	-13.7	-3.3	6.0
			8 Months	1913	133.8	17.3	122.7	133.3	143.0	1913	-3.1	17.1	-13.0	-3.0	6.7
			12 Months	1843	133.6	17.3	121.7	133.0	143.7	1843	-3.2	16.8	-13.0	-3.0	6.7
			16 Months	1793	133.8	16.8	122.7	133.3	144.0	1793	-2.9	17.6	-13.0	-2.3	7.3
			20 Months	1721	133.9	16.9	122.0	133.3	143.7	1721	-2.7	17.4	-13.0	-2.3	8.0
			24 Months	1556	133.8	17.3	122.0	133.0	143.7	1556	-2.9	17.5	-13.0	-2.5	7.0
			28 Months	1123	134.2	17.1	122.7	133.0	144.0	1123	-3.2	17.8	-13.3	-2.7	8.0
			32 Months	652	135.2	16.2	125.3	134.3	145.0	652	-2.1	18.2	-13.0	-1.8	8.0
			36 Months	213	133.7	14.7	124.7	133.0	141.3	213	-2.2	16.6	-11.7	-1.3	7.3
		Placebo (N=2149)	Baseline	2149	137.4	17.3	126.0	136.3	147.3	2149					
			14 days	2094	136.2	17.4	124.3	135.3	146.3	2094	-1.3	14.3	-9.0	-0.7	6.7
			2 Months	2048	136.7	17.6	125.0	135.3	147.3	2048	-0.9	15.2	-10.0	-1.0	8.0
			4 Months	2024	136.5	17.0	125.5	135.3	146.3	2024	-1.0	16.3	-10.0	-0.3	8.3
			8 Months	1878	137.8	17.0	126.7	136.7	147.7	1878	0.1	16.9	-9.3	0.3	10.0
			12 Months	1810	136.9	17.5	125.3	136.2	146.7	1810	-0.7	17.3	-10.7	-0.7	9.0
			16 Months	1760	136.7	17.1	125.7	135.3	146.7	1760	-0.9	17.4	-11.0	-0.7	9.5
			20 Months	1685	137.3	17.1	125.7	136.7	147.3	1685	-0.2	17.8	-11.0	0.0	10.7
			24 Months	1517	136.6	16.7	125.3	136.3	146.0	1517	-1.1	17.8	-11.7	0.0	9.3
			28 Months	1072	137.1	16.7	126.3	136.0	146.7	1072	-1.0	18.0	-11.5	-1.0	10.0
			32 Months	595	138.3	17.6	127.0	136.7	147.7	595	0.9	19.2	-9.7	1.3	12.7
Diastolic Blood Pressure	mmHg	Dapa 10 mg (N=2149)	Baseline	2149	77.5	10.7	70.7	77.7	84.3	2149					
			14 days	2092	75.3	10.4	68.3	75.7	82.0	2092	-2.1	8.4	-7.3	-1.7	2.7
			2 Months	2048	75.7	10.8	69.0	76.0	82.7	2048	-1.9	9.2	-7.3	-1.7	3.3
			4 Months	2034	76.1	10.7	69.3	76.7	82.7	2034	-1.4	9.4	-7.0	-1.0	4.3
			8 Months	1913	76.3	10.6	69.3	76.7	83.3	1913	-1.2	9.9	-7.3	-1.3	5.0
			12 Months	1843	76.2	10.8	69.0	76.7	83.3	1843	-1.4	9.7	-7.3	-1.3	4.7
			16 Months	1793	76.1	10.7	69.0	76.7	83.3	1793	-1.4	10.2	-8.0	-1.3	4.7
			20 Months	1721	76.5	10.6	69.7	76.7	83.3	1721	-1.0	10.2	-7.7	-1.0	5.3
			24 Months	1556	76.1	10.7	68.8	76.7	83.0	1556	-1.6	10.2	-8.0	-1.0	4.7
			28 Months	1123	76.3	10.5	70.0	76.7	83.0	1123	-1.7	10.3	-8.3	-1.3	4.7
			32 Months	652	77.1	10.2	70.3	77.3	83.3	652	-1.4	10.8	-8.3	-1.0	5.5
			36 Months	213	76.3	10.0	69.7	76.7	82.7	213	-1.2	10.1	-7.7	-2.0	4.7
		Placebo (N=2149)	Baseline	2149	77.5	10.3	70.7	77.7	83.7	2149					
			14 days	2094	76.9	10.5	70.0	77.0	83.3	2094	-0.6	8.4	-5.7	-0.3	4.3
			2 Months	2048	77.1	10.5	70.3	77.0	83.3	2048	-0.5	8.9	-6.0	0.0	5.0
			4 Months	2024	77.4	10.4	70.3	77.7	83.7	2024	-0.1	9.2	-5.5	0.0	5.3
			8 Months	1878	77.8	10.4	71.0	78.3	84.3	1878	0.2	10.0	-6.0	0.0	6.3
			12 Months	1810	77.2	10.9	70.0	77.0	84.0	1810	-0.4	10.0	-6.7	0.0	5.7
			16 Months	1760	77.0	10.4	70.0	77.3	83.7	1760	-0.6	10.1	-6.7	-0.3	6.0
			20 Months	1685	77.2	10.5	70.0	77.0	83.7	1685	-0.3	10.2	-7.0	-0.3	6.0
			24 Months	1517	77.2	10.3	70.0	77.3	83.7	1517	-0.5	10.4	-7.0	-0.3	6.7
		Placebo (N=2149)	28 Months	1072	77.2	10.5	70.0	77.3	84.3	1072	-0.8	10.6	-7.7	-0.7	6.7
			32 Months	595	77.1	10.4	71.3	77.3	84.0	595	-0.8	10.5	-7.3	-1.3	6.0
			36 Months	205	76.9	9.8	71.0	76.7	83.7	205	0.6	10.6	-6.7	0.0	8.3

Safety in special populations

Effect of T2DM

T2DM at baseline was defined as a history of T2DM, or HbA1c ≥6.5% at both Visit 1 and Visit 2.

At baseline, of the 4,298 patients in the SAS, 2,903 (67.5%) patients had T2DM and 1,395 (32.5%) patients did not have diabetes. The effect of diabetes at baseline was analysed for all AE categories and for AEs of special interest (Table 37).

Among patients with and without T2Dm, the number of patients reporting SAEs or DAEs of UTIs (Table 38, Table 39, Table 40, Table 41) and genital infections (Table 42, Table 43) below. SAEs and DAEs of genital infections were not reported for any patients without diabetes.

Table 37 Number of Subjects with Adverse Events in Any Category, by T2DM Subgroup – on treatment (SAS)

	T2DM subjects		**Non-T2DM subjects**	
	Number (%) of subjects		**Number (%) of subjects**	
	Dapa 10 mg	**Placebo**	**Dapa 10 mg**	**Placebo**
AE category	**(N = 1453)**	**(N = 1450)**	**(N = 696)**	**(N = 699)**
Any AE with outcome = death (on-treatment)	56 (3.9)	66 (4.6)	11 (1.6)	19 (2.7)
Any AE with outcome = death (on- and off-treatment)	89 (6.1)	126 (8.7)	17 (2.4)	33 (4.7)
Any SAE, including events with outcome = death (on-treatment)	453 (31.2)	521 (35.9)	141 (20.3)	153 (21.9)
Any SAE, including events with outcome = death (on- and off-treatment)	483 (33.2)	562 (38.8)	150 (21.6)	167 (23.9)
Any AE leading to discontinuation of IP	82 (5.6)	94 (6.5)	36 (5.2)	29 (4.1)
Any AE leading to dose interruption	212 (14.6)	217 (15.0)	60 (8.6)	51 (7.3)
Any AE leading to dose reduction	26 (1.8)	19 (1.3)	13 (1.9)	12 (1.7)
Any AE possibly related to IP	186 (12.8)	165 (11.4)	89 (12.8)	57 (8.2)
Any definite or probable diabetic ketoacidosis	0	2 (0.1)	0	0
Any major hypoglycaemic event	14 (1.0)	28 (1.9)	0	0
Any event of symptoms of volume depletion	86 (5.9)	65 (4.5)	34 (4.9)	19 (2.7)
Any fracture	65 (4.5)	51 (3.5)	20 (2.9)	18 (2.6)
Any renal AE	113 (7.8)	131 (9.0)	31 (4.5)	38 (5.4)
Any amputation	35 (2.4)	38 (2.6)	0	1 (0.1)

Fractures and amputations are presented for the on- and off- treatment period; AEs with outcome death and SAEs are presented for both the on-treatment and on- and off- treatment periods. All other safety variables are presented for the on-treatment period (AE onset date on or after date of first dose and up to and including 30 days following last dose of study drug).

