EMA/476671/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Forxiga	dapagliflozin
Xigduo	dapagliflozin / metformin
Edistride	dapagliflozin
Ebymect	dapagliflozin / metformin

Procedure No. EMEA/H/C/xxxx/WS/1539

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
ACM	All-cause mortality
ADA	American Diabetes Association
AE	Adverse event
AEoSI	Adverse event of special interest
BP	Blood pressure
CEC	Clinical Event Adjudication Committee
CI	Confidence interval
CrCl	Creatinine clearance
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTD	Common Technical Document
CV	Cardiovascular
DAE	AE leading to discontinuation of study drug
DKA	Diabetic ketoacidosis
EASD	European Association for the Study of Diabetes
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESRD	End stage renal disease
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (US Department of Health and Human Sciences)
GCP	Good clinical practice
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated haemoglobin
HF	Heart failure
HR	Hazard ratio
ICF	Informed consent form

Abbreviation or special term	Explanation
LDL	low-density lipoprotein
MACE	Major adverse CV events
MI	Myocardial infarction
OT-SAS	On-treatment safety analysis set
PASS	Post-authorisation safety study
PBRER	Periodic benefit-risk evaluation report
PMR	Post-marketing requirement
RMP	Risk Management Plan
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety analysis set
SGLT2	Sodium-glucose cotransporter 2
SmPC	Summary of Product Characteristics
TIMI	Thrombolysis in Myocardial Infarction
T2DM	Type 2 diabetes mellitus
UACR	Urine albumin-to-creatinine ratio
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 8 January 2019 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested (as initially proposed by WSA):

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

Update of sections 4.1, 4.2, 4.4, 4.8, and 5.1 of Forxiga, Edistride, Xigduo and Ebymect of the SmPC to modify the current indication for improvement of glycaemic control based on final results from study D1693C00001 (DECLARE), which is listed as a category 3 study in the RMP (Forxiga: MEA 005):
- For the prevention of new or worsening HF or CV death
- For the prevention of new or worsening nephropathy

The Package Leaflets (PL) are updated accordingly. The updated dapagliflozin Risk Management Plan (RMP) version 17 and dapagliflozin/metformin fixed dose combination (FDC) RMP version 11 have also been submitted.
In addition, the Worksharing applicant took the opportunity to correct a typo error in Edistride marketing authorisation number in section 8 of SmPC and add the latest renewal date for Xigduo in section 9 of SmPC. Besides, the lactose wording in SmPC section 4.4 has been updated in line with the updated excipient guideline. The revised PI also include proposals for minor administrative changes for consistency throughout the PI.

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

Information on Paediatric requirements

Not applicable

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 applicant 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 not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

Timetable	**Dates**
Start of procedure:	27 Jan 2019
CHMP Co-Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	21 Mar 2019
PRAC Rapporteur Assessment Report	21 Mar 2019
PRAC members comments	03 Apr 2019
Updated PRAC Rapporteur Assessment Report	04 Apr 2019
PRAC endorsed relevant sections of the assessment report [3]	11 Apr 2019
CHMP members comments	15 Apr 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 Apr 2019
Request for Supplementary Information	26 Apr 2019
MAH responses by	28 May 2019
Re-start of the procedure	29 May 2019
PRAC Rapporteur Assessment Report	3 Jun 2019
PRAC members comments	5 Jun 2019
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	11 Jun 2019
PRAC Outcome	13 Jun 2019
CHMP members comments	17 Jun 2019
Updated CHMP Rapporteur Assessment Report	20 Jun 2019

Opinion	27 Jun 2019

2. Scientific discussion

2.1. Introduction

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. Dapagliflozin is approved in the European Union (EU) since November 2012 (FORXIGA: EMEA/H/C/002322; EDISTRIDE: EMEA/H/C/004161). Dapagliflozin can be given as monotherapy or in combination with other medicinal products indicated for the treatment of T2DM.

XIGDUO/EBYMECT (dapagliflozin/metformin immediate release) combines dapagliflozin and metformin in a fixed-dose combination (FDC) tablet designed to be administered twice daily. The XIGDUO FDC was first approved for the treatment of T2DM in the EU on 16 January 2014 and the EBYMECT FDC was approved on 16 November 2015.

This application is based on the recently completed Phase IIIb study D1693C00001/DECLARE-TIMI 58 (hereafter referred to as 'DECLARE'). DECLARE evaluated the effect of dapagliflozin compared to placebo on cardiovascular (CV) and renal outcomes in a broad T2DM population with or without established CV disease. DECLARE was a Category 3 post-authorisation safety study (PASS) in the EU (PAM 005) and was designed to address post-marketing requirements in the US.

In the EU, the PASS requirement was that DECLARE be designed to evaluate bladder cancer. Other potential safety concerns that the European Medicines Agency (EMA) requested be assessed were clinical consequences of increased haematocrit, renal impairment/failure, bone fracture, liver injury, breast cancer, prostate cancer, diabetic ketoacidosis (DKA), amputations, and pancreatitis. Some of these requests were made while the study was ongoing.

In addition to addressing these safety concerns, the MAH also seeks to modify the current indication for improvement of glycaemic control to also allow for the use of FORXIGA/EDISTRIDE/XIGDUO/EBYMECT in adults with T2DM:

- for the prevention of new or worsening HF or CV death
- for the prevention of new or worsening nephropathy.

Updates are proposed to the Summary of Product Characteristics (SmPC) and Risk Management Plan (RMP) based on the assessment of DECLARE data.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1

Type of study	Study identifier	Location of study report in Module 5	Objective(s) of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Controlled Clinical Studies									
Safety and Efficacy	D1693C00001 (DECLARE)	5.3.5.1	Safety and Efficacy	Phase IIIb, Multi-centre, randomised, double-blind, placebo-controlled	-Dapagliflozin 1 x 10 mg once daily -Matching placebo 1 x tablet once daily Oral administration	17160[a]/17143	Adult (≥40 years) with T2DM and either (1) established CV disease, or (2) multiple CV risk factors in addition to T2DM[b]	4-8 week placebo run-in, 4.2 years[c] randomized treatment	Complete; Full

[a] 30 patients were randomised at site 5709 (bringing the total number of randomised patients to 17190) that is suspected for GCP violations in another AstraZeneca-sponsored study. It was decided prior to unblinding to exclude these patients from all analyses; these patients are not included in the number of randomised patients provided in this table

[b] Multiple CV risk factors defined as age >55 years for men, ≥60 for women, and at least one of the following: dyslipidaemia, hypertension, or current tobacco use

[c] Median

T2DM Type 2 diabetes mellitus; CV Cardiovascular; GCP Good clinical practice

2.4. Clinical efficacy

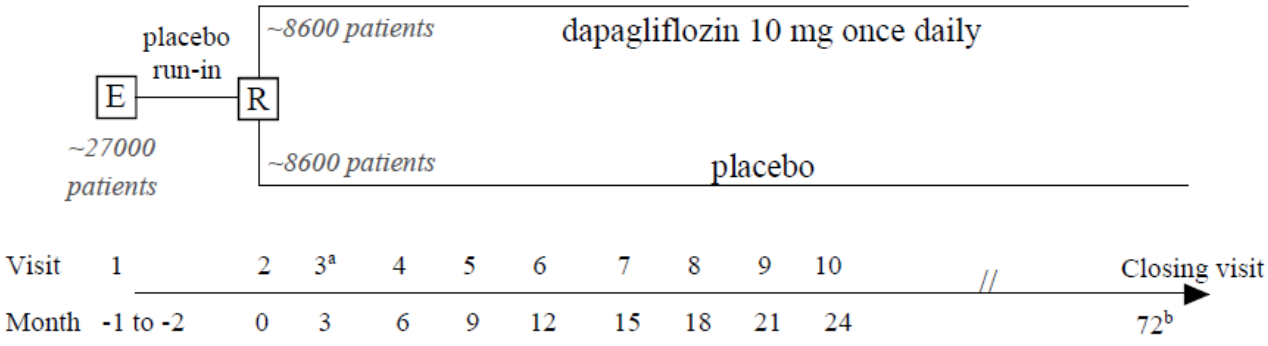
2.4.1. Main study

Dapagliflozin Effect on Cardiovascular and Renal Outcomes in Patients with Type 2 Diabetes Mellitus with and without Established Cardiovascular Disease (DECLARE)

Methods

This was a multi-centre, randomised, double-blind, placebo-controlled Phase IIIb study to evaluate the effect of dapagliflozin on CV and renal outcomes in patients with T2DM with or without established CV disease.

Figure 1 Study design



E = Enrolment, R = Randomisation

[a] Visit 3 and every other visit thereafter (ie, Visit 3, 5, 7 etc) were conducted by phone contact, with the option to do a site visit instead if requested by the patient.

[b] The study was event-driven. The enrolment period lasted for approximately 2 years and the follow-up period for approximately 3 to 5 years.

Study participants

No substantive alterations of eligibility criteria were made after start of patient recruitment. Following a CSP amendment, the proportion of patients with an HbA1c between 6.5% and <7.0% was capped at approximately 5%.

Key inclusion criteria

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

Female or male aged ≥40 years, diagnosed with T2DM with a high risk for CV event defined as having either established CV disease and/or multiple risk factors. Patients with no known CV disease should have at least 2 CV risk factors in addition to T2DM, defined as: Age (>55 years in men and >60 in women) and the presence of at least 1 of the following additional risk factors – dyslipidaemia, hypertension or current tobacco use.

Key exclusion criteria

Exclusion criteria were applied to limit bias and ensure patient safety. Key exclusion criteria included:

- Recent acute CV event, or systolic BP >180 or diastolic BP >100 mmHg
- History of bladder cancer, history of other malignancy within 5 years
- Haematuria with no explanation as judged by the investigator
- HbA1c ≥12% or HbA1c <6.5% from the central laboratory
- Creatinine clearance (CrCl) <60 mL/min (based on the Cockcroft-Gault equation)

Exclusion criteria for CV history and hypertension were included to limit data skewing due to a large contribution of primary endpoint events from a high-risk patient subpopulation. Criteria relating to bladder cancer were included to ensure robust and unbiased evaluation of bladder cancer safety information. Patients considered unlikely to be compliant or unlikely to complete the study were also excluded.

Treatments

During the placebo run-in period, the treatment regimen for all patients was:

- Placebo administered orally once daily for 4 to 8 weeks

During the double-blind treatment period, the doses and treatment regimens were:

- Dapagliflozin 10 mg tablets, administered orally once daily until the end of the study (predicted median duration of treatment period 4.5 years)
- Matching placebo for dapagliflozin 10 mg administered orally once daily until the end of the study (predicted median duration of treatment period 4.5 years)

The study drug was to be taken once daily in the morning and at approximately the same time of the day during the study period.

Objectives

Primary objective

The primary objective was to determine the effect of dapagliflozin relative to placebo on CV outcomes when added to current background therapy in patients with T2DM with either established CV disease or at least 2 CV risk factors.

Secondary objectives

The secondary objective was to determine whether treatment with dapagliflozin compared with placebo when added to current background therapy in patients with T2DM with either established CV disease or at least 2 CV risk factors in addition to T2DM will result in a reduction of renal events or all-cause mortality.

Outcomes/endpoints

Primary efficacy variable:

The co-primary outcome variables of the study are the composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke (time to first event) and the composite endpoint of hospitalization for heart failure or CV death (time to first event). All components of these composites will be adjudicated.

Primary safety variable:

The primary safety variable is the composite endpoint of cardiovascular death, MI or ischemic stroke (time to first event).

Secondary efficacy variables:

- Renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m^2 (using CKD-EPI equation) and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15ml/min/1.73m^2) and/or renal or CV death (time to first event)
- All-cause mortality (time to event)

Exploratory efficacy variables:

- The individual components of the co-primary endpoints (cardiovascular death, MI, ischemic stroke, and hospitalization for heart failure) (time to first event)
- The composite endpoint of cardiovascular death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary or non-coronary revascularization and the additional individual components of hospitalization for unstable angina pectoris and hospitalization for coronary or noncoronary revascularization (time to first event)
- HbA1c
- Initiation of insulin therapy in patients not receiving insulin therapy at baseline
- Need for an increase in dose for oral anti-diabetes medication or ≥25% increase in insulin dose for ≥3 months or addition of new anti-diabetes medication
- Major hypoglycaemia and/or hospitalization for hypoglycaemia
- Development of confirmed sustained macroalbuminuria (UACR ≥300 mg/g) in subjects without macroalbuminuria at baseline (time to first event)
- Development of confirmed sustained albuminuria in patients without albuminuria at baseline (UACR ≥30 mg/g; time to first event)
- Regression in sustained confirmed albuminuria (defined in three ways: 1. Baseline microalbuminuria to normoalbuminuria, 2. Baseline macroalbuminuria to microalbuminuria, 3. The previous two combined) (proportions)
- eGFR (sustained confirmed decrease ≥30% to sustained confirmed eGFR <60 ml/min/1.73m^2 using CKD-EPI equation; time to first event)
- eGFR (sustained confirmed decrease ≥40% to sustained confirmed eGFR <60 ml/min/1.73m^2 using CKD-EPI equation; time to first event)
- Albumin to Creatinine Ratio (adjusted mean percent change after 2 and at 3 years)
- Change in body weight at 2 years and at 3 years
- Proportion of patients with 5% body weight loss and 10 % body weight loss after 2 years and after 3 years
- Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy
- Blood pressure change from baseline
- Peripheral revascularization/limb ischemic event
- Surgical amputation and related events
- Any stroke (ischemic, haemorrhagic, or undetermined)

Sample size

The sample size was primarily determined based on the MACE superiority objective; 1390 primary events were required to have 85% power to demonstrate superiority of dapagliflozin to placebo if the true HR

was 0.85, i.e., a 15% relative risk reduction using a one-sided alpha of 2.31%. To achieve this number of primary events, 17150 randomised patients were required for the study assuming 33% was to be from a primary prevention population and 67% from a secondary prevention population with assumed annual event rates of 1.0% and 2.6% respectively on placebo, and an annual withdrawal rate of 1.0% over a 3-year accrual period and 3-year minimum follow-up.

With study protocol amendment 3 (28 April 2014), the enrolment target was increased from approximately 22,000 to 27,000 to ensure a sufficient number of randomised patients as the screen failure rate was higher than expected (estimated to 35% instead of 22%).

With amendment 3, the aim also became to continue recruitment allowing patients to be included with no exact proportions defined regarding primary and secondary prevention. As of 28 April 2014, 9285 patients had been randomised and the proportion of patients randomised from the primary and secondary populations were approximately 60% (instead of 33%) and 40% (instead of 67%), respectively.

The assumptions initially made were changed to read; an assumed annual event rate of 2.1% on placebo.

With these assumptions and 1390 MACE events collected, the study was estimated to have >99% power to test the hypothesis of non-inferiority of dapagliflozin to placebo (H0:HR [dapa:placebo] ≥1.3 vs. H1:HR <1.3).

Initially, the study had a single primary endpoint (MACE). With study protocol amendment 5 (25 September 2016), a composite endpoint of hospitalisation for HF and CV death was added as an additional primary efficacy variable. Using the above sample size and assumptions for study withdrawal and follow-up, approximately 770 events were expected of the composite of CV death and hospitalisation for HF; collection of 770 events would provide 87% power to detect a HR of 0.80 with a 1-sided α of 2.31%.