Table 38 Number of subjects with SAEs of urinary tract infection by T2DM status by preferred term - on treatment (SAS) T2DM subjects

	Number (%) of subjects[a]	
Preferred term	Dapa 10 mg (N=1453)	Placebo (N=1450)
Subjects with any SAE of UTI[b]	23 (1.6)	14 (1.0)
Urinary tract infection	17 (1.2)	10 (0.7)
Pyelonephritis acute	2 (0.1)	1 (0.1)
Cystitis	1 (0.1)	2 (0.1)
Escherichia urinary tract infection	1 (0.1)	0
Pyonephrosis	1 (0.1)	0
Urinary tract infection bacterial	1 (0.1)	0
Urogenital infection bacterial	1 (0.1)	0
Pyelonephritis	0	1 (0.1)

Table 39 Number of subjects with SAEs of urinary tract infection by T2DM status by preferred term - on treatment (SAS) Non-T2DM subjects

	Number (%) of subjects[a]	
Preferred term	Dapa 10 mg (N=696)	Placebo (N=699)
Subjects with any SAE of UTI[b]	6 (0.9)	4 (0.6)
Pyelonephritis acute	3 (0.4)	0
Urinary tract infection	3 (0.4)	3 (0.4)
Pyelonephritis	1 (0.1)	1 (0.1)

Table 40 Number of subjects with DAEs of urinary tract infection by T2DM by preferred term (SAS) T2DM subjects

	Number (%) of subjects[a]	
Preferred term	Dapa 10 mg (N=1453)	Placebo (N=1450)
Subjects with any DAE of UTI[b]	7 (0.5)	3 (0.2)
Urinary tract infection	6 (0.4)	3 (0.2)
Urogenital infection bacterial	1 (0.1)	0

Table 41 Number of subjects with DAEs of urinary tract infection by T2DM by preferred term (SAS) Non-T2DM subjects

	Number (%) of subjects[a]	
Preferred term	Dapa 10 mg (N=696)	Placebo (N=699)
Subjects with any DAE of UTI[b]	1 (0.1)	0
Urinary tract infection	1 (0.1)	0

Table 42 Number of subjects with SAEs of genital infection by T2DM status by preferred term - on treatment (SAS) T2DM subjects

	Number (%) of subjects[a]	
Preferred term	Dapa 10 mg (N=1453)	Placebo (N=1450)
Subjects with any SAE of GI[b]	3 (0.2)	0
Balanoposthitis	1 (0.1)	0
Urogenital infection bacterial	1 (0.1)	0
Vulval cellulitis	1 (0.1)	0

Table 43 Number of subjects with DAEs of genital infection by T2DM by preferred term (SAS) T2DM subjects

Preferred term	Number (%) of subjects[a] Dapa 10 mg (N=1453)	Placebo (N=1450)
Subjects with any DAE of GI[b]	3 (0.2)	0
Vulvovaginal mycotic infection	2 (0.1)	0
Urogenital infection bacterial	1 (0.1)	0

Effect by Renal Function

The effect of renal function at baseline was analysed for all AE categories and for AEs of special interest (Table 44,

Table 45 and Table 46). At baseline, of the 4,298 patients in the SAS, 1780 (41.4%) had an eGFR ≥45 mL/min/1.73 $m^{2,}$, 2,518 (58.6%) had an eGFR <45 mL/min/1.73 m^2, and 624 (14.5%) had an eGFR <30 mL/min/1.73 m^2.

Table 44 Number of Subjects with Adverse Events in Any Category, by eGFR (< 45 and ≥ 45 mL/min/1.73 m^2) Subgroup (SAS)

	Baseline eGFR <45 Number (%) of subjects [a]		**Baseline eGFR ≥ 45 Number (%) of subjects [a]**	
	Dapa 10 mg (N=1270)	**Placebo (N=1248)**	**Dapa 10 mg (N=879)**	**Placebo (N=901)**
AE category				
Any AE with outcome = death (on-treatment)	44 (3.5)	60 (4.8)	23 (2.6)	25 (2.8)
Any AE with outcome = death (on- and off--treatment)	72 (5.7)	104 (8.3)	34 (3.9)	55 (6.1)
Any SAE, including events with outcome = death (on-treatment)	372 (29.3)	406 (32.5)	222 (25.3)	268 (29.7)
Any SAE, including events with outcome = death (on- and off-treatment)	396 (31.2)	440 (35.3)	237 (27.0)	289 (32.1)
Any AE leading to discontinuation of IP	88 (6.9)	81 (6.5)	30 (3.4)	42 (4.7)
Any AE leading to dose interruption	172 (13.5)	164 (13.1)	100 (11.4)	104 (11.5)
Any AE leading to dose reduction	22 (1.7)	18 (1.4)	17 (1.9)	13 (1.4)
Any AE possibly related to IP	174 (13.7)	133 (10.7)	101 (11.5)	89 (9.9)
Any definite or probable diabetic ketoacidosis	0	2 (0.2)	0	0
Any major hypoglycaemic event	10 (0.8)	17 (1.4)	4 (0.5)	11 (1.2)
Any event of symptoms of volume depletion	73 (5.7)	49 (3.9)	47 (5.3)	35 (3.9)

Any fracture	60 (4.7)	43 (3.4)	25 (2.8)	26 (2.9)
Any renal AE	103 (8.1)	111 (8.9)	41 (4.7)	58 (6.4)
Any amputation	17 (1.3)	15 (1.2)	18 (2.0)	24 (2.7)

Table 45 Number of Subjects with Adverse Events in Any Category in Subjects with eGFR <30 mL/min/1.73 m^2 (SAS)

	Baseline eGFR <30 Number (%) of subjects	
	Dapa 10 mg (N=293)	**Placebo (N=331)**
AE category		
Any AE with outcome = death (on-treatment)	11 (3.8)	17 (5.1)
Any AE with outcome = death (on- and off--treatment)	21 (7.2)	36 (10.9)
Any SAE, including events with outcome = death (on-treatment)	93 (31.7)	123 (37.2)
Any SAE, including events with outcome = death (on- and off-treatment)	101 (34.5)	138 (41.7)
Any AE leading to discontinuation of IP	28 (9.6)	36 (10.9)
Any AE leading to dose interruption	47 (16.0)	46 (13.9)
Any AE leading to dose reduction	9 (3.1)	3 (0.9)
Any AE possibly related to IP	42 (14.3)	43 (13.0)
Any definite or probable diabetic ketoacidosis	0	1 (0.3)
Any major hypoglycaemic event	2 (0.7)	8 (2.4)
Any event of symptoms of volume depletion	13 (4.4)	14 (4.2)
Any fracture	11 (3.8)	15 (4.5)
Any renal AE	42 (14.3)	39 (11.8)
Any amputation	3 (1.0)	4 (1.2)

For renal AEs, the difference between treatment groups was 3 patients: 42 patients (14.3%) in the dapagliflozin group compared with 39 patients (11.8%) in the placebo group. Renal SAEs were few and had a similar distribution as the non-serious AEs with 19 patients (6.5%) in the dapagliflozin group and 17 patients (5.1%) in the placebo group.-The most frequently reported PT was renal impairment with 22 (7.5%) patients in the dapagliflozin group and 18 (5.4%) in the placebo group (Table 46). A similar number of patients reported the PT of acute kidney injury in both treatment groups: 16 (5.5%) in the dapagliflozin group and 18 (5.4%) in the placebo group.

Table 46 Renal adverse events by preferred term in subjects with eGFR < 30 (ml/min/1.73 m2) - on treatment (SAS)

Preferred term	Baseline eGFR <30 Number (%) of subjects[a] Dapa 10 mg (N=293)	Placebo (N=331)
Subjects with a renal AE[b]	42 (14.3)	39 (11.8)
Renal impairment	22 (7.5)	18 (5.4)
Acute kidney injury	16 (5.5)	18 (5.4)
Renal failure	4 (1.4)	4 (1.2)
Nephropathy toxic	2 (0.7)	0

eGFR over time

Line graphs showing model-adjusted mean changes from baseline in eGFR over time are provided for the subgroups of patients with baseline eGFR < 30, ≥ 30, < 45, and ≥ 45 mL/min/1.73 m^2 in Figures below.

Figure 20 Adjusted Mean eGFR (CKD-EPI) Change from Baseline and 95% CIs from Repeated Measures Model by Baseline eGFR Subgroup (FAS). Baseline eGFR < 30 (upper) and ≥ 30 (lower) ml/min/1.73 m^2

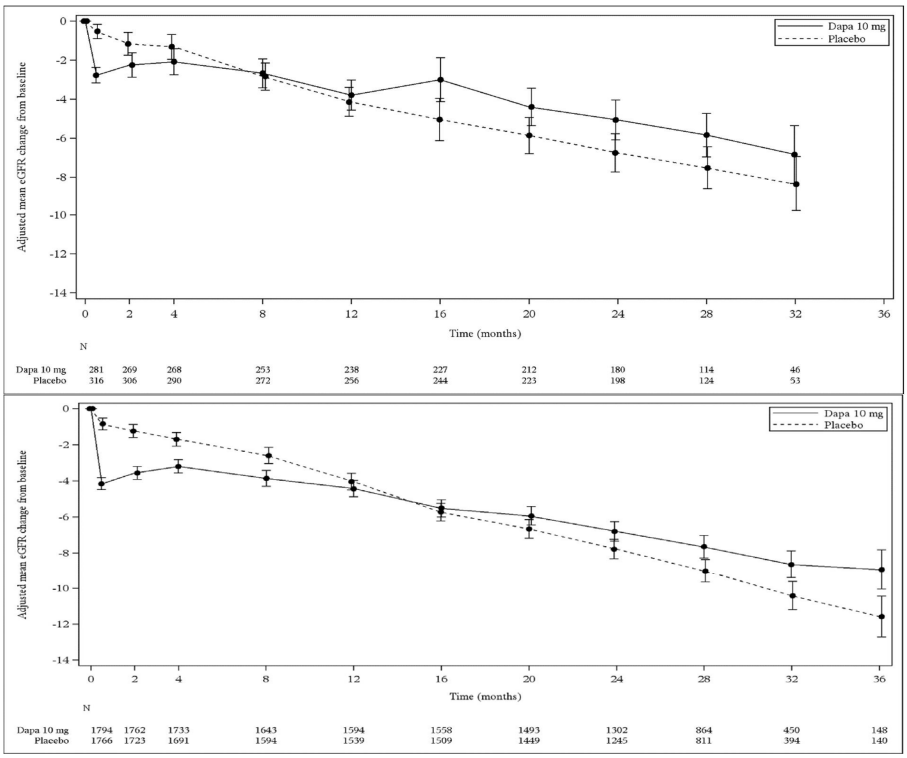
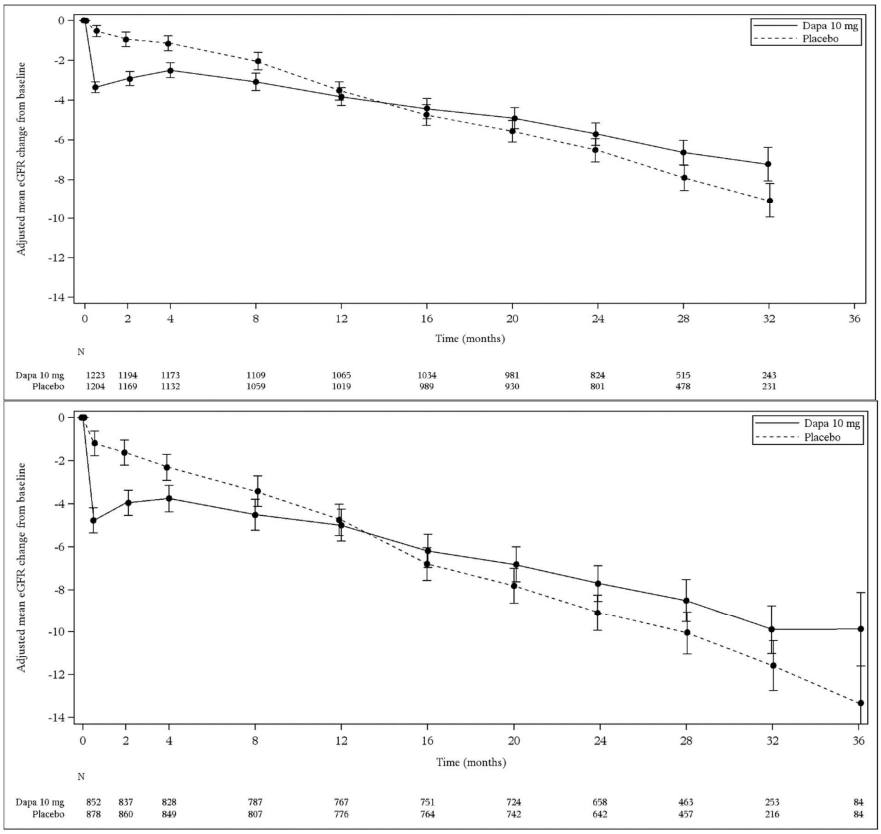


Figure 21 Adjusted Mean eGFR (CKD-EPI) Change from Baseline and 95% CIs from Repeated Measures Model by Baseline eGFR Subgroup (FAS). Baseline eGFR < 45 (upper) and ≥ 45 (lower) ml/min/1.73 m²



UACR over time

Line graphs showing model-adjusted mean changes from baseline in UACR over time are provided for the subgroups of patients with baseline eGFR < 30, ≥ 30, < 45, and ≥ 45 mL/min/1.73 m^2 in Figures below.

Figure 22 Adjusted Mean UACR (mg/g) Percent Change from Baseline and 95% CIs from Repeated Measures Model for Subjects with Baseline eGFR < 30 (upper) and ≥ 30 (lower) mL/min/1.73 m^2 (FAS)

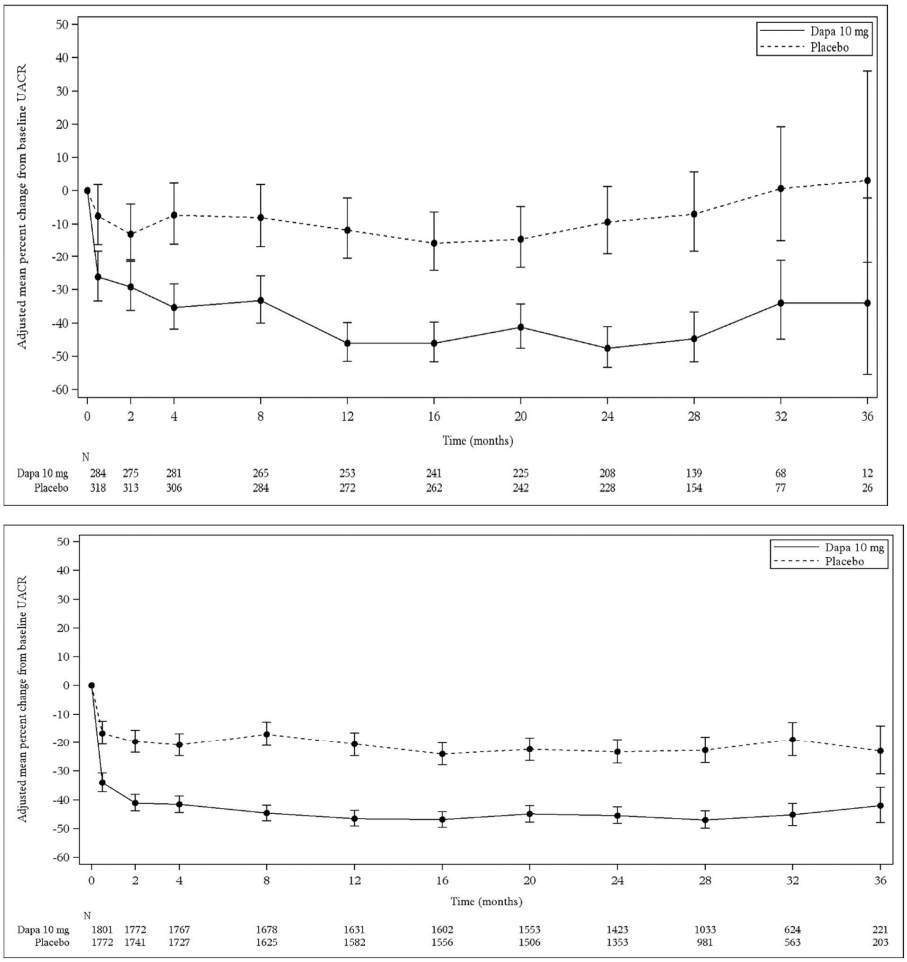
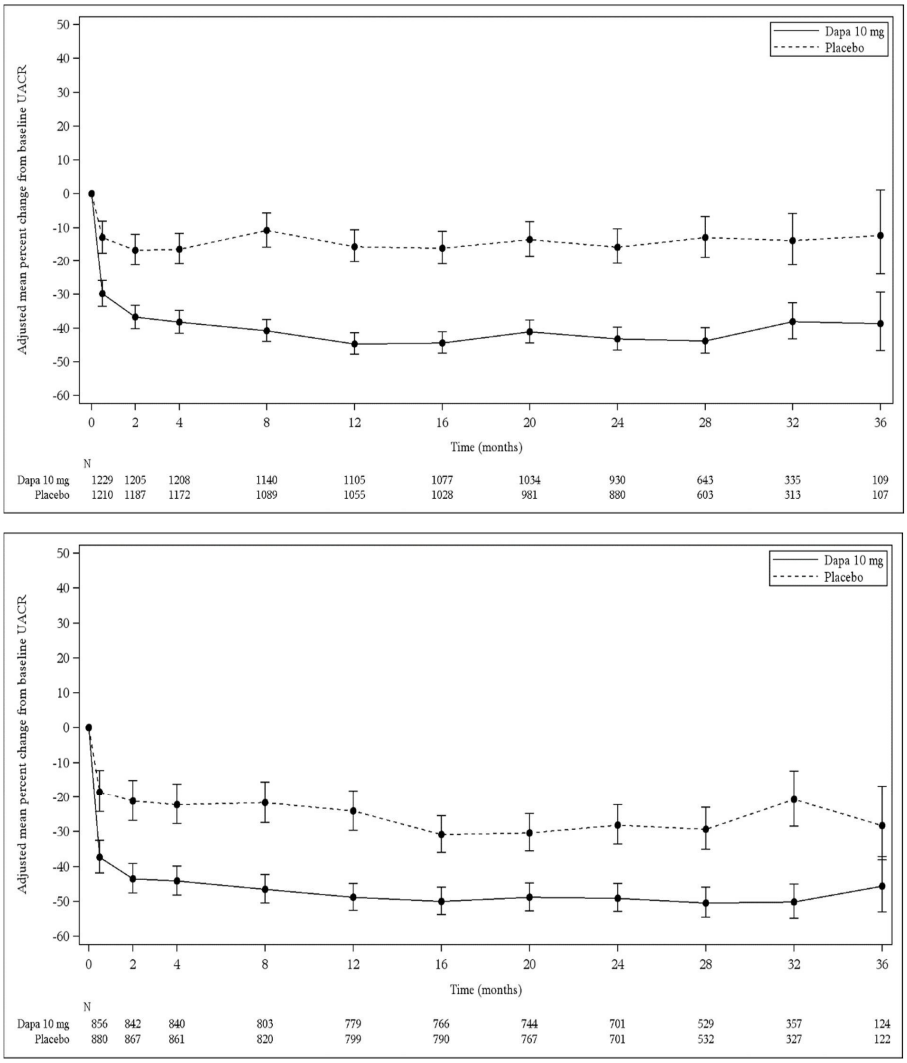


Figure 23 Adjusted Mean UACR (mg/g) Percent Change from Baseline and 95% CIs from Repeated Measures Model for Subjects with Baseline eGFR < 45 (upper) and ≥ 45 (lower) mL/min/1.73 m^2 (FAS)



Effect by Age (≤ 65, >65 years)

At baseline, of the 4298 patients in the SAS, 2484 (57.8%) were ≤ 65 years old and 1814 (42.2%) were > 65 years old. The effect of age at baseline was analysed for all AE categories and for AEs of special interest (*Table 47*).