Randomisation

To help identify non-adherent patients, the study included a 4 to 8-week placebo run-in period (+ 14 days) starting at Visit 1. Randomisation was performed via an IVRS/IWRS at Visit 2 in balanced blocks to ensure approximate balance between the two treatment arms (1:1).

Randomisation was stratified by CV risk category (established CV disease; multiple risk factors without established CV disease) and baseline haematuria status. Enrolment of patients based on disease state, geographic region, and gender were to be monitored and could be capped to ensure adequate representation; recruitment was e.g. to be monitored to randomise approximately 30% of patients each from North America and Europe.

With amendment 2 (19 December 2013), the proportion of patients with HbA1c >6.5% to <7.0% was to be capped at 5% to allow for a broad representation of patients with different levels of glycaemic control.

With study protocol amendment 3 (28 April 2014) it was implemented that the proportions of patients with established CV disease vs. CV risk factors were to be monitored both overall and by region. This was to ensure that at least approximately 33% of randomised patients overall had established CV disease, and to avoid large differences between regions. The overall proportions of patients with established CV disease vs. CV risk factors were not to be precisely defined but based on randomisation so far it was expected that approximately 33% would have established CV disease.

Blinding (masking)

The run-in was performed single-blind and the randomised treatment period was performed double-blind. Masking of treatments was to be achieved using matching placebo; the active tablets and the respective placebo tablets were to be identical in size, colour, smell, and taste. The bottles with investigational products were labelled with unique identification numbers allocated from the IVRS/IWRS.

The primary and secondary CV efficacy variables were adjudicated by a blinded independent Clinical Event Adjudication Committee (CEC). The purpose of the CEC was to adjudicate reported and suspected CV endpoint events and selected safety events in a consistent and unbiased manner.

An independent Data Monitoring Committee (DMC) regularly monitored the progress of the study and was responsible for safeguarding the interests of the patients in the study, reviewing the safety of the study drug and the overall conduct of the study, and for determining whether stopping criteria were met during the interim analyses. The DMC were to be provided with fully or partially unblinded data at regular intervals to fulfil their review commitment as specified in the DMC charter.

Statistical methods

Study D1693C00001 (DECLARE) had a group sequential design with two interim analyses. The appointed DMC was responsible for assessing the data at the two interim analyses, occurring when 1/3 and 2/3 of the primary events had accumulated, and make recommendations based upon stopping guidelines. Using O-Brian Fleming boundaries, a one-sided alpha of 2.31% was used for the final analysis.

The primary efficacy variables were the time to first event included in the composite endpoint of CV death, MI or ischemic stroke and the time to first event included in the composite of hospitalization for heart failure and CV death. The composite endpoint of HF hospitalisation and CV death was added as an additional primary efficacy variable while the study was ongoing (amendment 5, see Study conduct).

Description of analysis sets

Full analysis set

The FAS included all randomised patients, irrespective of protocol adherence and continued participation in the study. Patients were analysed according to their randomised study drug assignment, irrespective of whether an event occurred before or after discontinuation of study drug. Patients who withdrew consent or were lost to follow-up for vital status were included up to the date of their study termination, except for vital status known through public records (for use in analysis of all-cause mortality).

The FAS was considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables.

On-treatment full analysis set

The OT-FAS included all randomised patients irrespective of protocol adherence, and only observations collected during treatment with study drug or within a certain number of days of the last dose of study drug:

- Primary and secondary variables: within 30 days of last dose of study drug
- eGFR (as exploratory efficacy variable): within 7 days of last dose of study drug

As for the FAS for the full study period, patients were analysed according to their randomised study drug assignment. The on-treatment safety analysis set (OT-SAS) was used for sensitivity analyses of the efficacy variables.

Analysis of primary and secondary endpoints

All analyses were stratified according to baseline atherosclerotic cardiovascular disease category and the presence or absence of haematuria at baseline. Stratification of analyses were performed using the stratification values as entered in IVRS to determine the randomisation assignment.

Censoring

The end of study was defined as the time of the last visit or study contact (where a clinical event assessment was performed) for each individual patient. If no event occurred for an endpoint or a patient withdrew consent, the last clinical event assessment or death (whichever was earliest) was treated as the censoring event. If none of these were available, date of last documented contact (ie, last visit) was be used for censoring. For all-cause mortality and CV death, censoring occurred at the Closing Visit for patients known to be alive, or otherwise at the date last known to be alive. If none of these were available, the date of last documented contact (ie, last visit) was used for censoring. For analysis of CV death, a patient who died of a non-CV cause (or undetermined cause) was censored at the time of death. Deaths occurring after the date of withdrawal of consent (and for patients lost to follow-up) and documented in publicly available source data was recorded in the eCRF, adjudicated if possible, and included in the analyses of deaths.

The primary efficacy analysis

The primary efficacy analysis was based on the Full Analysis Set (FAS), using events adjudicated and confirmed to meet endpoint definitions by the Clinical Event Adjudication Committee (CEC). The analysis was performed using a Cox proportional hazards model with a factor for treatment group stratified by cardiovascular risk category (established cardiovascular disease, or multiple risk factors without established cardiovascular disease), and baseline haematuria. Hazard ratios, 95% confidence intervals, and P values for time-to event analyses were reported for the primary outcomes and event rates by 1000 patient years presented.

The contribution of each component of the primary composite endpoints to the overall treatment effect were examined using methods similar to those described for the primary analysis.

HRs and CIs for overall analysis and subgroups were presented with forest plots. Kaplan-Meier estimates of the cumulative incidence to the first occurrence of any event in the primary endpoints were calculated and plotted, for the overall analysis and for the individual components. Kaplan-Meier plots, overall and by CV risk category were presented, by treatment, for the primary analyses as well as for the individual components.

A sensitivity analysis was performed using the same methods as above on the on-treatment analysis set.

The analysis of secondary endpoints

Secondary efficacy time-to-event variables were analysed in a similar manner to the primary variable.

For the secondary variable components of time to decrease of $\geq$ 40% to eGFR <60 mL/min/1.73m2 and eGFR <15 mL/min/1.73 m2, the observation needed to be confirmed by 2 central laboratory measurements separated by at least 4 weeks. Time to onset was the first of the 2 subsequent laboratory assessments. If the observation could not be confirmed, the observation was excluded from the main analysis.

Confirmatory testing procedure

A closed test procedure was used to control for overall Type I error rate across the analyses of the primary efficacy and secondary endpoints. The primary objective was evaluated in two steps where the

first step aimed to determine if dapagliflozin was non-inferior to placebo for the primary composite endpoint of CV death, MI or ischemic stroke. If non-inferiority was shown the second step aimed to show if dapagliflozin was superior to placebo on both primary endpoints: the alpha was split and testing was performed in parallel for superiority for MACE and for superiority for hospitalization for heart failure/CV death. Recycling of alpha was to be used, and if both superiority for MACE and superiority for hospitalization for heart failure/CV death had been reached, then testing was to proceed with full alpha further down the hierarchy. (Burman et al 2009).

Confirmatory testing procedures using 1-sided α

<table>
<tr><td colspan="2">H1: Non-inferiority for MACE (α=0.0231)[a]</td></tr>
<tr><td colspan="2">The α splits into independent testing of the primary composites in parallel:</td></tr>
<tr><td>H02: Superiority for MACE (α=50% of primary α)[b]</td><td>H03: Superiority for hospitalisation for heart failure or CV death (α=50% of primary α)[b]</td></tr>
<tr><td colspan="2">H04: Superiority for renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73 m^2) and/or renal or CV death[c]</td></tr>
<tr><td colspan="2">H05: Superiority for all-cause mortality[d]</td></tr>
</table>

[a] At the interim analyses, the α for superiority was replaced by 0.000095 (first interim) and 0.00614 (second interim), and no testing for non-inferiority was performed.

[b] The α was 0.01155 (50% of 0.0231) for superiority for MACE and 0.01155 (50% of 0.0231) for superiority for hospitalisation for heart failure or CV death.

[c] With the exception of all-cause mortality, secondary endpoints were only tested once. The α was controlled for the overall Type I error across the primary and secondary variables and across the interims and final analysis.

[d] All-cause mortality was assessed at interim analyses as part of the stopping guidelines. At the interim analyses, it was tested second following MACE. If the study had been stopped following an interim analysis, all-cause mortality would have remained as the 2nd endpoint following the test for superiority of MACE. Because the study ran to completion, all-cause mortality was tested as presented in this table.

CV Cardiovascular; eGFR Estimated glomerular filtration rate; ESRD End-stage renal disease; H Hypothesis; MACE Major adverse cardiovascular events

Sensitivity analyses

Sensitivity analyses to test the robustness of the primary analysis included analyses:

- Using the on-treatment full analysis set (OT-FAS)
- With censoring at a fixed calendar date (the date that the executive committee instructed the sites to commence study close-out)
- By time interval
- Of recurrent events according to the Andersen-Gill method
- Including all causes of death
- With imputed time to event information
- By tipping point

Sensitivity analysis of the primary variables with imputed time to event information.

In the primary analysis of the primary endpoints, the patients with incomplete follow-up of the endpoint events were censored at the date of last clinical assessment. A multiple imputation approach, based on missing-not-at-random assumption, was used to impute the endpoint events (missing data) between the censoring date and 21 May 2018, the date when the Executive Committee instructed the sites to

commence closing visit. Specifically, the off-treatment hazard rates from the patients who discontinued treatment but continued to be followed up were used to inform the imputation models generating time to event for the patients with incomplete follow-up. Of note, patients with endpoint events occurring prior to discontinuation of study drug were not used in imputing missing values. The estimated hazard rates and the simulations models were adjusted for CV disease history with respect to MACE and for both CV disease history and HF history with respect to hHF/CV death. Imputations were conducted separately within each treatment group.

The imputation models were based on an exponential distribution if the assumption of constant hazard rates over time was appropriate, or a piece-wise exponential distribution if this assumption is not appropriate. For either distribution, the variability in the hazard rate was incorporated by taking a random draw of the log hazard rate from a normal distribution. When a simulated time was less than the elapsed time between the original censoring date and 21 May 2018, an event was imputed for the corresponding patient with the time to event set to be the original censoring date plus the simulated time. Otherwise, the patient was censored. Imputed events and time to events were integrated with the observed data and analysed using the same statistical model as in the analyses of the dual primary variables. This was repeated 1000 times and the results were combined into overall estimates of HRs, p-values, and 95% CIs using Rubin's rules.

Sensitivity analysis of the primary variables by tipping point

A tipping point analysis was conducted to assess the robustness of the statistically significant results, i.e., inferiority in MACE and superiority in hHF/CV death. Specifically, various scenarios of the hazard rate in the dapagliflozin group, relative to that in the placebo group, were explored to find to a point where the statistical significance was lost. For the tipping point analysis, missing data were imputed for patients with incomplete follow-up of the endpoint events. Similar to the multiple imputation analysis, the estimated hazard rates and the simulations models were adjusted for CV disease history with respect to MACE, and for both CV disease history and HF history with respect to hHF/CV death. Imputations were conducted separately within each treatment group.

Exploratory efficacy variables

For e.g. the changes from baseline to each visit for HbA1c, BP, eGFR, body mass index (BMI), body weight, and albumin-to-creatinine ratio analyses were performed using a repeated measures method based on all non-missing visit data. Missing data were not imputed. The models included terms for treatment group, CV risk category, baseline haematuria, visit, visit*treatment group and baseline as covariates providing estimates of the treatment difference with 95% CI and corresponding 2-sided nominal p-value. Two-sided 95% CIs for the mean change within each treatment group were calculated.

Interim analyses

Two efficacy interim analyses were performed with the study to be considered for an early stop only if dapagliflozin provided unequivocal and overwhelming benefit compared with placebo for the occurrence of MACE and all-cause mortality. The interim analyses took place when 1/3 and 2/3 of the planned total of 1390 MACE events had occurred.

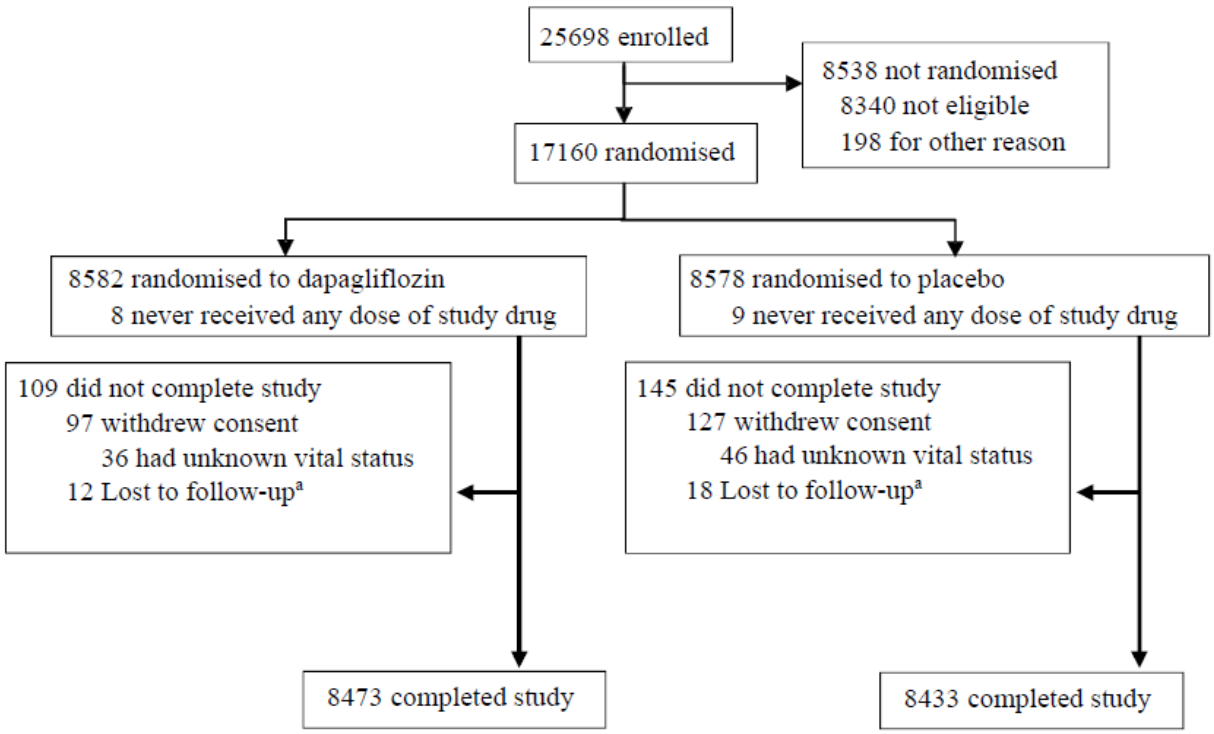
The first interim analysis had a 1-sided α level of 0.00095 and the second interim analysis had a 1-sided α level of 0.00614. At each interim analysis, MACE was to be tested at the specified α level, and if statistically significant, all-cause mortality was to be tested at the same α level. If superiority had been achieved for both endpoints, the DMC was to evaluate the CV and safety data for a decision whether justified to stop the study early. Following both interim analyses, the DMC recommended for the study to continue as planned.

Interim monitoring for bladder cancers was conducted regularly to be able to communicate potential signals with regulatory authorities. Interim analyses for bladder cancer took place after 8, 16, 24, and 32 events and additional analyses could occur at the discretion of the DMC. The interim analyses were assessed at an overall α-level of 0.10 with a Pocock spending rule.

Results

Participant flow

Figure 2 Patient disposition and study participation



Derived from: Tables 11.1.1.1 and 11.1.1.2

[a] Category is described as 'incomplete follow-up of primary endpoints' in Section 11.