Table 47 Number of Subjects with Adverse Events in Any Category, by Age Subgroup (SAS)

	≤ 65 years		> 65 years	
	Number (%) of subjects		Number (%) of subjects	
	Dapa 10 mg (N=1246)	Placebo (N=1238)	Dapa 10 mg (N=903)	Placebo (N=911)
AE category				
Any AE with outcome = death (on-treatment)	31 (2.5)	38 (3.1)	36 (4.0)	47 (5.2)

Any AE with outcome = death (on- and off--treatment)	45 (3.6)	68 (5.5)	61 (6.8)	91 (10.0)
Any SAE, including events with outcome = death (on-treatment)	282 (22.6)	348 (28.1)	312 (34.6)	326 (35.8)
Any SAE, including events with outcome = death (on- and off-treatment)	296 (23.8)	374 (30.2)	337 (37.3)	355 (39.0)
Any AE leading to discontinuation of IP	56 (4.5)	62 (5.0)	62 (6.9)	61 (6.7)
Any AE leading to dose interruption	127 (10.2)	133 (10.7)	145 (16.1)	135 (14.8)
Any AE leading to dose reduction	20 (1.6)	21 (1.7)	19 (2.1)	10 (1.1)
Any AE possibly related to IP	137 (11.0)	120 (9.7)	138 (15.3)	102 (11.2)
Any definite or probable diabetic ketoacidosis [c]	0	2 (0.2)	0	0
Any major hypoglycaemic event	2 (0.2)	14 (1.1)	12 (1.3)	14 (1.5)
Any event of symptoms of volume depletion	63 (5.1)	44 (3.6)	57 (6.3)	40 (4.4)
Any fracture	44 (3.5)	25 (2.0)	41 (4.5)	44 (4.8)
Any renal AE	61 (4.9)	95 (7.7)	83 (9.2)	74 (8.1)
Any amputation	22 (1.8)	29 (2.3)	13 (1.4)	10 (1.1)

Effect by sex

Of the 4,298 patients in the SAS, 66.8% were male and 33.2% were female. Subgroup analysis by sex was performed for amputations and fractures.

The number of patients with amputations in the subgroup analysis by sex was generally consistent between treatment groups (1.7% vs 2.1% for DAPA vs placebo in males and 1.4% vs 1.3% for DAPA vs placebo in females).

The number of patients with fractures in the subgroup analysis by sex was also generally consistent between treatment groups and the small difference seen between treatments in the overall population (3.3% vs 2.4% for DAPA vs placebo in males and 5.2% vs 4.7% for DAPA vs placebo in females).

Effect by Baseline Blood Pressure

Subgroup analysis by systolic blood pressure at baseline (≤ 130, >130 mmHg) was performed for AEs of symptoms of volume depletion. In the subgroup of patients with a systolic blood pressure of < 130 mmHg, the proportion of patients reporting any AEs in both treatment groups was higher (7.3% vs 4.4% for DAPA vs placebo) compared to the subgroup with a higher baseline systolic blood pressure (4.6% vs 3.6% for DAPA vs placebo). The number of patients reporting SAEs were similar between treatments in both subgroups. The overall pattern in both subgroups was consistent with the overall results.

Extrinsic Factors

No extrinsic factors were analysed in the DAPA-CKD study.

Safety related to drug-drug interactions and other interactions

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

Discontinuation due to adverse events

The treatment discontinuation rate was similar between treatment groups throughout the study. Overall, the numbers of DAEs were 118 (5.5%) patients and 123 (5.7%) patients in the dapagliflozin and placebo treatment groups, respectively (Table 48). The most commonly reported AEs that led to permanent discontinuation of study drug were chronic kidney disease, glomerular filtration rate decreased, and renal impairment in the dapagliflozin treatment group and renal impairment, glomerular filtration rate decreased, and end-stage renal disease in the placebo group.

Table 48 Number of Subjects with Adverse Events (≥ 0.1% in Either Treatment Group) Leading to Discontinuation of Investigational Product by Preferred Term (SAS)

	Number (%) of subjects[a]	
	Dapa 10 mg (N=2149)	**Placebo (N=2149)**
Preferred term		
Subjects with any AE leading to discontinuation of IP[b]	118 (5.5)	123 (5.7)
Chronic kidney disease	11 0.5)	6 (0.3)
Glomerular filtration rate decreased	9 (0.4)	10 (0.5)
Renal impairment	9 (0.4)	12 (0.6)
Urinary tract infection	7 (0.3)	3 (0.1)
End stage renal disease	6 (0.3)	7 (0.3)
Acute kidney injury	5 (0.2)	6 (0.3)
Diarrhoea	4 (0.2)	3 (0.1)
Ischaemic stroke	4 (0.2)	2 (0.1)
Acute myocardial infarction	2 (0.1)	5 (0.2)
Blood creatinine increased	2 (0.1)	1 (0.0)
Cardiac failure	2 (0.1)	1 (0.0)
Hypovolaemia	2 (0.1)	1 (0.0)
Osteomyelitis	2 (0.1)	0
Prostate cancer	2 (0.1)	1 (0.0)
Renal failure	2 (0.1)	2 (0.1)

Skin ulcer	2 (0.1)	0
Vulvovaginal mycotic infection	2 (0.1)	0
Cardiac failure congestive	1 (0.0)	2 (0.1)
Hyperkalaemia	1 (0.0)	2 (0.1)
Asthenia	0	2 (0.1)
Diabetic nephropathy	0	2 (0.1)
Hypoglycaemia	0	2 (0.1)
Pneumonia	0	3 (0.1)
Respiratory failure	0	2 (0.1)

Use in pregnancy and lactation

Pregnant patients were excluded from participating in the DAPA-CKD study.

In total 8 pregnancies were reported during the study, 2 in the dapagliflozin group and 6 in the placebo group. Of the 2 pregnancies in the dapagliflozin group, 1 was an anembryonic pregnancy (reported as an SAE, and 1 was terminated through elective abortion. Of the 6 pregnancies reported in the placebo group, 2 ended in spontaneous abortion (reported as SAEs, and 1 was terminated through elective abortion. The birth of 1 healthy baby and the birth of 1 baby with congenital abnormalities have been reported through the sponsor's safety database. The outcome of 1 pregnancy is unknown.

Overdose

No events of overdose of study drug were reported during the DAPA-CKD 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

Dapagliflozin was first approved for treatment of patients with T2DM in Australia on 05 October 2012 and it is currently approved in over 100 countries.

Post-marketing experience in the approved indications is summarised in regular PBRERs that are submitted to regulatory authorities worldwide. The dapagliflozin PBRER with data lock 04 April 2020 included more than 9.5 million patient-years of post-marketing exposure (cumulative until 31 March 2020) and is dated 25 May 2020. At the data lock of the dapagliflozin PBRER (04 April 2020), there was no new information to alter the overall positive benefit-risk profile for dapagliflozin in the approved indications.

4.5.1. Discussion on clinical safety

The established safety profile of dapagliflozin is based on the original dapagliflozin (submission for treatment of T2DM). The evaluation of the DAPA-CKD study provides information on the safety profile of dapagliflozin

in subjects with chronic kidney disease (eGFR ≥25 and ≤75 mL/min/1.73 m^2) with albuminuria (UACR ≥200 and ≤5000 mg/g). The study population included patients with T2DM (70%) and without diabetes (30%).

In the study DAPA-CKD, 2,149 subjects were treated with dapagliflozin for a total exposure of 4,448 PY, regardless of interruptions (i.e. 'on and off' treatment), with 1,865 subjects (87%) for at least 52 weeks, 1,773 subjects (82%) for at least 1,5 years and 1423 subjects (66%) for at least 2 years. The mean and median duration of exposure was 24.8 and 27.3 months for dapagliflozin and 24.3 and 27.0 months for placebo. The median duration of follow-up was 27.1 months for dapagliflozin.

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

The number of SAEs was higher in the placebo group (31%) than dapagliflozin group (28%). The most frequently reported SAEs for dapagliflozin vs placebo were acute kidney injury (1.7% vs 2.0%), pneumonia (1.7% vs 2.7%), cardiac failure (1.6% vs 2.2%) and acute myocardial infarction (1.3% vs 1.8%). There were more fatal cases in the placebo group compared with the dapagliflozin group (3.1% vs 4.0% on-treatment; 4.9% vs 7.4% on- and off-treatment for dapagliflozin vs placebo).

Discontinuation rates due to AE were similar across the treatment groups in DAPA-CKD (6%). The most frequently reported AEs leading to study drug discontinuation for dapagliflozin was chronic kidney disease (0.5% vs 0.3%), GFR decreased (0.4% vs 0.5%) and renal impairment (0.4% vs 0.6%) for dapagliflozin vs placebo.

Urinary tract infections

The incidence of SAEs of UTIs was increased for dapagliflozin versus placebo (1.3% vs 0.8%), of which urinary tract infection was the most frequently reported PT for both dapagliflozin and placebo. There were 6 reports of pyelonephritis and 1 report of pyonephrosis for dapagliflozin and 3 reports of pyelonephritis for placebo. DAEs of UTIs were reported with an incidence of 0.4% for dapagliflozin and 0.1% for placebo. The majority of subjects (79%) reporting SAEs of UTIs were in the subgroup with T2DM.

Genital infections

Three SAEs of genital infections (1 balanoposthitis, 1 urogenital infection bacterial and 1 vulval cellulitis) in subjects with T2DM were reported, all in the dapagliflozin group. Three patients (0.1%), all in the dapagliflozin treatment group, reported DAEs of genital infection.

Volume depletion

The incidence of adverse events suggestive of volume depletion was higher for dapagliflozin (5.6%) compared with placebo (3.9%). The incidence of serious AEs of volume depletion was 0.7% for dapagliflozin and placebo, respectively.

The results were consistent in the subgroup analyses. Events of volume depletion was reported more frequently with dapagliflozin than with placebo in subjects with T2DM (5.9% vs 4.5%) and without T2DM (4.9% vs 2.7%) and in subjects with eGFR <45 mL/min/1.73 m^2 (5.7% vs 3.9%) and eGFR ≥45 mL/min/1.73 m^2 (5.3% vs 3.9%). However, in the subgroup with eGFR <30 mL/min/1.73 m^2, the incidence of volume depletion was similar for dapagliflozin (4.4%) and placebo (4.2%).

Renal events

Renal events occurred more frequently in the placebo group (7.9%) than in the dapagliflozin group (6.7%) in the overall population and for subjects *with T2DM* (7.8% vs 9.0% for DAPA vs placebo) and *without T2DM* (4.5% vs 5.4% for DAPA vs placebo). SAEs of renal events overall were also higher in the placebo (3.2%) relative the dapagliflozin group (2.5%).

In subjects with *eGFR ≥45 mL/min/1.73 m²* and *eGFR <45 mL/min/1.73 m²,* the incidence of renal events was higher for placebo than for dapagliflozin. However, in subjects with eGFR *≤30 mL/min/1.73 m²,* renal events occurred more frequently for dapagliflozin compared to placebo, including serious renal events.

In the DAPA-CKD study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial (day 14) decrease in mean eGFR was -4.0 mL/min/1.73 m^2 in the dapagliflozin group and -0.8 mL/min/1.73 m^2 in the placebo group. At 28 months, change from baseline in eGFR was -7.4 mL/min/1.73 m^2 in the dapagliflozin group and -8.6 mL/min/1.73 m^2 in the placebo group.

Fractures

Fractures were reported for 4.0% of patients in the dapagliflozin group and 3.2% in the placebo group, corresponding to an event rate of 1.75 and 1.43 events per 100 patient-years. The Kaplan-Meier plot indicates a slightly increase in fractures with dapagliflozin after about 20 months of treatment. The incidence of osteoporotic fractures was balanced between the groups (1.2% vs 1.1%) and location of the fractures varied with no specific pattern. Among subjects with osteoporotic fractures in the dapagliflozin group, low trauma fractures were reported in 50%, high trauma in 12% and unclear whether high or low in 38% of the fractures. In the placebo group, 43% high trauma, 9% low trauma and 48% unknown/unclear fractures were reported.

The increase in fractures could be caused by an increased number of falls related to dapagliflozin-induced symptoms of volume depletion (e.g. dizziness/ hypotension); however, only 2 patients reported AE of symptoms of volume depletion prior the event of the fracture in the dapagliflozin group. A higher incidence of fractures in both treatment groups was observed in subjects ≥65 years of age and in females, respectively. Moreover, the incidence of fractures for dapagliflozin vs placebo was increased in subjects with T2DM (4.5% vs 3.5%) and in subjects with eGFR <45 mL/min/1.73m^2 (4.7% vs 3.4%); although, in subjects with eGFR <30 mL/min/1.73m^2 the incidence of fractures was higher in the placebo group (4.5%) compared with the dapagliflozin group (3.8%). The incidence of fracture was balanced in subjects without T2DM (2.9% vs 2.6%), in subjects with eGFR >45 mL/min/1.73m^2 (2.8% vs 2.9%) and in subjects ≥65 of age (4.5% vs 4.8%). In the risk group of post-menopausal women (>55 years), there were slightly more patients reporting fractures in the placebo group (6.1%) than the dapagliflozin group (5.7%).

Amputations

The incidence of subjects who underwent at least 1 surgical amputation was balanced (1.6% and 1.8%) and the event rate (0.72 vs 0.81 events per 100 PY) was balanced between dapagliflozin and placebo. All events of amputations were in the lower limbs, apart from one event in the upper limbs (in the placebo group). There were numerically more subjects in the placebo group (n=20; 51%) than in the dapagliflozin group (n=13; 36%) with major amputations (below knee and above knee).

All patients with amputations, except one in the placebo group, were T2DM patients. The incidence of subjects suffering at least one amputation among subjects with T2DM was 2.4% and 2.6% for dapagliflozin and placebo, respectively. The incidence of amputations did not increase with decreased eGFR.

The number of patients with an adverse event related to risk for lower amputation was 10% for dapagliflozin and 9.3% for placebo; of which diabetic foot related AEs was the most frequently reported preceding event followed by volume depletion and vascular AEs, such as peripheral ischaemia/ PAD. The number of subjects who underwent subsequent amputations was 8% (n=18) in the dapagliflozin treatment group and 12% (n=23) in the placebo group. The incidence of patients with preceding events in the subgroup of patients with eGFR<30 mL/min/1.73m^2 was similar to the overall population.

Diabetic ketoacidosis

In total 2 subjects had an event adjudicated as a definite DKA, both in the placebo group. Both cases were reported for patients with T2DM and eGFR ≥45 mL/min/1.73 m^2, neither of them had a fatal outcome.

Major hypoglycaemic events

In the DAPA-CKD study only major hypoglycaemic events were collected. Subjects with major hypoglycaemic events were slightly more common in the placebo (1.3%; n=28) than in the dapagliflozin group (0.7%; n=14). Six cases (0.3%) in the dapagliflozin group and 14 (0.7%) in the placebo group were serious. All subjects with major hypoglycaemic events had T2DM at baseline and were using antidiabetic agents (sulfonylureas or insulin, or a combination) at the time of event, except for 3 subjects (1 subject in the dapagliflozin group and 3 subjects in the placebo group).

Fournier's gangrene

In total 6 cases indicating genital area infections or necrotising fasciitis were identified; 3 (0.1%) in the dapagliflozin groups and 3 (0.1%) in the placebo group. One of these cases (in the placebo group) was assessed as Fournier's gangrene.

Laboratory findings/ vital signs

During the study, an increase in mean haematocrit for dapagliflozin (5.1%) compared with placebo (-2.6%) was observed. Increased haematocrit is adequately labelled (frequency 'common') for dapagliflozin.

The eGFR decreased over time in both the dapagliflozin and the placebo group. The change in eGFR was initially (within 2 weeks) and up to 16 weeks of treatment more pronounced for dapagliflozin compared to placebo (-6.5% vs -1.7%); however, the decrease in eGFR was larger in the placebo from 16 weeks and onwards.

There was a decrease in mean body weight over time in the dapagliflozin group compared to placebo; mean change from baseline up to 36 months of treatment was -1.9 kg (-2.3%) for dapagliflozin and -1.0 kg (-1.2%) for placebo.

The decline in SBP and DBP from baseline in the dapagliflozin group was most pronounced early in the study, at Day 14 (-4.6 mmHg and -2.1 mmHg) and up to 2 months of treatment (-4.4 mmHg and -1.9 mmHg). Thereafter, SBP and DBP tended to increase, except for a slight decrease in SBP and DBP at month 24 and 28.

Subgroups

Effect by age

In the DAPA-CKD study, 58% were ≤65 and 42% were >65 years of age. In total, 363 subjects were >75 years of age, of which 177 subjects were treated with dapagliflozin. A slightly higher reporting rate was noted in subjects >65 years of age, as expected.

In general, the safety profile for patients ≤ 65 and >65 years of age was in line with that for the overall population; however, renal events were slightly more frequently common for dapagliflozin (9.2%) than for placebo (8.1%) in subjects >65 years. The incidence of fractures was increased for dapagliflozin versus placebo in subjects ≤65 years (3.5% vs 2.0%) and was balanced in subjects >65 years of age (4.5% vs 4.8%).

Effect by sex

The number of fractures was increased overall (4.0% vs 3.2%) and in the subgroup of males (3.3% vs 2.4%) and females (5.2% vs 4.7%), respectively, for dapagliflozin compared with 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 7.3% vs 4.4% (SAEs: 0.8% vs 0.5%) in subjects <130 mmHg and 4.6% vs 3.6% (SAEs: 0.7% vs 0.8%) 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 (31%), including eGFR <30 mL/min/1.73 m^2 subgroup (35%), compared to the eGFR ≥45 mL/min/1.73 m^2 (28%); although, the incidence was higher in the placebo group vs the dapagliflozin group in all subgroups.

In the overall population (4.0% vs 3.2%) and in subjects eGFR <45 mL/min/1.73 m^2 (4.7% vs 3.4%), the incidence of fractures was higher for dapagliflozin relative placebo; however, in the subgroup with eGFR <30 mL/min/1.73 m^2 the incidence of fractures was higher in the placebo group (4.5%) than in the dapagliflozin group (3.8%).

Renal events were more common in subjects with eGFR <30 mL/min/1.73 m^2 treated with dapagliflozin (14.3%) than with placebo (11.8%), including serious renal events (6.5% vs 5.1%). The most frequently reported event was renal impairment (7.5% vs 5.4%).

In the subgroup with eGFR <30 mL/min/1.73 m^2, subjects with AEs leading to dose interruption (16.0% vs 13.9%) and dose reductions (3.1% vs 0.9%) were higher in the dapagliflozin group versus the placebo group; however, AEs leading to discontinuation were slightly more frequent in placebo than in the dapagliflozin group (9.6% vs 10.9%).

Initially there was a decrease in eGFR in the dapagliflozin group compared with placebo group, across all subgroups. Over time, the eGFR declined more in the placebo group than in the dapagliflozin group. The pattern was similar across the eGFR subgroups (eGFR ≥45 vs <45 and eGFR ≥30 vs <30, respectively); however, the magnitude of the initial decrease in eGFR was more pronounced in the subgroups with higher baseline eGFR (≥45 and ≥30) compared with the subgroups with lower baseline eGFR (<45 and <30). The DAPA-CKD study did not include any follow-up of eGFR after discontinuation of treatment.