Patients were considered to have completed the study if they did not withdraw consent and were not lost to follow-up.

49 patients were randomised more than once (86 incorrect additional randomisations). The enrolment codes for the additional randomisations were deleted and do not appear in the diagram above. 52 patients were enrolled and 30 were randomised at a site suspected GCP violations in another AstraZeneca-sponsored study, a decision was made prior to unblinding to exclude these patients from all analyses. These patients do not appear in the diagram above.

GCP Good clinical practice

Of the 25 698 subjects enrolled, 8 340 were not eligible for inclusion. The major reasons for not being eligible were exclusion criteria on HbA1c (5 903 patients) or renal function (CrCl <60 ml/min; 1824 patients).

Duration of follow-up

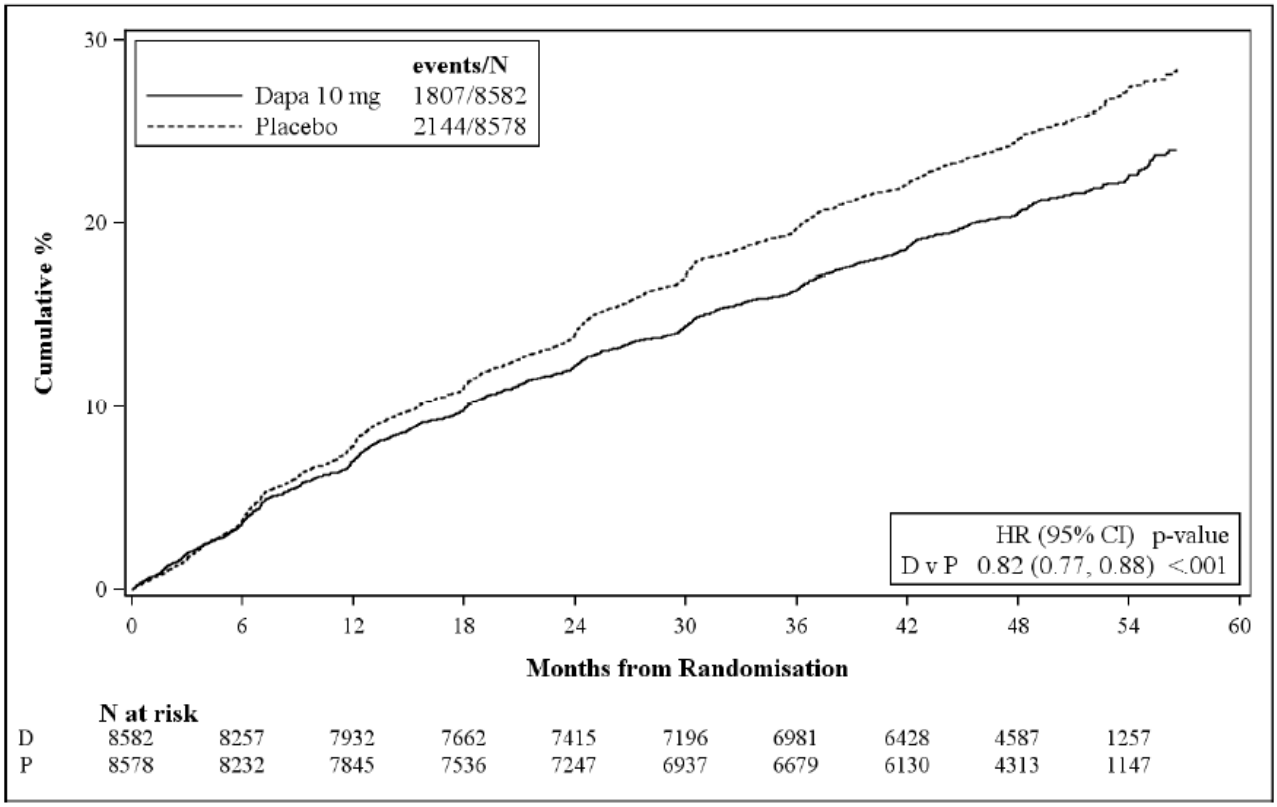
The study had a median follow-up time of 4.2 years and 16 906 (98.5%) patients had complete follow-up of the first occurrence of the primary efficacy endpoints (see Figure 2).

Completion of the study on study drug

In total, 13 181 (76.8%) patients completed the study on study drug. There were more patients prematurely and permanently discontinuing study drug in the placebo group: 1 807 (21.1%) and 2 144 (25.0%) in the dapagliflozin and placebo groups, respectively. There were 17 randomised patients who did not receive any dose of study drug (Figure 3).

All patients, including those who prematurely permanently discontinued treatment with study drug but did not withdraw consent for follow up, were to be followed up until the end of the study. There were 112 patients who had unknown vital status at the end of the study. Of these, 82 patients withdrew consent and 30 patients were lost to follow-up for vital status.

Figure 3 Kaplan-Meier plot of time from randomisation to premature permanent discontinuation of study drug (FAS)



Source: Figure 11.1.4.1

N at risk is the number of patients at risk at the beginning of the period. Event indicates premature permanent discontinuation of study drug. Patients without premature permanent discontinuation of study drug are counted as censored. 1 month corresponds to 30 days. 2-sided p-value is displayed.

CI Confidence interval; Dapa Dapagliflozin; D Dapa 10 mg; FAS Full analysis set; HR Hazard ratio; N Number of patients per treatment group; P Placebo; v Versus

Recruitment

The study was conducted at 882 sites across 33 countries. The first patient was enrolled on 25 April 2013, the last patient was randomised on 30 June 2015, and the last patient completed the last visit on 11 September 2018.

Conduct of the study

Changes in the conduct of the study

The original CSP was dated 12 November 2012. Five CSP amendments were prepared; the 4th amendment was never implemented. All amendments were approved by the international coordinating Investigator. The full EC approved Amendment 5, which involved changes to study objectives. Amendments were then approved by local ECs/IRBs and regulatory authorities according to local regulations.

The first amendment came into effect before the inclusion of the first patient. The second and third amendments included changes to the enrolment target and measures to ensure that sufficient numbers of patients with CV disease were included. The third amendment (April 2014) also included additional AEoSI (previously collected in the CRF) but also added new AEoSIs. The fifth amendment came into effect in September 2016 and added new safety events for which data were to be collected, i.e. HF that did not require hospitalisation, potential DKA, all amputations and related events. Adjudication of all potential DKA events was also included.

Protocol deviations

Overall, there were 1 731 patients with at least 1 important protocol deviation. Important protocol deviations were balanced between treatment groups with respect to frequency and type. All important protocol deviations were reviewed and agreed before database lock. The most commonly occurring protocol deviation was patients assigned a randomisation code according to incorrect entry of baseline stratification factors (1 550/1 731).

Baseline data

CV disease characteristics and CV risk category

Overall, 40.6% of patients had established CV disease and 59.4% did not have established CV disease at baseline. Most patients without established CV disease had 2 risk factors in addition to T2DM and age (≥55 years for men and ≥60 years for women); 74% had dyslipidaemia, 91.3% had hypertension, and 14.4% were current tobacco users. Ischaemic heart disease was the most common type of CV disease (81.1% of patients). The proportions of patients with and without established CV disease at baseline were balanced between treatment groups (Table 2).

Table 2 Cardiovascular disease risk category and risk factors (FAS)

	Number (%) of patients		
	Dapa 10 mg (N=8582)	Placebo (N=8578)	Total (N=17160)
Baseline CV risk category[a]			
Patients with CV risk factors, but without established CV disease	5108 (59.5)	5078 (59.2)	10186 (59.4)
Patients with established CV disease	3474 (40.5)	3500 (40.8)	6974 (40.6)
CVRF (additional risk factors)[b]	5096	5063	10159
Dyslipidaemia	3738 (73.4)	3778 (74.6)	7516 (74.0)
Hypertension	4686 (92.0)	4588 (90.6)	9274 (91.3)
Current tobacco use	732 (14.4)	727 (14.4)	1459 (14.4)
CVRF (number of risk factors in addition to T2DM and age)	5096	5063	10159
1 risk factor	1439 (28.2)	1417 (28.0)	2856 (28.1)
2 risk factors	3254 (63.9)	3262 (64.4)	6516 (64.1)
3 risk factors	403 (7.9)	384 (7.6)	787 (7.7)
eCVD[c]			
Ischaemic heart disease	2824 (81.3)	2834 (81.0)	5658 (81.1)
Cerebrovascular disease	653 (18.8)	648 (18.5)	1301 (18.7)
Peripheral arterial disease	522 (15.0)	503 (14.4)	1025 (14.7)
eCVD (Number of documented CV diseases)[c]			
1 CV disease	2992 (86.1)	3064 (87.5)	6056 (86.8)
2 CV diseases	439 (12.6)	387 (11.1)	826 (11.8)
3 CV diseases	43 (1.2)	49 (1.4)	92 (1.3)

Source: Table 11.1.3.3.1

[a] Percentages are based on the total number of patients in each treatment group. 27 patients without documented eCVD or CVRF assigned to CVRF group.

[b] Percentages based on subset of patients with documented CVRF (excluding the 27 patients mentioned above).

[c] Percentages based on subset of patients with documented eCVD.

Current tobacco use means 5 cigarettes/day or more for at least 1 year at randomisation.
Patients being neither eCVD nor CVRF were assigned to the CVRF category.
N Number of patients per treatment group; CV Cardiovascular; Dapa Dapagliflozin; eCVD Established cardiovascular disease; FAS Full analysis set; CVRF CV risk factors; T2DM Type 2 diabetes mellitus

Demographic and baseline characteristics

Patient demographic characteristics were generally balanced between the 2 baseline CV risk groups. When compared with patients without established CV disease, patients with established CV disease were generally younger (mean age 62.6 vs. 64.8 years) and more commonly male (72.1% vs. 56.1%).

In the overall patient population, mean age was 63.9 years. 46.1% of patients were ≥65 years and 6.4% were ≥75 years. 62.6% of patients were male and 37.4% were female. Patients were randomised worldwide, with 44.5% of patients randomised in Europe, 31.9% in North America, 10.9% in Latin

America, and 12.7% in Asia/Pacific. 79.6% of patients were white, 13.4% were Asian, and 3.5% were black or African-American. Patient demographic characteristics were balanced between the 2 treatment groups

Patient baseline characteristics were generally balanced between the 2 baseline CV risk groups: mean duration of T2DM and mean baseline eGFR were similar between baseline CV risk groups. However, when compared with patients without CV disease, patients with established CV disease more frequently had a history of HF (16.6% vs. 5.6%), baseline eGFR <60 mL/min/1.73m^2 (9.2% vs. 6.1%), microalbuminuria (25.6% vs. 22.0%), and macroalbuminuria (8.3% vs. 5.8%). Additionally, the proportion of patients with reported insulin use at baseline was higher in patients with established CV disease (45.7% vs. 37.5%).

In the overall patient population, most patients were overweight: the mean weight was 90.79 kg and the mean BMI was 32.05 kg/m^2. The mean duration of T2DM was 11.9 years and the mean HbA1c at randomisation was 8.29%. Mean eGFR was 85.2 mL/min/1.73m^2 and 7.4% of patients had eGFR <60 mL/min/1.73m^2 at randomisation; 30.3% of patients had microalbuminuria or macroalbuminuria (ie, albumin/creatinine ratio ≥30 to ≤300 mg/g or >300 mg/g, respectively). Patient baseline characteristics were balanced between the 2 treatment groups.

Medical history

CV and other relevant medical history was balanced between the treatment groups. Overall, 89.4% of patients had received therapy for hypertension, 40.6% of patients had a history of established vascular disease, 20.9% had a history of MI, 18.5% had low-density lipoprotein cholesterol >130 mg/dL within 12 months, 14.6% had a history of tobacco usage, 6.5% had a history of ischaemic stroke, 6% had a history of peripheral artery disease.

Use of concomitant medication and treatment compliance

Medications at randomisation

Most patients (98.1%) used diabetic medication at baseline and most (approximately 74%) used 2 or more diabetic medications. The use of different categories of diabetic medications was balanced between treatment groups. Overall, 40.9% of patients used insulin. The most common class of diabetic medications was metformin, which was used by 82.0% of patients.

The use of different categories of CV medications at baseline was balanced between treatment groups. The most common categories of baseline CV medications were ACE inhibitor/ARB (81.3% of patients), Statin/Ezetimibe (75.0% of patients), and Any antiplatelets (61.1% of patients). Use of CV medications at baseline was generally higher in patients with established CV disease compared to patients without established CV disease.

Medications after randomisation

Patients were to be treated for their T2DM during the study with glycaemic goals as recommended by the ADA and EASD and in accordance with local guidelines and practices.

The use of non-diabetic medications after randomisation was generally balanced between treatment groups. Patients in the placebo group used more concomitant diabetic medications.

Use of prohibited concomitant medications including pioglitazone, rosiglitazone, and any SGLT2 inhibitors other than study drug was infrequent and generally balanced between treatment groups: overall, approximately 6% patients received prohibited concomitant medications, predominantly SGLT2 inhibitors. A numerical imbalance in the proportion of patients using SGLT2 inhibitors, other than study drug, at or after randomisation was observed: 3.4% in the dapagliflozin group and 6.1% in the placebo group.

Treatment compliance

Treatment compliance was only assessible for patients with a complete record of tablets returned. Among the patients considered assessible, treatment compliance was high and similar between treatment groups.

Numbers analysed

Table 3 Summary of analysis sets

	Number of patients		
	Dapa 10 mg	**Placebo**	**Total**
Full analysis set	8 582	8 578	17 160
Safety analysis set	8 574	8 569	17 143

The FAS includes all randomised patients assessed according to their randomised study drug assignment.

The SAS includes all randomised patients who received at least 1 dose of study drug and for whom any data are available from any time after first dose of study drug until the end of the study, assessed according to the treatment they actually received.

Dapa Dapagliflozin; FAS Full analysis set; SAS Safety analysis set

Outcomes and estimation

Summary of testing hierarchy and efficacy results

The primary safety endpoint was met: Dapagliflozin was non-inferior to placebo for MACE. Confirmatory testing proceeded to the primary efficacy variables. Dapagliflozin was superior to placebo for reduction of the composite of hospitalisation for heart failure and CV death. Superiority of dapagliflozin over placebo was not demonstrated for MACE. Confirmatory testing stopped before the secondary variables were assessed. However, the incidence of renal composite events was reduced, and there were numerically fewer patients with an all-cause mortality event, in the dapagliflozin group compared with the placebo group.

The confirmatory analysis of the primary and secondary efficacy variables is summarised in Table 4.

Table 4 Confirmatory analysis of endpoint hierarchy (FAS)

Priority and type	Order tested	Analysis	HR dapagliflozin to placebo (CI)	p-value[a]	Statistically significant
Primary safety	First	Non-inferiority: MACE	0.93 (0.84, 1.03)	<0.001	Yes
Primary efficacy	Second	Superiority: Hospitalisation for HF/CV death	0.83 (0.73, 0.95)	0.005	Yes
		Superiority: MACE	0.93 (0.84, 1.03)	0.172	No
Secondary efficacy	Third	Superiority: Renal composite endpoint	0.76 (0.67, 0.87)	<0.001	Not tested
	Fourth	Superiority: All-cause mortality	0.93 (0.82, 1.04)	0.198	Not tested

[a] 1 sided p-value presented for MACE non-inferiority, all other p-values are 2-sided

Non-inferiority for MACE was tested at α=0.0231 (1-sided). Superiority for hospitalisation for heart failure or CV death, and superiority for MACE were tested in parallel following closed testing procedure at α =0.0231 (2-sided); as the composite of hospitalisation for HF and CV death was statistically significant, the full α was recycled to test MACE at α=0.0462 (2-sided). As MACE was not significant the renal composite endpoint and all-cause mortality were not tested as part of the confirmatory testing procedure.

Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk and haematuria with treatment as a model term.

CI Confidence interval; CV Cardiovascular; HF Heart failure; HR Hazard ratio; MACE Major adverse cardiovascular event (cardiovascular death, ischaemic stroke, and myocardial infarction); FAS Full analysis set.

Cardiovascular outcomes

Primary variable: Hospitalisation for HF and CV death

Dapagliflozin reduced the incidence of the composite of hospitalisation for HF and CV death (HR 0.83 [95% CI 0.73 to 0.95], p=0.005). There were 417 and 496 patients with hospitalisation for HF or CV death events in the dapagliflozin and placebo groups, respectively, corresponding to event rates per 1000 patient-years of 12.2 and 14.7 (Table 5).

Table 5 Time from randomisation to first occurrence of any event of hospitalisation for heart failure and CV death (FAS)

Efficacy variable	Dapa 10 mg (N=8582)		Placebo (N=8578)		Hazard ratio (CI)	p-value
	Patients with events n (%)	Event rate	Patients with events n (%)	Event rate		
Composite endpoint hospitalisation for heart failure/CV death	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73, 0.95)	0.005[a]
Hospitalisation for heart failure	212 (2.5)		286 (3.3)			
CV death	205 (2.4)		210 (2.4)			
Single components[c]						
Hospitalisation for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61, 0.88)	<0.001[b]
CV death	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82, 1.17)	0.830[b]

[a] Two-sided p-value.

[b] Nominal p-value.

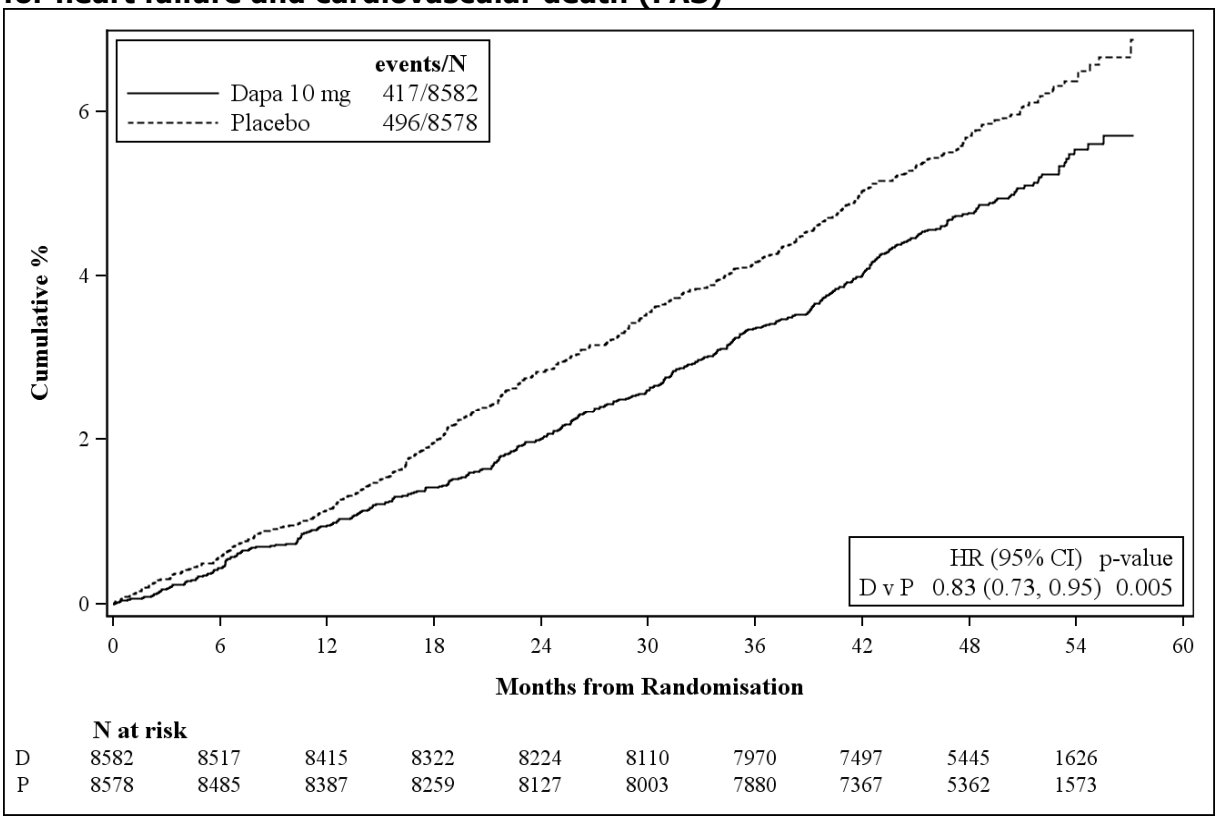
[c] Single components were analysed as exploratory variables. The number of first events for the single components are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

All events were adjudicated and confirmed by CEC. Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk and haematuria with treatment as a model term. 95% CIs were calculated for the composite endpoints. Event rate displayed as event rate per 1000 subject years.

CI Confidence interval; Dapa Dapagliflozin; FAS Full analysis set; N Number of patients per treatment group; n Number of patients with events; CEC Clinical Event Adjudication Committee; CV Cardiovascular

A Kaplan-Meier analysis of the composite of hospitalisation for HF and CV death is presented in Figure 4.

Figure 4 Kaplan-Meier plot of adjudicated event of the composite of hospitalisation for heart failure and cardiovascular death (FAS)



N at risk is the number of patients at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p-value is displayed. Analysis of time from randomisation to first occurrence of event or censoring.

CI Confidence interval; Dapa Dapagliflozin; D Dapa 10 mg; FAS Full analysis set; HR Hazard ratio; N Number of patients per treatment group; P Placebo; v Versus

Exploratory analyses of the single components suggest that the difference in treatment effect was driven by hospitalisation for HF (HR 0.73 [95% CI 0.61, 0.88]), with no clear difference in CV death (HR 0.98 [95% CI 0.82 to 1.17]) (Table 5).

Primary variable: MACE

Superiority of dapagliflozin over placebo was not demonstrated for MACE variable. There were numerically fewer MACE events in the dapagliflozin group compared with the placebo group (HR 0.93 [95% CI 0.84 to 1.03], p=0.172). There were 756 vs. 803 patients with CV death, MI, or ischaemic stroke events in the dapagliflozin and placebo groups, respectively, corresponding to event rates per 1000 patient-years of 22.6 and 24.2 (Table 6).

Table 6 Time from randomisation to first occurrence of any event of the composite of CV death, myocardial infarction, and ischaemic stroke (FAS)

Efficacy variable	Dapa 10 mg (N=8582)		Placebo (N=8578)		Hazard ratio (CI)	p-value
	Patients with events n (%)	Event rate	Patients with events n (%)	Event rate		
Composite endpoint CV death/myocardial infarction/ischaemic stroke (MACE)	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84, 1.03)	0.172[a]
CV death	166 (1.9)		167 (1.9)			
Myocardial infarction	377 (4.4)		428 (5.0)			
Ischaemic stroke	213 (2.5)		208 (2.4)			
Single components[c]						
CV death	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82, 1.17)	0.830[b]
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77, 1.01)	0.080[b]
Ischaemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84, 1.21)	0.916[b]

[a] Two-sided p-value.

[b] Nominal p-values.

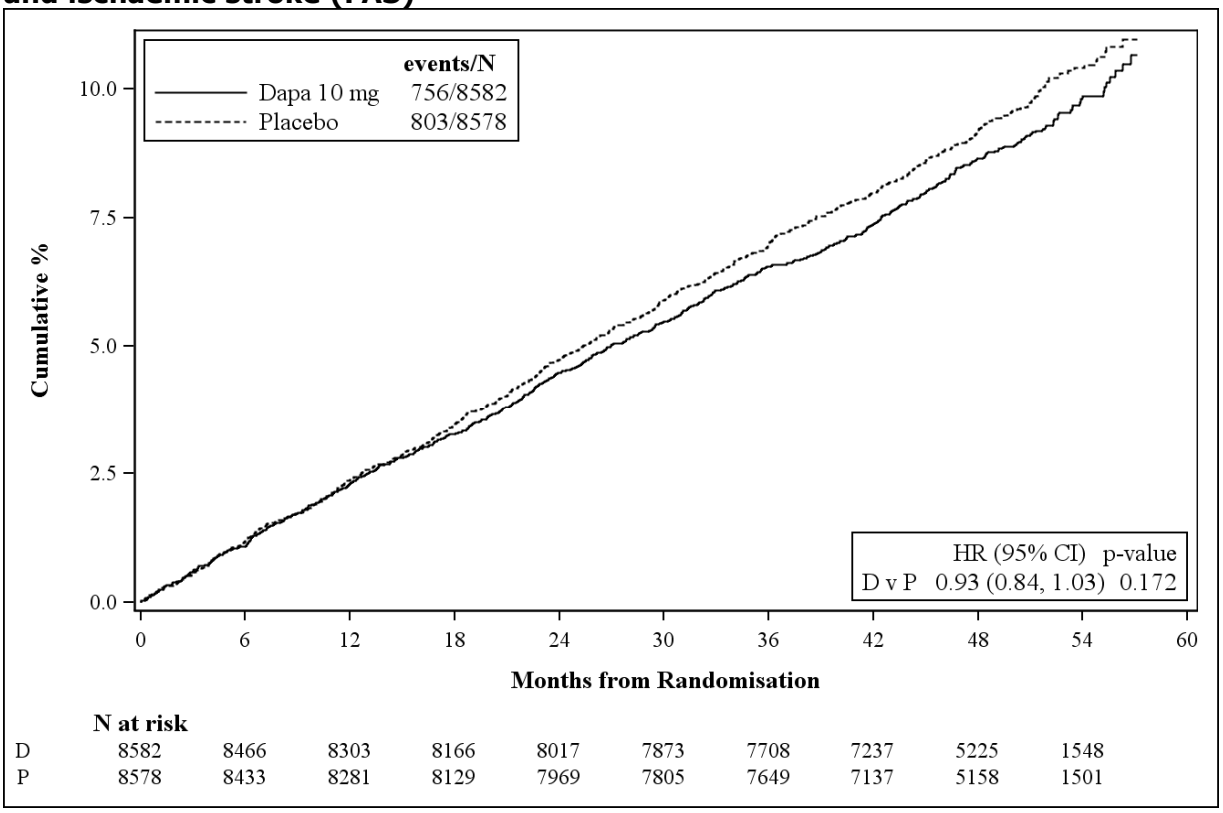
[c] Single components were analysed as exploratory variables. The number of first events for the single components are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

All events were adjudicated and confirmed by CEC. Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk and haematuria with treatment as a model term. 95% CIs were calculated for the composite endpoints. Event rate displayed as event rate per 1000 subject years.

CI Confidence interval; Dapa Dapagliflozin; FAS Full analysis set; MACE Major adverse cardiovascular event (cardiovascular death, ischaemic stroke, and myocardial infarction); CV cardiovascular; CEC Clinical Event Adjudication Committee; N Number of patients per treatment group; n Number of patients with events

A Kaplan-Meier analysis of MACE is presented in Figure 5.

Figure 5 Kaplan-Meier plot of adjudicated event of CV death, myocardial infarction, and ischaemic stroke (FAS)



[a] N at risk is the number of patients at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p-value is displayed. Analysis of time from randomisation to first occurrence of event or censoring.

[b] CI Confidence interval; Dapa Dapagliflozin; D Dapa 10 mg; FAS Full analysis set; HR Hazard ratio; N Number of patients per treatment group; P Placebo; CV Cardiovascular; v Versus

Single components of MACE were analysed as exploratory variables. The incidence of MI was numerically lower in the dapagliflozin group compared with the placebo group (HR 0.89 [95% CI 0.77 to 1.01]), with no clear difference observed for CV death or ischaemic stroke (Table 6).

Renal outcomes

Secondary variable: Renal composite variables and single components

Analysis of the secondary renal composite variable was not conducted as part of the confirmatory testing sequence.

The incidence of renal composite events was reduced in the dapagliflozin group compared to the placebo group (HR 0.76 [95% CI 0.67 to 0.87], nominal p<0.001). There were fewer patients with renal composite events in the dapagliflozin and placebo groups: 370 and 480, respectively, corresponding to event rates per 1000 patient-years of 10.8 and 14.1 (Table 7 and Figure 6).

The renal-specific nature of the overall treatment effect was confirmed in a pre-specified exploratory analysis of the renal composite without CV death (confirmed sustained ≥40% decrease in eGFR, ESRD, and renal death): There were 127 and 238 patients with events of the renal composite without CV death in the dapagliflozin and placebo groups, respectively, corresponding to event rates per 1000 patient-years of 3.7 and 7.0 (HR 0.53 [95% CI 0.43 to 0.66]) (Table 7).

Table 7 Time from randomisation to first occurrence of any event of renal composite endpoints (FAS)

Efficacy variable	Dapa 10 mg (N=8582)		Placebo (N=8578)			
	Patients with events n (%)	Event rate	Patients with events n (%)	Event rate	Hazard ratio (95% CI)	p-value[a]
Renal composite endpoint	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67, 0.87)	<0.001
Sustained eGFR decrease[b]	120 (1.4)		220 (2.6)			
ESRD	2 (<0.1)		11 (0.1)			
Renal or CV death	248 (2.9)		249 (2.9)			
Renal death	5 (<0.1)		7 (<0.1)			
CV death	243 (2.8)		242 (2.8)			
Renal composite without CV death	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43, 0.66)	<0.001
Single components						
Sustained eGFR decrease	120 (1.4)	3.5	221 (2.6)	6.5	0.54 (0.43, 0.67)	<0.001
ESRD	6 (<0.1)	0.2	19 (0.2)	0.6	0.31 (0.13, 0.79)	0.013
Renal or CV death	251 (2.9)	7.2	259 (3.0)	7.4	0.97 (0.81, 1.15)	0.698
Renal death	6 (<0.1)	0.2	10 (0.1)	0.3	0.60 (0.22, 1.65)	0.324
CV death	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82, 1.17)	0.830

[a] All p-values are nominal.