Treatment with dapagliflozin was associated with a greater reduction in UACR for dapagliflozin compared with placebo across the subgroups; eGFR ≥45 vs <45 and eGFR ≥30 vs <30, respectively. The difference in UACR between dapagliflozin and placebo was maintained throughout the duration of the study. The frequency of ESRD was increased in the subgroups eGFR <45 (7.9% vs 10.5%) and eGFR <30 (16.7% vs 21.8%) compared with the subgroups eGFR ≥45 (1.0% vs 3.3%) and eGFR ≥30 (3.2% vs 4.9%); however, the frequency of ESRD was higher in the placebo group compared with the dapagliflozin group across the subgroups.

Effect of T2DM

The incidence of SAEs was higher in the T2DM subgroup (34%) compared with the non-diabetes subgroup (21%); however, the incidence was higher in the placebo group versus dapagliflozin in both subgroups.

Overall, there was no substantial difference in safety profile for subjects with and without T2DM apart from that the incidence of fractures was increased for dapagliflozin compared to placebo in subjects with T2DM (4.5% vs 3.5%) and was more balanced in subjects with non-T2DM (2.9% vs 2.6%).

4.5.2. Conclusions on clinical safety

The DAPA-CKD study provides information on the safety profile of dapagliflozin in subjects with chronic kidney disease (eGFR ≥25 and ≤75 mL/min/1.73 m^2) with albuminuria.

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

The safety profile for dapagliflozin in the DAPA-CKD study was overall similar compared with previously identified adverse drug reactions for dapagliflozin. However, the incidence of fractures was increased for dapagliflozin compared with placebo. The incidence of osteoporotic fractures was balanced between the groups (1.2% vs 1.1%) and location of the fractures varied with no specific pattern.

Renal events, including serious renal events, were more common in the subgroup with eGFR <30 mL/min/1.73 m^2 treated with dapagliflozin compared with placebo. Moreover, adverse events leading to dose reductions and dose interruptions were increased for dapagliflozin compared with placebo for subjects with eGFR <30 mL/min/1.73 m^2; however, AEs leading to discontinuation were slightly more frequent in placebo than in the dapagliflozin group. There is no experience to initiate treatment with dapagliflozin in patients with eGFR <25 mL/min. Dapagliflozin is not recommended for initiation in patients with eGFR <25 mL/min.

The MAH has submitted an updated RMP with this application. No new safety concerns have been raised. The proposed changes are discussed in section 6 of this report.

4.5.3. 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.

5. Risk management plan

The MAH submitted an updated RMP version 22 with this extension of indication application and thereafter a consolidated RMP version 25.3 (which consolidated version 22 with version 25.2, agreed as part of Forxiga/Edistride EMEA/H/C/WS2069 for which a CHMP Positive Opinion was granted on 10/06/2021).

The CHMP received the following PRAC Advice on the submitted consolidated RMP:

The PRAC considered that the RMP version 25.3 is acceptable. The CHMP endorsed this advice without changes.

The CHMP endorsed the RMP version 25.3 with the following content:

Safety concerns

Important identified risks	Diabetic Ketoacidosis including events with atypical presentation

Important potential risks	Bladder cancer Breast cancer Prostate cancer Lower limb amputation
Missing information	Use in patients with NYHA class IV

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				
D1695C00011 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. Type 1 diabetes mellitus indication is only applicable for FORXIGA.	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)				
MB102118 (D1690R00007) - Observational study: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment Ongoing	To assess the incidence of breast and bladder cancer among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Risk of cancer	Submission of Interim data Submission of final data	2016, 2019, 2021, 2023 2025
Nonclinical mechanistic model studies - Postdoc project	Studies aimed to elucidate the metabolic adaptations in term of glucose flux, lipolysis, and ketogenesis	Ketoacidosis	Submission of final data	When available

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
Ongoing	following insulin withdrawal in subjects with diabetes mellitus and absolute or relative endogenous insulin deficiency, when treated with dapagliflozin.			
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	
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

Safety concern	Risk minimisation measures
	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. Type 1 diabetes mellitus indication is only applicable for FORXIGA.
Important potential risks	
Bladder cancer	No risk minimisation measures.
Breast cancer	No risk minimisation measures.
Prostate cancer	No risk minimisation measures.
Lower limb amputation	Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance provided on potential class effect (SmPC section 4.4) and counsel on routine preventative foot care (SmPC section 4.4 and PL section 2).
Missing information	
Use in patients with NYHA class IV	Routine risk minimisation measures: SmPC section 4.4

6. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on the data obtained with the DAPA-CKD study. The Package Leaflet (PL) is updated accordingly.

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

6.1.1. User consultation

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

7. Benefit-Risk Balance

7.1. Therapeutic Context

7.1.1. Disease or condition

CKD is a serious and progressive condition that is associated with CV disease and increased risk of adverse outcomes including HF, premature death, ESRD, and the need for RRT. The most common causes of CKD are diabetes (42%), hypertension (18%), and glomerulonephritis of varying aetiologies (18%). An estimated 700 million people worldwide live with CKD. The global prevalence of CKD stage 3 to 5 is estimated at 10.6% and estimates of global incidence, prevalence, and mortality of CKD have all increased dramatically since 1990.

7.1.2. Available therapies and unmet medical need

Standard of care for CKD in patients with and without diabetes is represented by blood pressure control and reduction of proteinuria through RAAS blockade (ACE-I or ARB) combined with CV risk management and/or and glycaemic control as necessary.

However, interventional studies assessing the use of ACE-I or ARB for the treatment for DKD indicate that patients treated with these drugs remain at risk of morbidity, mortality, and progression to ESRD. An unmet need remains for safe and effective therapies that further reduce CKD morbidity, mortality, and progression towards ESRD, irrespective of the presence or absence of diabetes or albuminuria.

7.1.3. Main clinical studies

DAPA-CKD was an international, multicentre, event-driven, randomized, double-blind, parallel-group, placebo-controlled study, evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily in addition to standard of care, to prevent the progression of CKD and renal or CV death.

The study population was defined as having CKD (eGFR ≥ 25 and ≤ 75 mL/min/1.73 m^2 with albuminuria [UACR] ≥ 200 and ≤ 5000 mg/g), with or without T2DM, on stable and maximum-tolerated daily dose of ACE-I or ARB.

The study was designed to test the hypothesis that dapagliflozin is superior to placebo for the prevention of progression of CKD and renal or CV death, as measured by the primary composite endpoint of ≥ 50% sustained decline in eGFR, ESRD (sustained eGFR < 15 mL/min/1.73 m^2, chronic dialysis or renal transplant), and renal or CV death when added to current background therapy. The secondary endpoints were (1) the composite of ≥ 50% sustained decline in eGFR, ESRD, and renal death, (2) the composite of hospitalisation for HF and CV death, (3) all-cause mortality. The safety objective was to evaluate the safety and tolerability of dapagliflozin in the target patient population.

DAPA-CKD was an event-driven study. It was planned to observe 681 primary endpoint events in order to provide a statistical power of 90% for the primary endpoint, assuming a true HR of 0.78 and based on a one-sided alpha of 0.025. The DMC recommended to stop the trial early following a routine assessment of study data, based on positive efficacy results.

In the study, 4304 patients were randomised at 386 study sites in 21 countries: 2152 in the placebo group and 2152 in the dapagliflozin group.

Demographic and baseline patient characteristics were balanced between treatment groups. At baseline, 67.5% of patients had T2DM. Mean eGFR was 43.1 mL/min/1.73 m^2, median UACR was 949.3 mg/g, and mean systolic BP was 137.1 mmHg. In all, 14.5% of the study population had an eGFR < 30 mL/min/1.73 m^2.

7.2. Favourable effects

Dapagliflozin was superior to placebo for the primary efficacy endpoint initiated reducing the incidence of the composite primary endpoint of ≥50% sustained decline in eGFR, ESRD, and renal or CV death (HR 0.61 [95% CI 0.51, 0.72], p < 0.0001). All components contributed to the observed treatment effect. Demonstration sequential testing of the secondary efficacy endpoints.

Dapagliflozin was superior to placebo for the reduction of the secondary endpoints renal composite endpoint without CV death (HR 0.56 [95% CI 0.45, 0.68], p < 0.0001), the composite of CV death or hospitalisation for HF (HR 0.71 [95% CI 0.55, 0.92]), and all-cause mortality (HR 0.69 [95% CI 0.53, 0.88]). The effects of dapagliflozin on the primary and secondary endpoints were generally consistent across the analysed subgroups, including diabetes status, eGFR and UACR level at baseline.

Dapagliflozin also reduced exploratory variables related to progression to kidney failure, such as eGFR decline over time and time to ≥ 30 and ≥ 40% decline in eGFR. Additionally, dapagliflozin reduced the incidence of acute worsening in kidney function (evaluated by doubling of serum creatinine between visits) and reduced risk markers for progressive kidney failure, such as UACR and SBP during the study.

7.3. Uncertainties and limitations about favourable effects

Statistical methods applied are in general acceptable. Given the compelling efficacy results, the decision for early stop seems reasonable, however, without any consideration of its impact on evaluability of the safety data and disregarded from the uncertainties around the informal statistical analyses. The explanation of the circumstances around the early stop showed that the decision to perform an early efficacy analysis was made based on unblinded descriptive analysis of the primary composite endpoint, which was not part of the safety review according to the DMC charter. The unplanned early stop has therefore implications on the interpretation of statistical significance of the primary and secondary endpoints, and the appropriate way of presentation of these endpoints in the SmPC. In this respect, p-values for the secondary endpoints "Composite of cardiovascular death and hospitalisation for heart failure" and "All-cause mortality" are considered nominal due to the early stop.

Roughly 200 patients with diabetes in each treatment group were not judged to have diabetic nephropathy as the main cause of their kidney disease. The Applicant has reviewed data for the primary and secondary endpoints in patients with T2D according to the adjudicated cause of their CKD aetiology. The fact that there were few events in the non-DKD group for the all endpoints limits the interpretation of the data. The treatment effect of dapagliflozin seems to be consistent between the CKD aetiology categories diabetic and non-diabetic nephropathy for the primary endpoint and all secondary endpoints.