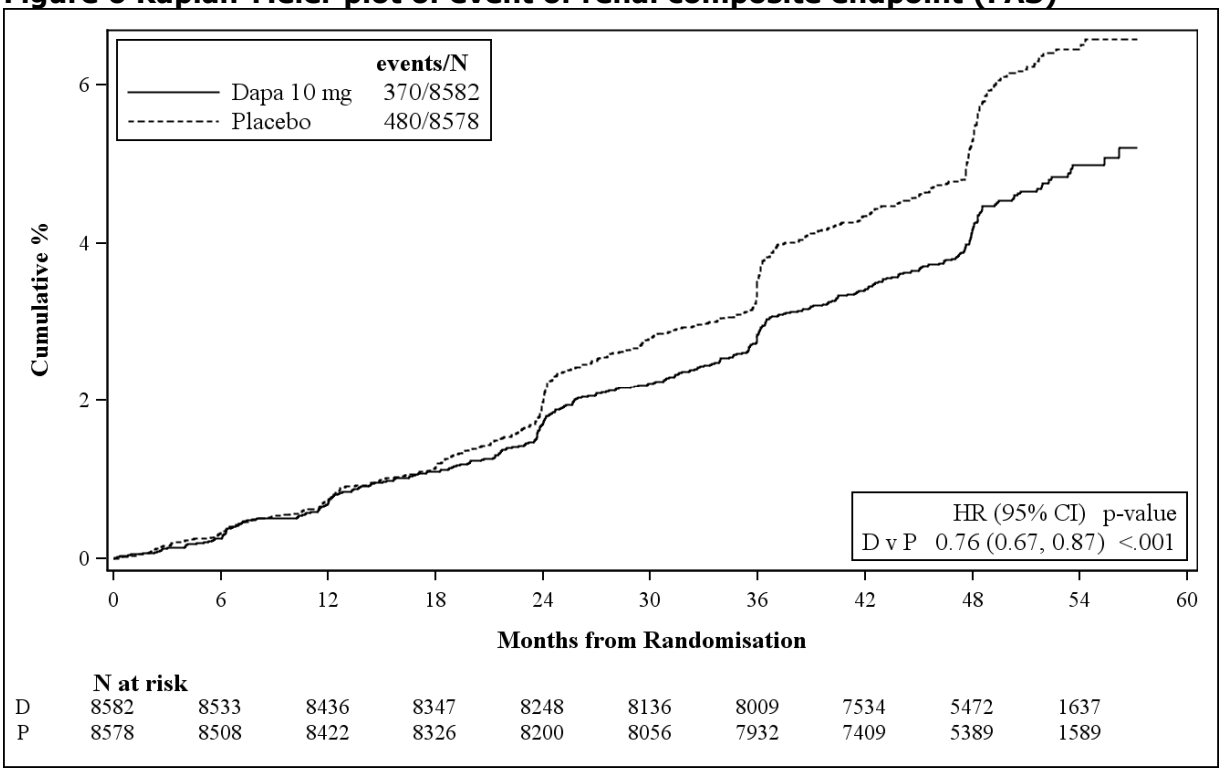
[b] Time to onset would be the first of the 2 subsequent laboratory assessments.

Renal composite endpoint defined as: sustained confirmed ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 using CKD-EPI equation and/or ESRD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73 m^2) and/or renal or CV death as adjudicated by CEC.

Event rate displayed as event rate per 1000 patient-years. Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk group and haematuria with treatment as a model term.

CI Confidence interval; CV Cardiovascular; Dapa Dapagliflozin; ESRD End-stage renal disease; FAS Full analysis set; N Number of patients per treatment group; n Number of Patients with events; eGFR Estimated glomerular filtration rate; CKD-EPI Chronic kidney disease epidemiology collaboration; CEC Clinical event adjudication committee

Figure 6 Kaplan-Meier plot of event of renal composite endpoint (FAS)



N at risk is the number of patients at risk at the beginning of the period. Analysis of time from randomisation to first occurrence of event or censoring.

Renal composite endpoint defined as sustained confirmed eGFR decrease ≥40% to eGFR <60 mL/min/1.73 m^2 using CKD-EPI equation and/or ESRD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73 m^2) and/or renal or CV death as adjudicated by Clinical Event Adjudication Committee.

1 month corresponds to 30 days. 2-sided p-value is displayed.

CI Confidence interval; CV Cardiovascular; Dapa Dapagliflozin; D Dapa 10 mg; FAS Full analysis set; HR Hazard ratio; N Number of patients per treatment group; CKD-EPI Chronic kidney disease epidemiology collaboration; eGFR Estimated glomerular filtration rate; ESRD End-stage renal disease; P Placebo; v Versus

Single components of the renal composite variables were analysed as exploratory variables. The difference in treatment effect between groups was driven by the renal components: reduced event rates were observed for sustained eGFR decrease (HR 0.54 [95% CI 0.43 to 0.67]) and ESRD events (HR 0.31 [95% CI 0.13 to 0.79]), and a numerical reduction was observed for renal death events (HR 0.60 [85% CI 0.22 to 1.65]) (Table 7).

Exploratory analyses of pre-specified renal variables

This section presents exploratory analyses of pre-specified efficacy variables considered supportive to the assessment of the efficacy of dapagliflozin for the prevention of new or worsening nephropathy in patients with T2DM.

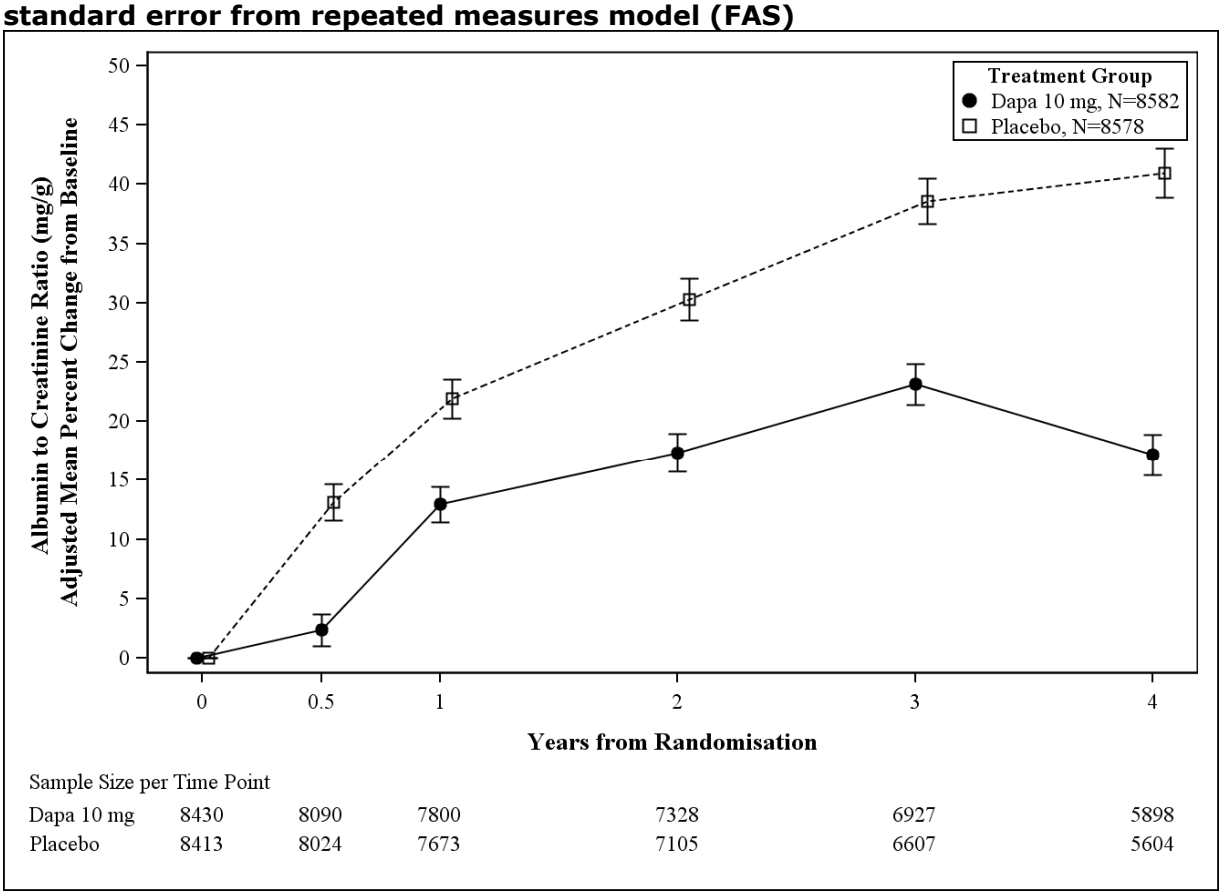
Albumin to creatinine ratio

In the overall DECLARE population, increases in UACR occurred at a slower rate in the dapagliflozin group compared with the placebo group (Figure 7).

Patients in the dapagliflozin group with pre-existing albuminuria (UACR ≥30 mg/g) consistently displayed reductions of >30% for placebo-corrected change in UACR relative to baseline: -32.06% to -47.97% reduction at years 1 to 4.

In patients without pre-existing albuminuria, UACR levels increased over time but at a slower rate in the dapagliflozin group compared with the placebo group**.**

Figure 7 Line graph for albumin to creatinine ratio plotting model adjusted mean and standard error from repeated measures model (FAS)



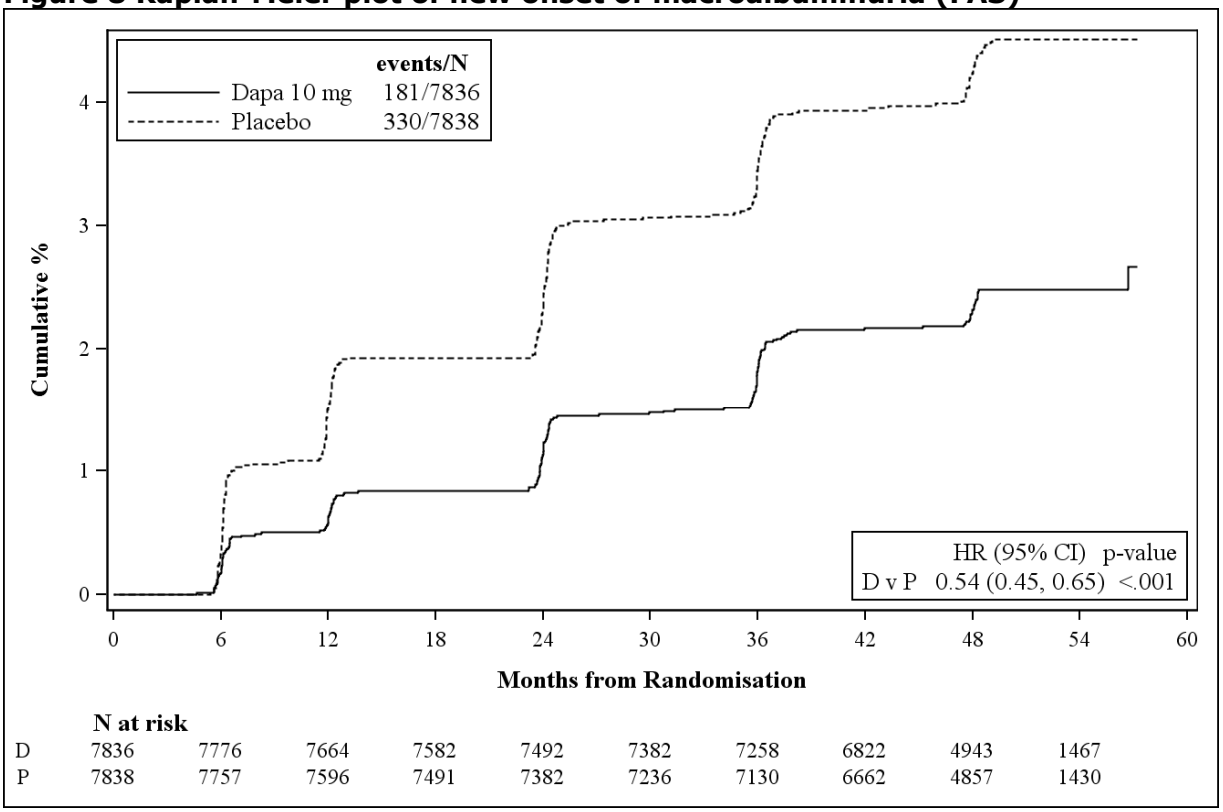
FAS Full analysis set; Dapa Dapagliflozin; N Number of patients

New onset of albuminuria

New onset of macroalbuminuria (UACR >300 mg/g) in the 15 674 patients without pre-existing macroalbuminuria was reduced in the dapagliflozin group compared with the placebo group (HR 0.54 [95% CI 0.45 to 0.65], nominal p<0.001) (see Figure 8).

Similarly, new onset of albuminuria in the 11 644 patients without pre-existing albuminuria was reduced in the dapagliflozin group compared with the placebo group (HR 0.79 [95% CI 0.72 to 0.87], nominal p<0.001).

Figure 8 Kaplan-Meier plot of new onset of macroalbuminuria (FAS)



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

Only patients without macroalbuminuria (UACR >300 mg/g) at baseline are included here. Analysis of time from randomisation to first occurrence of event or censoring. HR, CI and p-value are from Cox proportional hazard model.

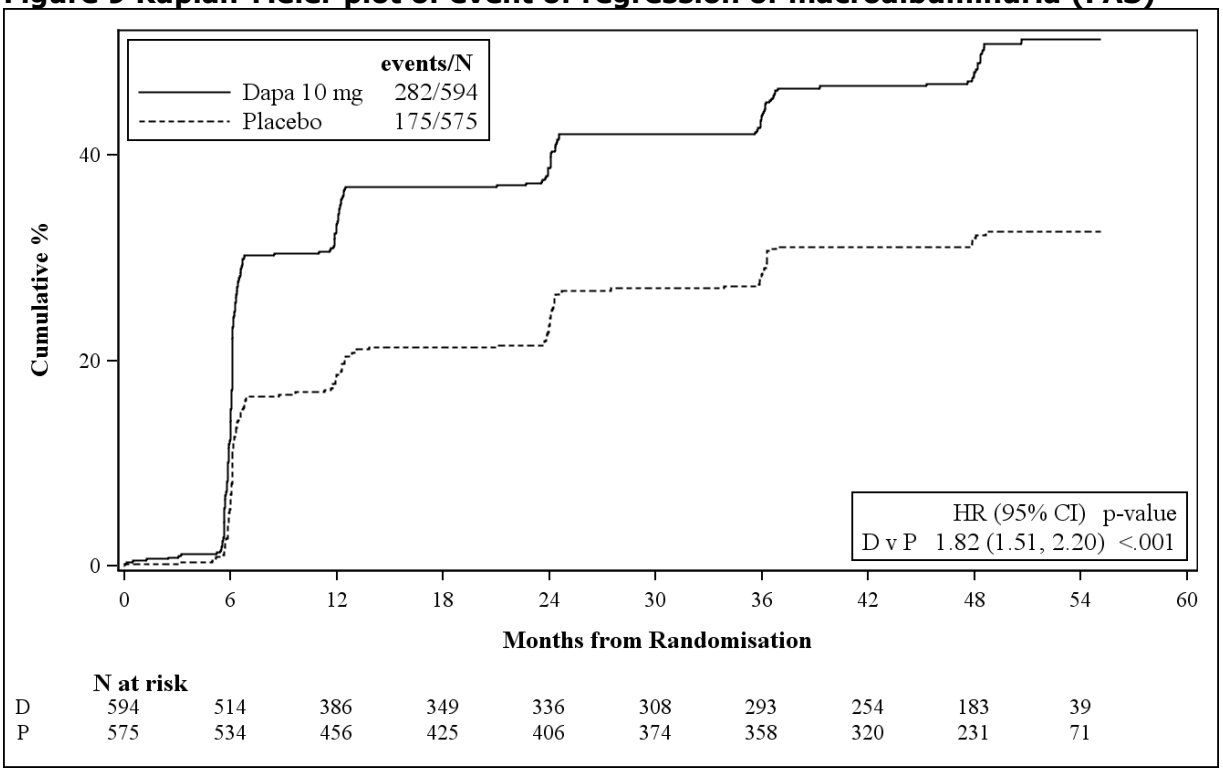
CI Confidence interval; Dapa Dapagliflozin; D Dapa 10 mg; FAS Full analysis set; HR Hazard ratio; N Number of patients per treatment group; P Placebo; UACR Urine albumin-to-creatinine ratio; v Versus

Regression in severity of albuminuria

Regression of macroalbuminuria in the 1 169 patients with pre-existing macroalbuminuria was greater in the dapagliflozin group compared with the placebo group (HR 1.82 [95% CI 1.51 to 2.20], nominal p<0.001) (Figure 9).