Patients in the lower systolic blood pressure category (<130 mmHg) had a higher reduction of the primary endpoint, vs those with higher SBP (>130 mmHg). Of note, several main categories of CKD and CV medications were less frequently used in the patients with lower SBP. Additional analyses on the primary endpoint shows that the effect of dapagliflozin was generally consistent across categories of baseline CKD or CV medication.

The reduction of the secondary endpoint CV death and hospitalization for HF was similar across demographic and baseline renal parameters but seems to be more pronounced in patients with eGFR >45 than those with eGFR <45, even though the interaction was not significant. Even though no firm conclusion can be drawn from smaller subgroup analyses due to the low number of events, a numerical benefit in favour of dapagliflozin can be seen in all subgroups. These indicates a consistent efficacy across all eGFR levels and provides no indication of a trend towards reduced efficacy with decreased renal function.

Although the benefit of dapagliflozin on the primary endpoint and secondary endpoint composite CV death and hospitalisation for HF was generally consistent across subgroups based on demographic and baseline renal parameters (eGFR (< 30, ≥ 30, < 45, ≥ 45 mL/min/1.73m2)), due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 mL/min. This is reflected in section 4.2 of the SmPC. If GFR falls below 45 mL/min, additional glucose lowering treatment should be considered in patients with diabetes mellitus if further glycaemic control is needed. This is also appropriately reflected in the SmPC.

The new claimed indication concerns all patients with CKD, independent of the aetiology. Patients with active inflammatory and immunosuppressive treatments where excluded from the trial, so were patients with T1D and PKD. The fact that the pathophysiology of CKD in these aetiologies share the same mechanism, namely glomerular hyperfiltration, makes dapagliflozin a plausible drug candidate, even if data from the DAPA-CKD study concerning these aetiologies is very limited. The exclusion of patients with T1D is acknowledged and addressed in SmPC section 4.4.
Only patients with albuminuria levels ≥200 mg/g have been included in the study, as a prognostic enrichment factor and not due to any expectation that dapagliflozin would have less efficacy in patients without albuminuria. As SLGT-2 mediated nephroprotection is not only based on the reduction of albuminuria levels, it seems plausible that patients without albuminuria might benefit from treatment with dapagliflozin (albeit likely to a less extent). There is no experience with dapagliflozin for the treatment of CKD in patients without T2DM who do not have albuminuria. As it is expected that the effect of dapagliflozin correlates to the degree of albuminuria and that patients with albuminuria may benefit more of the treatment, this is reflected in the SmPC. Treatment with dapagliflozin in the DAPA-CKD study was in conjunction with ARB/ACEi. This is also reflected in section 4.2 of the SmPC.

7.4. Unfavourable effects

The evaluation of the DAPA-CKD study provides information on the safety profile of dapagliflozin in subjects with chronic kidney disease (eGFR ≥25 and ≤75 mL/min/1.73 m^2) with albuminuria. The study population included patients with T2DM (70%) and without diabetes (30%).

In the study DAPA-CKD, 2,149 subjects were treated with dapagliflozin for a total exposure of 4,448 PY, regardless of interruptions (i.e. 'on and off' treatment), with 1,865 subjects (87%) for at least 52 weeks and 1423 subjects (66%) for at least 2 years. The mean and median duration of exposure was 24.8 and 27.3 months for dapagliflozin and 24.3 and 27.0 months for placebo. The median duration of follow-up was 27.1 months for dapagliflozin.

The number of fatal cases (3.1% vs 4.0%), including SAEs (28% vs 31%), was lower in the dapagliflozin group than in the placebo group.

The incidence of SAEs of *UTIs* was increased for dapagliflozin versus placebo (1.3% vs 0.8%), of which the majority of subjects (79%) were in the subgroup with T2DM.

Three SAEs of *genital infection*s in subjects with T2DM were reported, all in the dapagliflozin group (0.1% vs 0%).

Events of *volume depletion* was reported more frequently with dapagliflozin (5.6%) than with placebo (3.9%). The incidence of SAEs of volume depletion was 0.7% for dapagliflozin and placebo, respectively.

Renal events occurred more frequently in the placebo group (7.9%) than in the dapagliflozin group (6.7%), including SAEs of renal events (3.2% and 2.5% for placebo and dapagliflozin).

Fractures were reported for 4.0% of patients in the dapagliflozin group and 3.2% in the placebo group, corresponding to an event rate of 1.75 and 1.43 events per 100 patient-years. The Kaplan-Meier plot indicates a slightly increase in fractures with dapagliflozin after about 20 months of treatment. The incidence of osteoporotic fractures was balanced between the groups (1.2% vs 1.1%) and location of the fractures varied with no specific pattern. Among subjects with osteoporotic fractures in the dapagliflozin group, low trauma fractures were reported in 50%, high trauma in 12% and unclear whether high or low in 38% of the fractures. In the placebo group, 43% high trauma, 9% low trauma and 48% unknown/unclear fractures were reported.

The incidence of subjects who underwent at least 1 surgical *amputation* (1.6% and 1.8%) and the event rate (0.72 vs 0.81 events per 100 PY) was balanced between dapagliflozin and placebo. All events of amputations were in the lower limbs, apart from one event in the upper limbs (in the placebo group). There were numerically more subjects in the placebo group (n=20; 51%) than in the dapagliflozin group (n=13; 36%) with major amputations (below knee and above knee). All patients with amputations, except one in the placebo group, were T2DM patients.

In total 2 subjects had an event adjudicated as a definite *DKA*, both in the placebo group. Both cases were reported for patients with T2DM and eGFR ≥45 mL/min/1.73 m^2, neither of them had a fatal outcome.

Major hypoglycaemic events

In the DAPA-CKD study only major hypoglycaemic events were collected. Subjects with major hypoglycaemic events were slightly more common in the placebo (1.3%; n=28) than in the dapagliflozin group (0.7%; n=14). Six cases (0.3%) in the dapagliflozin group and 14 (0.7%) in the placebo group were serious. All subjects with major hypoglycaemic events had T2DM at baseline and the majority were using antidiabetic agents (sulfonylureas or insulin, or a combination) at the time of event.

Laboratory findings/ vital signs

The eGFR decreased over time in both the dapagliflozin and the placebo group. The change in eGFR was initially (within 2 weeks) and up to 16 weeks of treatment more pronounced for dapagliflozin compared to placebo (-6.5% vs -1.7%); however, the decrease in eGFR was larger in the placebo from 16 weeks and onwards.

The decline in SBP and DBP from baseline in the dapagliflozin group was most pronounced early in the study, at Day 14 (-4.6 mmHg and -2.1 mmHg) and up to 2 months of treatment (-4.4 mmHg and -1.9 mmHg). Thereafter, SBP and DBP tended to increase, except for a slight decrease in SBP and DBP at month 24 and 28.

Subgroups

Effect by age

In general, the safety profile for patients ≤ 65 and >65 years of age was in line with that for the overall population; however, renal events were slightly more frequently common for dapagliflozin (9.2%) than for placebo (8.1%) in subjects >65 years.

The incidence of fractures was increased for dapagliflozin versus placebo in subjects ≤65 years (3.5% vs 2.0%); however, balanced in subjects >65 years of age (4.5% vs 4.8%).

Effect by sex

Subgroup analysis by sex was performed for amputations and fractures. The number of subjects with amputations was similar between males (1.7% vs 2.1%) and females (1.4% vs 1.3%) treated with dapagliflozin versus placebo and was in line with the overall population.

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 7.3% vs 4.4% (SAEs: 0.8% vs 0.5%) in subjects <130 mmHg and 4.6% vs 3.6% (SAEs: 0.7% vs 0.8%) 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 (31%), including eGFR <30 mL/min/1.73 m^2 subgroup (35%), compared to the eGFR ≥45 mL/min/1.73 m^2 (28%); although, the incidence was higher in the placebo group vs the dapagliflozin group in all subgroups.

Renal events (14.3% vs 11.8%), including serious renal events (6.5% vs 5.1%) were more common in subjects with eGFR <30 mL/min/1.73 m^2 treated with dapagliflozin than with placebo. The most frequently reported event was renal impairment (7.5% vs 5.4%).

Initially there was a decrease in eGFR in the dapagliflozin group compared with placebo group, across all subgroups. Over time, the eGFR declined more in the placebo group than in the dapagliflozin group. The pattern was similar across the eGFR subgroups (eGFR ≥45 vs <45 and eGFR ≥30 vs <30, respectively); however, the magnitude of the initial decrease in eGFR was more pronounced in the subgroups with higher baseline eGFR (≥45 and ≥30) compared with the subgroups with lower baseline eGFR (<45 and <30). The DAPA-CKD study did not include any follow-up of eGFR after discontinuation of treatment.

Treatment with dapagliflozin was associated with a greater reduction in UACR for dapagliflozin compared with placebo across the subgroups; eGFR ≥45 vs <45 and eGFR ≥30 vs <30, respectively. The difference in UACR between dapagliflozin and placebo was maintained throughout the duration of the study. The frequency of ESRD was increased in the subgroups eGFR <45 (7.9% vs 10.5%) and eGFR <30 (16.7% vs 21.8%) compared with the subgroups eGFR ≥45 (1.0% vs 3.3%) and eGFR ≥30 (3.2% vs 4.9%); however, the frequency of ESRD was higher in the placebo group compared with the dapagliflozin group across the subgroups.

Effect of T2DM

The incidence of SAEs was higher in the T2DM subgroup (34%) compared with the non-diabetes subgroup (21%); however, the incidence was higher in the placebo group versus dapagliflozin in both subgroups.