A similar pattern was observed for regression of albuminuria in the 5 199 patients with micro- or macroalbuminuria (UACR ≥30 mg/g) at baseline in the dapagliflozin group compared with the placebo group: HR 1.54 (95% CI 1.4 to 1.69), nominal p<0.001.

Figure 9 Kaplan-Meier plot of event of regression of macroalbuminuria (FAS)



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

Event defined as baseline macroalbuminuria (UACR >300 mg/g) to microalbuminuria (UACR ≥30 - ≤300 mg/g) or normoalbuminuria (UACR 0 - <30 mg/g).

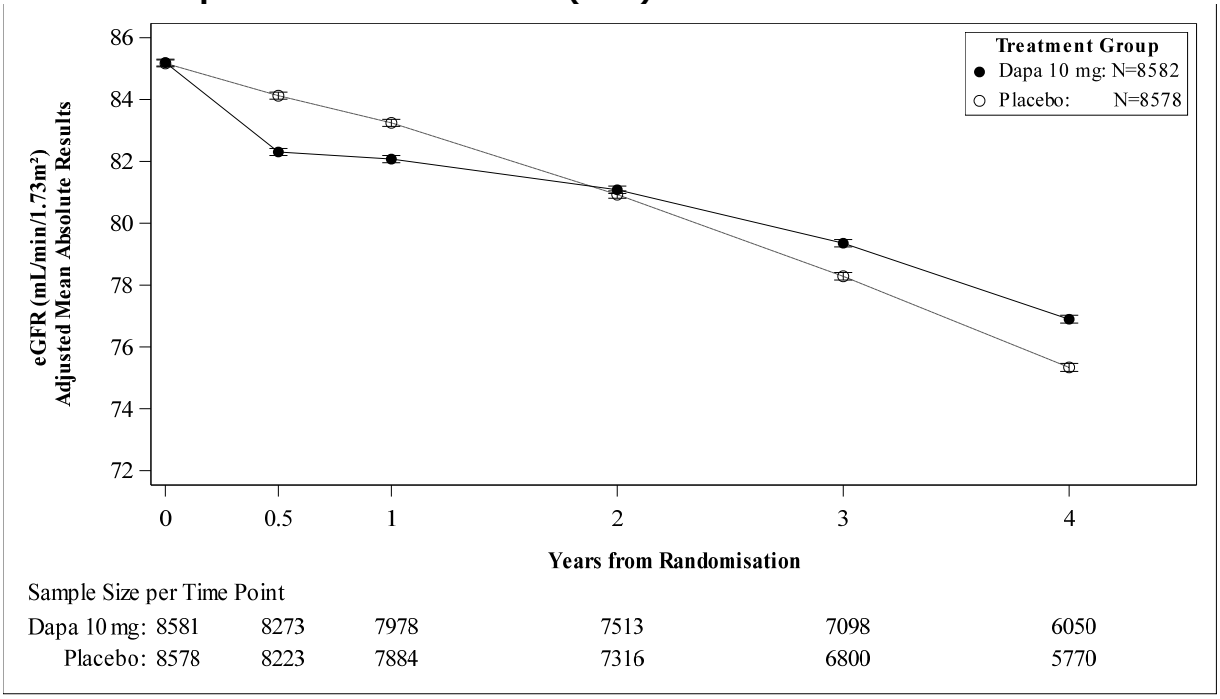
Only patients with macroalbuminuria at baseline are included here. Analysis of time from randomisation to first occurrence of event or censoring. HR, CI and p-value are from Cox proportional hazard model.

CI Confidence interval; Dapa Dapagliflozin; D Dapa 10 mg; FAS Full analysis set; HR Hazard ratio; N Number of patients per treatment group; P Placebo; UACR Urinary albumin-to-creatinine ratio; v Versus

eGFR: Repeated measures

A line graph displaying model adjusted mean for eGFR (CKD-EPI) is displayed in Figure 10. Mean eGFR decreased over time in both treatment groups. At 6 months, the mean decrease from baseline in eGFR was greater in the dapagliflozin group compared with the placebo group. After 6 months, the relative rate of eGFR decline was lower in the dapagliflozin group compared with the placebo group, resulting in a statistically significant treatment difference in mean change at year 3 and year 4 favouring dapagliflozin.

Figure 10 Line graph for eGFR (CKD-EPI) plotting model adjusted mean and standard error from repeated measures model (FAS)



FAS Full analysis set; N Number of patients per treatment group; Dapa Dapagliflozin; eGFR Estimated glomerular filtration rate; CKD-EPI Chronic kidney disease epidemiology collaboration

Secondary variable: All-cause mortality

Analysis of the secondary all-cause mortality variable was not conducted as part of the confirmatory testing sequence.

The incidence of all-cause mortality was numerically lower in the dapagliflozin group compared with the placebo group (HR 0.93 [95% CI [0.82 to 1.04], nominal p=0.198). There were 529 and 570 patients who died in the dapagliflozin and placebo groups, respectively, corresponding to event rates per 1000 patient-years of 15.1 and 16.4 (Table 8, and Figure 11).

Table 8 Time from randomisation to all-cause mortality (FAS)

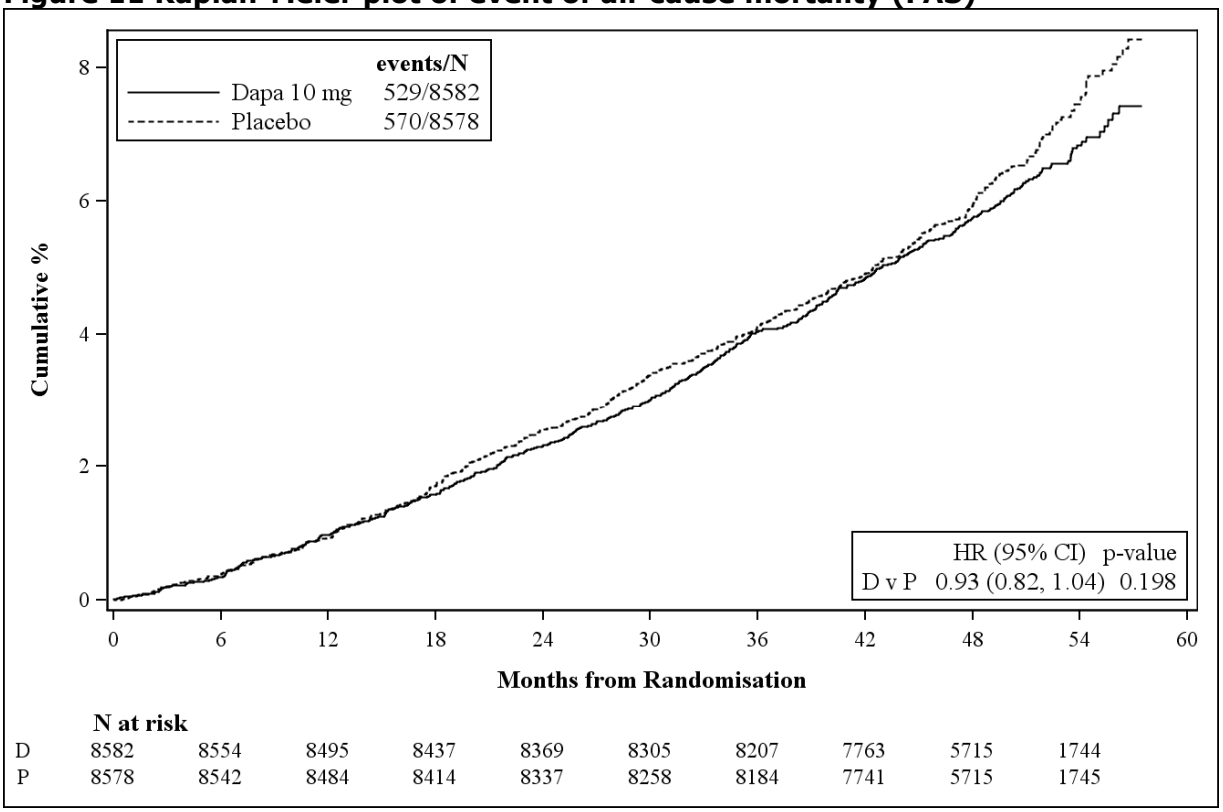
Efficacy variable	Dapa 10 mg (N=8582)		Placebo (N=8578)		Hazard ratio (95% CI)	p-value
	Patients with events n (%)	Event rate	Patients with events n (%)	Event rate		
All-cause mortality	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82, 1.04)	0.198

Deaths occurring after the date of withdrawal of consent (and for patients lost to follow-up) and documented in publicly available source data will be included in the analysis of all-cause mortality. Event rates are based on observed patient counts.

Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk group and haematuria with treatment as a model term. Event rate displayed as event rate per 1000 patient years.

CI Confidence interval; FAS Full analysis set; N Number of patients per treatment group; n Number of patients with events; Dapa Dapagliflozin; CV Cardiovascular

Figure 11 Kaplan-Meier plot of event of all-cause mortality (FAS)



N at risk is the number of patients at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p-value is displayed. Analysis of time from randomisation to death or censoring.

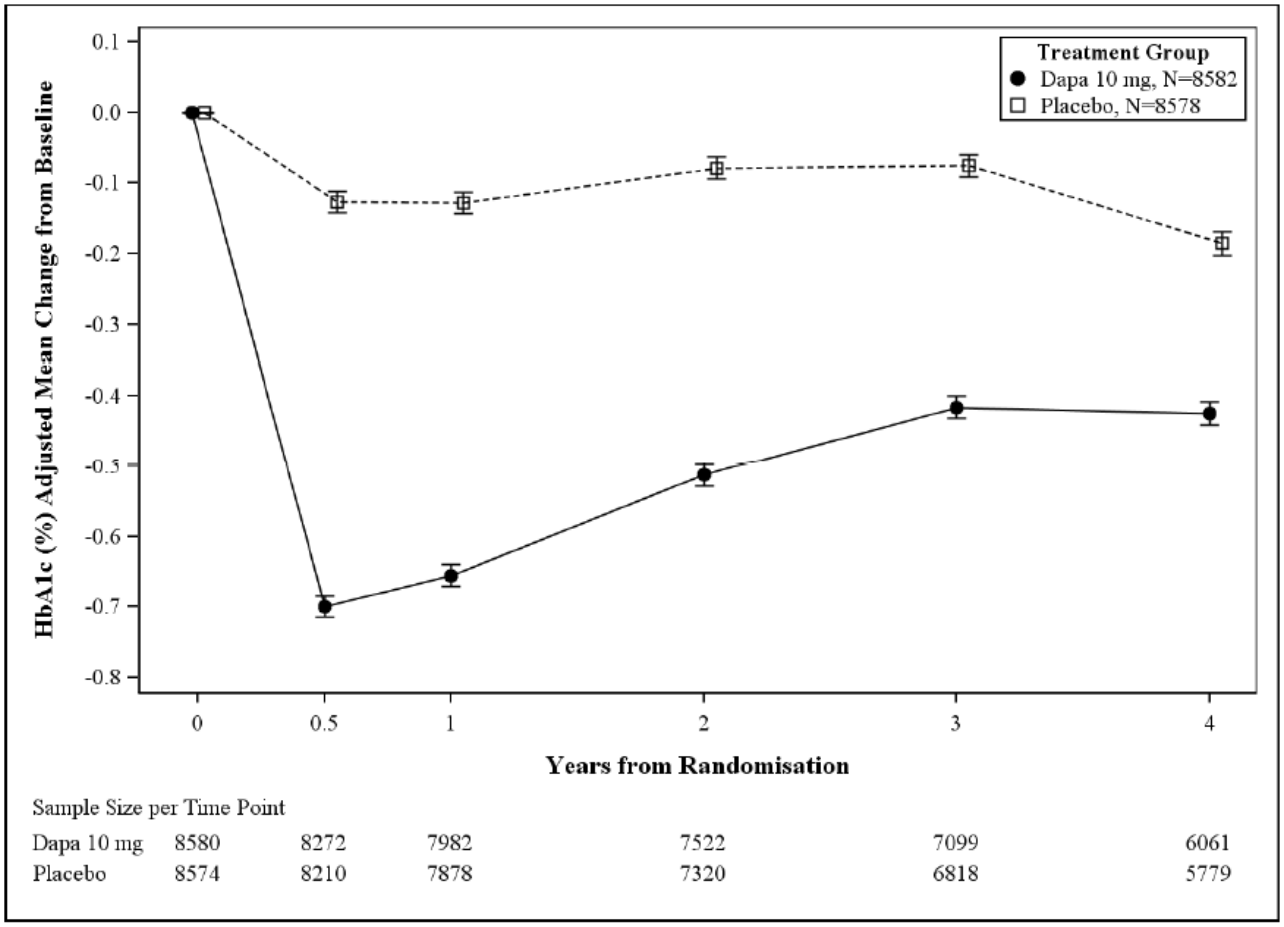
CI Confidence interval; Dapa Dapagliflozin; D Dapa 10 mg; FAS Full analysis set; HR Hazard ratio; N Number of patients per treatment group; P Placebo; v Versus

According to the adjudicated classifications, 46.3% and 43.7% of patients died from CV causes, 39.9% and 41.8% of patients died from non-CV causes, and 13.8% and 14.6% of patients died from undetermined causes in the dapagliflozin and placebo groups, respectively.

Exploratory variable: HbA1c

HbA1c was consistently reduced in the dapagliflozin group compared with the placebo group (Figure 12):

Figure 12 Line graph for HbA1c plotting model adjusted mean and standard error from repeated measures model (FAS)



Sensitivity analyses of the dual primary variables

A number of pre-specified sensitivity analyses were conducted on the two primary variables. The results of these pre-specified sensitivity analyses were consistent with the primary analyses of both the composite of hospitalisation for HF and CV death, and MACE.

A single sensitivity analysis involving imputation of time to event data suggested a beneficial treatment effect on MACE. The primary analysis of the primary endpoints assumed non-informative censoring of un-observed outcomes; patients with incomplete follow-up of primary endpoint events were censored at the last date of clinical assessment. However, the DECLARE data indicated that event rates of the primary endpoints during the off-treatment period tended to be higher than the event rates observed in the entire study, which suggested a possible departure from the assumption of non-informed censoring. This possible departure was addressed by a pre-specified sensitivity analysis which used available off-treatment event rates to impute time to event information for patients with incomplete follow-up (i.e., any patients censored before 21 May 2018): under this imputation approach, a positive treatment effect on MACE was suggested.

Ad-hoc sensitivity analyses

Ad-hoc sensitivity analyses were conducted to assess the potential impact of inclusion of deaths due to undetermined cause as CV deaths, and exclusion patients who initiated either GLP-1 receptor agonist or SGLT2 inhibitor classes of drugs at any time during study, regardless of on- or off- study drug, on the primary analyses. The results of these analyses were consistent with the primary analyses.