7.5. Uncertainties and limitations about unfavourable effects

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 increase in fractures could be caused by an increased number of falls related to dapagliflozin-induced symptoms of volume depletion (e.g. dizziness/ hypotension); however, only 2 patients reported AE of symptoms of volume depletion prior to the fracture in the dapagliflozin group. It is not possible to draw any firm conclusions on the incidence of high vs low trauma fractures in the study since a substantial amount of the reports was lacking information on this point.

The incidence of renal events, including SAEs renal events, was increased in subjects with eGFR <30 mL/min/1.73 m^2 treated with dapagliflozin compared with placebo. Moreover, adverse events leading to dose reductions and interruptions were increased for dapagliflozin compared with placebo. There is no experience in initiation of treatment with dapagliflozin in patients with eGFR <25 mL/min. Dapagliflozin is not recommended for initiation in patients with eGFR <25 mL/min.

7.6. Effects Table

Table 2. Effects Table for dapagliflozin and CKD

Effect	Short description	Unit	Treatment (DAPA)	Control (Plc)	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary composite endpoint						
Primary composite endpoint	first occurrence (1) ≥50% eGFR decline (2) ESRD (3) renal death **or** CV death	n (%)	197 (9.2)	312 (14.5)	HR (95% CI) 0.61 (0.51, 0.72) p < 0.0001	DAPA-CKD study
Secondary composite endpoints						
Secondary composite endpoint	(1) ≥50% eGFR decline (2) ESRD (3) **and** death	n (%)	142 (6.6)	243 (11.3)	HR (95% CI) 0.56 (0.45, 0.68) p < 0.0001	DAPA-CKD study
Secondary composite endpoint	(1) CV death (2) **and** hospitalisation for HF	n (%)	100 (4.6)	138 (6.4)	HR (95% CI) 0.71 (0.55, 0.92)	
Secondary composite endpoint	Death from any cause	n (%)	101 (4.7)	146 (6.8)	HR (95% CI) 0.69 (0.53, 0.88)	
Individual primary and secondary endpoint components						
≥ 50% decline in eGFR		n (%)	112 (5.2)	201 (9.3)	HR (95% CI) 0.53 (0.42, 0.67)	DAPA-CKD study
ESRD	• eGFR < 15 ml/min/1.73 m^2 • Chronic dialysis • Receiving renal transplant	n (%)	109 (5.1)	161 (7.5)	HR (95% CI) 0.64 (0.50, 0.82)	
Renal death		n (%)	2 (<0.1)	6 (0.3)		
CV death		n (%)	65	80	HR (95% CI)	

Effect	Short description	Unit	Treatment (DAPA)	Control (Plc)	Uncertainties / Strength of evidence	References
			(3.0)	(3.7)	0.81 (0.58, 1.22)	
Hospitalisation for HF		n (%)	37 (1.7)	71 (3.3)	HR (95% CI) 0.51 (0.34, 0.76)	
Unfavourable Effects						
Any SAE	On-treatment	n (%)	594 (27.6)	674 (31.4)		DAPA-CKD study
Any event of symptom of volume depletion		n (%)	120 (5.6)	84 (3.9)		
Any renal AE		n (%)	144 (6.7)	169 (7.9)		
Any fracture		n (%)	85 (4.0)	69 (3.2)		
Any major hypoglycaemic event		n (%)	14 (0.7)	28 (1.3)		
Any definite or probable DKA		n (%)	0	2 (0.1)		
Any amputation		n (%)	35 (1.6)	39 (1.8)		
Effect of T2DM						
Any SAE						
with T2DM		n (%)	453 (31.2)	521 (35.9)		
without T2DM		n (%)	141 (20.3)	153 (21.9)		
Volume depletion						
with T2DM		n (%)	86 (5.9)	65 (4.5)		
without T2DM		n (%)	34 (4.9)	19 (2.7)		
Renal events						
with T2DM		n (%)	113 (7.8)	131 (9.0)		
without T2DM		n (%)	31 (4.5)	38 (5.4)		
Fractures						
with T2DM		n (%)	65 (4.5)	51 (3.5)		
without T2DM		n (%)	20 (2.9)	18 (2.6)		
Amputations						
with T2DM		n (%)	35 (2.4)	38 (2.6)		
without T2DM		n (%)	0	1 (0.1)		
Effect of renal function						
Any SAEs						
eGFR ≥45		n (%)	222 (25.3)	268 (29.7)		
eGFR <45		n (%)	372 (29.3)	406 (32.5)		
eGFR <30		n (%)	101 (34.5)	138 (41.7)		

Effect	Short description	Unit	Treatment (DAPA)	Control (Plc)	Uncertainties / Strength of evidence		References
Volume depletion							
eGFR ≥45		n (%)	47 (5.3)		35 (3.9)		
eGFR <45		n (%)	73 (5.7)		49 (3.9)		
eGFR <30		n (%)	13 (4.4)		14 (4.2)		
Renal events							
eGFR ≥45		n (%)	41 (4.7)		58 (6.4)		
eGFR <45		n (%)	103 (8.1)		111 (8.9)		
eGFR <30		n (%)	42 (14.3)		39 (11.8)		
Fractures							
eGFR ≥45		n (%)	25 (2.8)		26 (2.9)		
eGFR <45		n (%)	60 (4.7)		43 (3.4)		
eGFR <30		n (%)	11 (3.8)		15 (4.5)		
Amputations							
eGFR ≥45		n (%)	18 (2.0)		24 (2.7)		
eGFR <45		n (%)	17 (1.3)		15 (1.2)		
eGFR <30		n (%)	3 (1.0)		4 (1.2)		

7.7. Benefit-risk assessment and discussion

7.7.1. Importance of favourable and unfavourable effects

CKD is a serious and progressive condition that is associated with CV disease and increased risk of adverse outcomes. The most common cause of CKD is diabetes. Despite widespread use of ARBs or ACEi, patients with CKD, including those with diabetes, remain at high risk of developing ESRD and/or experiencing CV events. Dapagliflozin, on top of an ARB or ACEi, resulted in a statistically significant and clinically relevant 40% reduction in the risk of the primary composite endpoint of ≥ 50% sustained decline in eGFR, ESRD and renal or CV death compared to placebo. Analyses of secondary renal (45% reduction of eGFR), CV composite (30% reduction) endpoints and all-cause mortality (30% reduction) also showed positive results.

Although the benefit of dapagliflozin on the primary endpoint and secondary endpoint composite CV death and hospitalisation for HF was generally consistent across subgroups based on demographic and baseline renal parameters (eGFR (< 30, ≥ 30, < 45, ≥ 45 mL/min/1.73m2)), due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR < 25 mL/min. This is reflected in section 4.2 of the SmPC. If GFR falls below 45 mL/min, additional glucose lowering treatment should be considered in patients with diabetes mellitus if further glycaemic control is needed. This is also appropriately reflected in the SmPC.

The results were similar in CKD patients with and without T2DM and across analysed subgroups, including parameters that reflect acute worsening in kidney function and progression of kidney failure. Of note, there was a trend towards less effect in patients within the lower eGFR categories, but the effect in these groups is still considered to be of clinical relevance.

A similar reduction of the primary composite endpoint in the dapagliflozin group was seen in the different subgroups of CKD aetiologies included in the study. However, other aetiologies leading to CKD such as T1DM, PKD, inflammatory and immunological diseases were excluded from the study. The fact that the pathophysiology of CKD in these aetiologies share the same mechanism makes dapagliflozin a plausible drug candidate, even if data from the DAPA-CKD study concerning these aetiologies is very limited. The exclusion of patients with T1D is acknowledged with addition of text to SmPC section 4.4.

Only patients with overt albuminuria levels > 200 mg/g have been included in the study. In a scientific advice, a lower inclusion limit of UACR 200 mg/g in the DAPA-CKD study was agreed as a prognostic enrichment strategy to select patients at higher risk of experiencing a disease related-endpoint event and not due to any expectation that dapagliflozin would have less efficacy in patients without albuminuria. The published literature elucidates the pathophysiological processes behind the development and progression of CKD and suggests other potential effects of SGLT2 inhibition, besides reduction of albuminuria. This supports the potential benefit of dapagliflozin in patients with CKD and without albuminuria. However, it is expected that the effect of SGLT2 inhibitor treatment is less pronounced in subjects without albuminuria. This is stated in the SmPC.

No new safety concerns arise from the data provided compared to what is previously known concerning the safety profile for dapagliflozin. In the overall population and in the additional subgroup analyses based 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.

There was no indication of worsening the safety profile with declining renal function, except for subjects with eGFR <30 mL/min/1.73 m^2 where the incidence of renal events and AEs leading to dose reductions and dose interruptions were increased for dapagliflozin relative to placebo; however, AEs leading to discontinuation were slightly more frequent in placebo than in the dapagliflozin group.

With regards to safety in the subgroup with eGFR 25-30 (n=624), the absolute number of events was low and therefore difficult to draw any firm conclusions. Treatment in this subgroup was beneficial (HR 0.73; 0.43-1.02).
Therefore, the benefit risk balance in subjects with eGFR 25-30 is considered positive. There is no experience in initiation of treatment with dapagliflozin in patients with eGFR <25 mL/min. Dapagliflozin is not recommended for initiation in patients with eGFR <25 mL/min.

Balance of benefits and risks

Overall, positive effects of dapagliflozin treatment in patients with CKD as represented by the study population of the DAPA-CKD study was documented. Although there is no clinical evidence generated by phase 3 clinical trials of dapagliflozin on kidney outcomes in patients without albuminuria, based on the mechanism of action, a beneficial effect is also expected in this population.

Since no new safety concerns arise from the data provided and as the known risks with dapagliflozin are considered manageable, the beneficial effects outweigh the risks in patients with CKD (with and without T2DM).

7.8. Conclusions

The overall benefit risk balance of Forxiga and Edistride for the proposed new indication *in adults for the treatment of chronic kidney disease* is considered positive.