An additional ad-hoc sensitivity analysis was conducted to assess the potential impact of discrepancies between data entered into the interactive voice/web response system (IVRS/IWRS) and RAVE database on the primary analysis: Patients were randomised using and interactive voice/web response system (IVRS/IWRS) operated by site staff and randomisation was stratified by CV risk category (CV risk factors or established CV disease), and haematuria status (Yes/No). In accordance with the statistical analysis plan (SAP), these randomisation strata were used as covariates in all statistical models. For a substantial number of patients (9%) the stratification information entered in the IWRS differed from the information entered and verified in the clinical database (RAVE). The discrepancy between the two sources did not impact the results and conclusion of the primary endpoints, as demonstrated in a post hoc analysis using the RAVE information as covariates.

Ancillary analyses

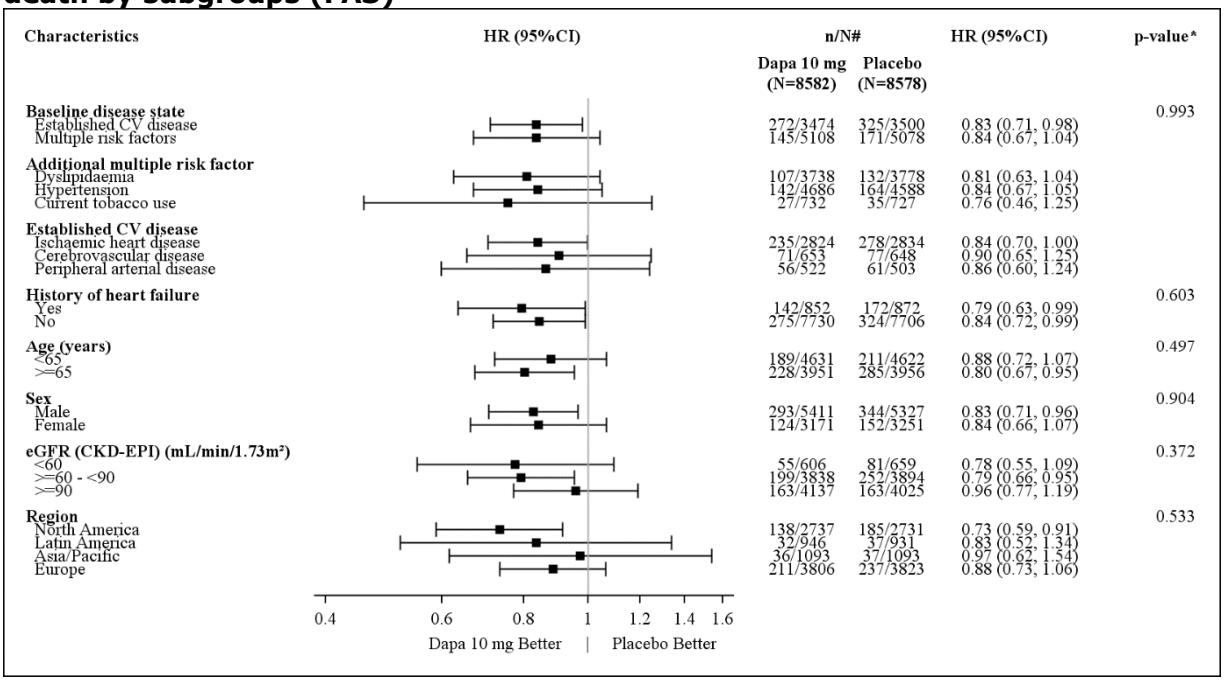
Subgroup analyses of the primary variables

Subgroup analyses: composite of hospitalisation for HF and CV death

The benefit of dapagliflozin on the composite of hospitalisation for HF and CV death was observed in patients with and without established CV disease, and in patients with and without a history of HF at baseline (Figure 13).

Similarly, the benefit of dapagliflozin on the composite of hospitalisation for HF and CV death was generally consistent across subgroups, including subgroups defined by, age, sex, renal parameters (eGFR and UACR), and region. There was no evidence of heterogeneity between subgroups based on interaction p-values (Figure 13).

Figure 13 Forest plot of the composite of hospitalisation for heart failure and CV death by subgroups (FAS)



Only adjudicated events with event date on or after date of randomisation are included. * p-value for interaction

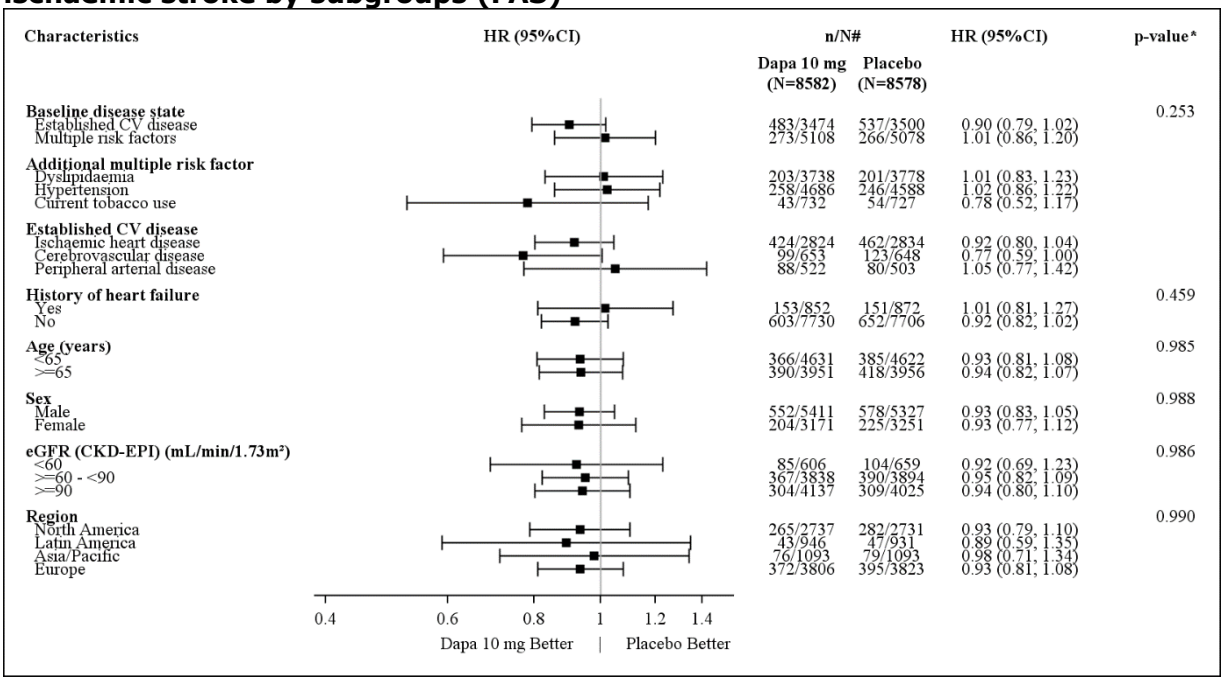
CI Confidence interval; CV Cardiovascular; FAS Full analysis set; HR Hazard ratio; N Number of patients; N# Number of patients within subgroup category; n Number of patients with event

Subgroup analyses: MACE

As superiority of dapagliflozin compared with placebo was not demonstrated for reduction of the incidence of MACE, subgroup analyses should be interpreted with caution.

There was a trend towards an effect of dapagliflozin on MACE in patients with established CV disease at baseline (HR 0.90 [95% CI 0.79 to 1.02] nominal p=0.089). However, the analysis of interaction for subgroups defined by baseline disease state was not significant (Figure 14).

Figure 14 Forest plot of the composite of CV death, myocardial infarction, and ischaemic stroke by subgroups (FAS)



Only adjudicated events with event date on or after date of randomisation are included. * p-value for interaction

CI Confidence interval; FAS Full analysis set; HR Hazard ratio; N Number of patients; N# Number of patients within subgroup category; n Number of patients with event

Subgroup analyses of secondary and related variables

Subgroup analyses: renal composite variables

The benefit of dapagliflozin on the secondary renal composite and the renal composite without CV death (renal composite variables) was observed in patients with and without established CV disease.

The benefit of dapagliflozin on the renal composite variables was consistent across subgroups defined by baseline renal function (eGFR). A potential interaction was observed for the secondary renal composite on subgroup categories defined by baseline UACR; patients with moderately and severely increased albuminuria appeared to derive greater benefit than patients with normal to mildly increased albuminuria. However, this potential interaction appeared to be driven by CV death; subgroup analyses of the renal composite without CV death indicated a consistent treatment benefit for patients with normal to mild to moderate, and severely increased albuminuria at baseline Table 9.

Table 9 Renal composite variables by renal subgroups (FAS)

	Renal composite with CV death			Renal composite without CV death		
		p-value			p-value	
Subgroup Categories	**Hazard ratio (95% CI)**	**[a]**	**[b]**	**Hazard ratio (95% CI)**	**[a]**	**[b]**
eGFR (CKD-EPI) (mL/min/1.73 m^2)			0.974			0.870
≥90	0.79 (0.63, 0.99)	0.042		0.50 (0.34, 0.73)	<0.001	
≥60 - <90	0.76 (0.63, 0.93)	0.006		0.54 (0.40, 0.73)	<0.001	
<60	0.77 (0.54, 1.09)	0.144		0.60 (0.35, 1.02)	0.059	
Urinary albumin/creatinine ratio (mg/g)			0.020			0.302
<30	0.89 (0.73, 1.08)	0.237		0.52 (0.37, 0.74)	<0.001	
≥30 - ≤300	0.73 (0.57, 0.94)	0.012		0.59 (0.39, 0.87)	0.008	
>300	0.52 (0.38, 0.72)	<0.001		0.38 (0.25, 0.58)	<0.001	

[a] p-value treatment effects within each subgroup category

[b] p-value interaction between randomised treatment and relevant subgroup

Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk and haematuria with treatment and subgroup category as model terms, and also including subgroup by treatment interaction when calculating the interaction p-values

CI Confidence interval; CV Cardiovascular; FAS Full analysis set; eGFR Estimated glomerular filtration rate; CKD-EPI Chronic kidney disease epidemiology collaboration

The benefit of dapagliflozin on the renal composite variables was generally consistent across all other subgroups, including those defined by history of HF, age, sex, and region.

Summary of main study

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

Table 10 Summary of Efficacy for trial DECLARE

Title: Dapagliflozin Effect on CardiovascuLAR Events (DECLARE): A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction, or Ischemic Stroke in Patients with Type 2 Diabetes		
Study identifier	D1693C00001	
Design	The DECLARE study was a multi-centre, randomised, double-blind, placebo-controlled Phase IIIb study to evaluate the effect of dapagliflozin on cardiovascular (CV) and renal outcomes in patients with type 2 diabetes mellitus (T2DM) with or without established CV disease. Patients were randomised in a 1:1 ratio to receive either 10 mg dapagliflozin once daily or placebo. The study included a placebo run-in period and a double-blind treatment period. The study was event-driven with an anticipated median duration of 4.5 years and anticipated total duration of 6 years for the double-blind treatment period.	
	Duration of main phase:	predicted median duration of treatment period 4.5 years

	Duration of Run-in phase: Duration of Extension phase:		4 to 8 weeks (placebo) not applicable
Hypothesis	1) Non-inferiority MACE, 2) Superiority MACE and HF hospitalisation/CV death		
Treatments groups	Dapagliflozin 10 mg		8 582 patients
	Placebo		8 578 patients
Endpoints and definitions	Primary safety endpoint	MACE (safety)	The composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke (time to first event)
	Co-Primary efficacy endpoint	HF/CV death	The composite endpoint of hospitalization for heart failure or CV death (time to first event)
	Co-Primary efficacy endpoint	MACE (efficacy)	The composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke (time to first event)
	Secondary endpoint	Renal	Composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m^2 (using CKD-EPI equation) and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15ml/min/1.73m^2) and/or renal or CV death (time to first event)
	Secondary endpoint	All-cause mortality	Time to event
Database lock	16 September 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	FAS: all randomised subjects. The study was event-driven with the primary analysis to be performed when 1390 MACE events had accumulated.		
Descriptive statistics and estimate variability	Treatment group	Dapagliflozin 10 mg	Placebo
	Number of subjects	8 582 patients	8 578 patients
	MACE (safety/efficacy) (n (%))	756 (8.8)	803 (9.4)
	K-M est. of cum prop of subj with an event up to month 60 (%)	10.9 (95% CI 9.9, 12.0)	11.2 (95% CI 10.3, 12.3)
	HF/CV death (n (%))	417 (4.9)	496 (5.8)
	K-M est. of cum prop of subj with an event up to month 60 (%)	5.7 (95% CI 5.1, 6.4)	7.1 (95% CI 6.3, 8.1)
	Renal (n (%))	370 (4.3)	480 (5.6)
	K-M est. of cum prop of subj with an event up to month 60 (%)	5.2 (95% CI 4.6, 5.9)	6.8 (95% CI 6.1, 7.7)

	All-cause mortality (n (%))	529 (6.2)	570 (6.6)
	K-M est. of cum prop of subj with an event up to month 60 (%)	8.0 (95% CI 6.8, 9.5)	10.7 (95% CI 8.5, 13.5)
Effect estimate per comparison	Primary safety endpoint: MACE (non-inferiority)	Comparison groups	Dapagliflozin vs Placebo
		Hazard ratio	0.93
		(95% CI)	(0.84, 1.03)
		P-value	<0.001
	Co-Primary efficacy endpoint: HF/CV death	Comparison groups	Dapagliflozin vs Placebo
		Hazard ratio	0.83
		(95% CI)	(0.73, 0.95)
		P-value	0.005
	Co-Primary efficacy endpoint: MACE (superiority)	Comparison groups	Dapagliflozin vs Placebo
		Hazard ratio	0.93
		(95% CI)	(0.84, 1.03)
		P-value	0.172
	Secondary endpoint: Renal	Comparison groups	Dapagliflozin vs Placebo
		Hazard ratio	0.76
		(95% CI)	(0.67, 0.87)
		P-value	<0.001
	Secondary endpoint: All-cause mortality	Comparison groups	Dapagliflozin vs Placebo
		Hazard ratio	0.93
		(95% CI)	(0.82, 1.04)
		P-value	0.198
Notes	<free text>		
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >**		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is based on the recently completed study DECLARE. DECLARE was a Category 3 post-authorisation safety study (PASS) in the EU (PAM 005) and was further designed to address post-marketing requirements in the US.

This was a large placebo-controlled, parallel-group study of adequate design. The study was event-driven, and patients were followed for approximately 3-5 years. The study included patients with T2DM who either had established CV disease or multiple risk factors for CV disease. Exclusion criteria were adequate. Patients with conditions likely to limit the possibility to follow-up were excluded. Patients with recent acute CV events could be enrolled provided that randomisation did not occur until 8 weeks after the event.

A total of 25 698 patients was enrolled, and 17 160 patients were randomised; 40.6% (6974) with established CV disease and 59.4% (10186) without established CV disease. During the study, the number

of subjects to be enrolled was increased (from 22 000 to 27 000) due to a higher screen failure rate than initially expected. In the end, approximately 1/3 were screening failures whereof the majority due to ineligibility based on HbA1c criteria. As of amendment 3 (28 April 2014), 9 285 patients had been randomised and the proportion of patients randomised from the primary and secondary populations were approximately 60% and 40%, instead of 33% and 67% respectively, as initially expected. With amendment 3, the aim became to continue recruitment allowing patients to be included with no exact proportions defined regarding primary and secondary prevention.

The primary objective was to determine the effect of dapagliflozin relative to placebo on CV outcomes and the secondary objective was to determine whether treatment with dapagliflozin compared with placebo will result in a reduction of renal events or all-cause mortality. These objectives were adequate.

The variables included both the composite endpoints and the individual components. Exploratory variables included effects on metabolic control and long-term complications. According to the CSR, an independent, blinded Clinical Event Adjudication Committee (CEC) adjudicated all primary and secondary CV endpoints. The variables selected are adequate.

The study was event-driven, 1390 subjects with adjudicated MACE events were required, and had a group sequential design with two interim analyses to occur when 1/3 and 2/3 of the primary events had been observed. A DMC was appointed to assess the interim data outcomes and the study was to be stopped only if dapagliflozin was shown to be superior to placebo on both the occurrence of MACE and all-cause mortality. The two interim analyses were performed where after the study continued until the prespecified number of MACE endpoint events had been reached and, the study remained blinded until database lock.

Several changes were implemented after study start (via protocol amendments) including changes to planned analyses; the most substantive being that hospitalisation for HF, initially a key secondary efficacy endpoint, was elevated to a primary efficacy endpoint as a component of a composite with CV death. In addition, after data became available suggesting SGLT2 inhibitors have a positive effect on renal outcomes, a renal composite endpoint comprising confirmed sustained ≥40% decrease in eGFR, confirmed sustained eGFR and/or renal death was added as a secondary efficacy variable.

The composite of HF hospitalisation and CV death was added as a primary endpoint with study protocol amendment 5. The MAH ~~has~~ stated that the changes to the components of composite endpoints and to the endpoint hierarchy were not based on knowledge of any blinded or unblinded results from DECLARE and that these changes were initiated prior to the first interim analysis conducted by DMC. However, the first interim analysis, when 1/3 of the MACE events had accumulated, was seemingly performed in February 2016 while amendment 5 was dated 25 September 2016. The MAH was requested to elaborate on the time-point for when the changes to the endpoint hierarchy including the adding of a primary endpoint, the composite of HF hospitalisation were initiated. In their response the draft protocol amendment stated to have been submitted to the FDA in December 2015 has been provided clarifying that the draft Protocol Amendment No. 5 was dated 18 December 2015 and also included the proposed change regarding the primary objective and the endpoint hierarchy. The changes to the components of composite endpoints and to the endpoint hierarchy is thereby accepted as having been initiated before the conduct of the interim analysis in February 2016. Upon request, the DMC minutes and the DMC charter have also been submitted, documents that, as explained by the MAH, had inadvertently been omitted.

The primary analysis population was FAS that included all randomised patients except for all patients randomised (n=30) at a site suspected of GCP violations in another study sponsored by MAH; the decision to exclude these was made prior to the unblinding of data. There was no per-protocol population defined; overall protocol deviations occurred among approximately 10% of the patients being very similar comparing the treatment arms. Considering the general importance of a PP analysis when the objective

is non-inferiority; the on-treatment FAS (OT-FAS) including only events that had occurred while on treatment (and up to 30 days after treatment discontinuation) is acceptable. Most of the protocol deviations were due to that for 9% of the patients the stratification information entered in the IWRS differed from the information entered and verified in the clinical database. Randomisation strata were used as covariates in all statistical models with the stratification of analyses performed using the stratification values as entered in IVRS. This is endorsed. The discrepancy between the two sources was however assessed in a post hoc analysis using the database information and was shown not to impact the results of the primary endpoints.

Accounting for the two interim analyses using O-Brian Fleming boundaries, the final analysis was performed based on a one-sided alpha of 2.31%. In addition, a closed test procedure was used to control for the overall type I error rate across the analyses of the primary and the secondary endpoints. After the adding of CF hospitalisation and CV death a primary endpoint, alfa was equally split for the two co-primary superiority analyses. A hierarchical testing order was used for control of the type I error rate across also secondary hypothesis. Hence, multiplicity adjustments were adequate.

Overall, 98.5% completed the study, i.e. had not withdrawn their consent and were not lost to follow-up. Drop-out rates were numerically higher in the placebo-treated group (145 vs 109 in the dapagliflozin group), but the difference was small, taking the large size of the study into account.

A large proportion of patients completed the study on study drug (76.8%). The proportion of patients permanently discontinuing study drug was somewhat higher in the placebo treated group (25% vs 21.1%). Of those who prematurely discontinued study treatment the most common reasons were subject decision; 825/1807 (45.7%) and 1086/2144 (50.7%) in the dapagliflozin and placebo arm respectively, and occurrence of an AE/SAE; 671/1807 (37.1%) in the dapagliflozin arm and 548/2144 (25.6%) in the placebo arm.

The total study duration was more than 5 years with the last patients included in June 2015, allowing for at least 3 years of follow-up. Study duration was very similar in the dapagliflozin and placebo arm with a study median follow-up time of 4.2 years.

A total of 5 amendments were made to the study protocol. The first amendment came into effect before the inclusion of the first patient. The 2nd and 3rd amendment included changes to the enrolment target and measures to ensure that sufficient numbers of patients with CV disease were included as discussed above. The 3rd amendment (April 2014) also included additional AEoSI (previously collected in the CRF) but also added new AEoSI. The 5th amendment came into effect in September 2016 and introduced changes to the primary endpoint (see discussion above) but also added new safety events for which data were to be collected, i.e. HF that did not require hospitalisation, potential DKA, all amputations and related events. Adjudication of all potential DKA events was also included. The late addition of AEoSIs may have some impact on the safety assessment as discussed in the safety part of this report.

For each category of protocol deviation, numbers were low except for incorrect entry of baseline stratification factors (see discussion above). Protocol deviations were generally balanced between groups. The protocol deviations are not considered to have affected the outcome or interpretation of the study and the study is considered well conducted.

Efficacy data and additional analyses

About 40% of the patients included in the study had established CV disease. Among patients without established CV disease, the majority (64%) had 2 risk factors in addition to T2DM and age. There were no imbalances between the treatment groups. Neither were any imbalances observed between treatment

groups with regards to demographic and baseline characteristics. As may be expected, the patients with established CV disease were somewhat older than those without. In the overall population, the medical history was typical for a population at high CV risk. A history of HF was more common in the patient with established CV disease (16.6% vs. 5.6%). In the overall population, 10% (1724 subjects) had a history of HF. Among the patients with HF, 56% were in NYHA Class II, and 7.3% were in NYHA Class III.

Although almost 2% of patients appears to have been naïve to antidiabetic medication at the time of inclusion, the majority were on 2 or more antidiabetic medications and 41% used insulin. As expected, a large proportion (82%) were on metformin treatment. CV medications were as expected.

The primary safety endpoint was met as the upper CI for MACE (CV death, MI and ischaemic stroke) was well within the non-inferiority margin of 1.3. Dapagliflozin was found to be superior to placebo for the added primary efficacy endpoint of hospitalisation for HF/CV death (HR 0.83 [95% CI 0.73, 0.95]), whereas this was not the case for MACE (HR 0.93 [95% CI 0.84, 1.03]). Therefore, confirmatory testing was not conducted for the secondary efficacy endpoints of renal events and all-cause mortality. Several pre-defined sensitivity analyses were performed supporting primary results.

For the composite endpoint of hospitalisation for HF and CV death, the outcome was driven by the reduction in hospitalisations for HF (HR 0.73 [95% CI 0.61, 0.88]). Although the number of MACE were numerically lower in the dapagliflozin group, superiority versus placebo was not shown. The difference in number of events was mainly due to a numerically lower incidence of MI in the dapagliflozin group (393 vs 441).

The overall pattern of the outcome compares with the data from the CVOT trial for another SGLT2 inhibitor (empagliflozin; EMPA-REG OUTCOME), although in the DECLARE study, superiority for dapagliflozin versus placebo with regards to MACE could not be shown. In the EMPA-REG 99.5% of patients had established CV disease compared to DECLARE where only 40.6% of patients had established CV disease. In EMPA-REG, a reduction in CV death and all-cause death was observed, whereas no effect on these endpoints were observed with dapagliflozin. When looking at the individual CV endpoints, both empagliflozin and dapagliflozin showed the most prominent effect on hospitalisation due to HF, which may be explained by the diuretic effect of these compounds.

The outcome of the secondary endpoint, renal events, was not formally tested. For the composite endpoint a HR of 0.76 [95% CI 0.67 to 0.87], was observed, mainly driven by the reduction of sustained GFR decrease and ESRD events.

A number of exploratory endpoints evaluated the effect of dapagliflozin on eGFR and albuminuria. eGFR measurements over time show that in the dapagliflozin group there was an initial drop in eGFR during the first 6 months after which the decrease in eGFR slowed down. From 6 months and onward the decrease in eGFR was slower in the dapagliflozin group, resulting in a higher mean eGFR at 4 years compared to placebo.

The increase in the albumin to creatinine ratio from baseline was slower in the dapagliflozin treated group compared to the placebo group and new onset of macroalbuminuria was delayed in the dapagliflozin group compared to the placebo group. Regression in severity of albuminuria in patients with pre-existing macroalbuminuria was greater with dapagliflozin than with placebo. Notably, improvements were also observed in the placebo group.

Thus, the data provided give no indication of a negative effect on renal function with dapagliflozin treatment and indeed, the data indicate that progression of nephropathy was slower in the dapagliflozin group compared to the placebo group.

The HR for all-cause mortality was 0.93 (95% CI 0.82-1.04).

In the dapagliflozin group, a mean decrease of -0.7% in HbA1c was observed at 6 months. After that time-point, HbA1c slowly increased and the mean change from baseline was -0.4% at 4 years. In the placebo group a mean decrease of -0.2% was observed at 4 years. This difference between dapagliflozin and placebo is comparable to the difference observed in the EMPA-REG trial at week 206.

Subgroup analyses for the composite of hospitalisation for HF and CV death, the composite of MACE and for the renal composite variables showed consistent findings across the subgroups tested. For most of the subgroups, the HR point estimate was in favour of dapagliflozin treatment or close to 1.

2.4.3. Conclusions on the clinical efficacy

DECLARE was a well-designed and well-conducted trial. The trial showed non-inferiority of dapagliflozin to placebo on the primary outcome MACE whereas superiority was not shown. A statistically significant effect on hospitalisations due to HF was observed, whereas no effect could be shown on CV death or all-cause mortality. Effects on renal events was investigated and the data indicate that progression of nephropathy was slower in the dapagliflozin group compared to the placebo group.

Section 5.1 of the SmPC has been amended to include information on the outcome of the DECLARE trial.

2.5. Clinical safety

Introduction

The safety and tolerability of dapagliflozin were investigated and documented in the original submission for approval of dapagliflozin for treatment of type 2 diabetes mellitus (T2DM). The original T2DM submission has been supplemented over time with updated information on the safety and tolerability of dapagliflozin, notably with data from a 30-month safety update (30-MSU) cut-off relative to the original data cut and with post-marketing data.

With this submission, information on the safety and tolerability of dapagliflozin in the Phase IIIb cardiovascular (CV) outcome study – study D1693C00001 (DECLARE) is provided.

The safety evaluation does not include pooled analyses of data from DECLARE together with other dapagliflozin studies. This approach is considered appropriate given the size of the DECLARE study and the differences in study design from previously completed dapagliflozin studies.

Methods

DECLARE was a Category 3 post-authorisation safety study (PASS) in the EU (PAM 005). The PASS requirement was that DECLARE be designed to evaluate bladder cancer. Other potential safety concerns that the European Medicines Agency requested be assessed were clinical consequences of increased haematocrit, renal impairment/failure, bone fracture, liver injury, breast cancer, prostate cancer, diabetic ketoacidosis (DKA), amputations, and pancreatitis. Some of these requests were made while the study was ongoing.

Safety variables collected

The safety database included pre-specified events for which extensive and pre-defined data points were collected to allow for a comprehensive assessment of these events. In addition, comprehensive

prospective and retrospective data collection for amputation and DKA events was implemented during the study.

The safety variables collected were: SAEs, adverse events leading to discontinuation of study drug (DAEs), amputation events, DKA events, and adverse events of special interest (AEoSIs). The AEoSIs were: malignancies, hepatic events, major hypoglycaemic events, fractures, renal events, symptoms suggestive of volume depletion, hypersensitivity reactions, urinary tract infections (UTIs), and genital infections. All AEs were collected for these events except for hypersensitivity reactions, UTIs, and genital infections, for which only SAEs and DAEs were collected.

Renal events were analysed in 2 ways. Renal events as an AEoSI (hereafter referred to as simply "renal events") were defined and analysed using a broad list of preferred terms (PTs) including PTs suggesting any impairment in renal function (acute, chronic, and laboratory changes). In addition, to capture events suggestive of acute renal impairment, renal events were analysed using the standardised Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) "Acute renal failure (narrow scope)" (hereafter referred to as "events of acute impairment of renal function").

In accordance with FDA guidelines (FDA 2008), the primary safety variable of the study was major adverse cardiovascular events (MACE), which was also one of the dual primary efficacy variables. MACE is discussed in detail in the efficacy part of this report.

Adjudication

An independent, blinded Clinical Event Adjudication Committee (CEC) adjudicated the following safety variables: potential malignancies, hepatic events, and potential DKA events.

Analysis sets

Safety analysis set

The safety analysis set (SAS) included all randomised patients who received at least 1 dose of randomised study drug and who had data observed at any time after first randomised dose till the end of the study. Erroneously treated patients (patients randomised to one treatment group but given the other treatment) were included in the group for the treatment they actually received rather than the treatment to which they were randomised, if they only received the erroneous treatment and none of the correct treatment. The SAS was considered the primary analysis set for malignancies, fractures, and amputations.

On-treatment safety analysis set

The on-treatment safety analysis set (OT-SAS) included all randomised patients who received at least 1 dose of study drug and who had data observed at any time after first randomised dose till the end of the study, and only observations collected during treatment with study drug or within a certain number of days of the last dose of study drug:

- Continuous safety variables (e.g. lab values and vital signs): within 7 days of last dose of study drug
- SAEs: within 30 days of last dose of study drug
- Non-serious AEoSIs: within 7 days of last dose of study drug

Patient exposure

The duration of exposure to study drug ranged from 0 to 62 months. In total, there were 30 623 p-y of exposure to dapagliflozin in the study. The median duration of exposure to study drug was 48 months in both treatment groups (Table 11). In total, there were 69 480 years of follow-up in the study: 34 812

years in the dapagliflozin group and 34 668 years in the placebo group. The median duration of follow-up was 50 months in both treatment groups.

Table 11 Extent of exposure to study drug (SAS)

	Number (%) of patients		
	Dapa 10 mg (N=8574)	**Placebo (N=8569)**	**Total (N=17143)**
Total number of patient years exposure (years)	30623	29749	60372
Exposure to study drug (months)			
n	8574	8569	17143
Mean	42.856	41.657	42.256
SD	14.6289	15.1854	14.9213
Median	48.100	47.830	48.000
Q1, Q3	39.930, 51.630	37.130, 51.330	38.500, 51.500
Min, Max	0.07, 61.20	0.03, 61.97	0.03, 61.97
Exposure to study drug (months) – descending cumulative (%)			
>0	8574 (100.0)	8569 (100.0)	17143 (100.0)
>1	8511 (99.3)	8519 (99.4)	17030 (99.3)
>3	8394 (97.9)	8410 (98.1)	16804 (98.0)
>6	8236 (96.1)	8214 (95.9)	16450 (96.0)
>12	7903 (92.2)	7814 (91.2)	15717 (91.7)
>18	7611 (88.8)	7474 (87.2)	15085 (88.0)
>24	7359 (85.8)	7178 (83.8)	14537 (84.8)
>30	7121 (83.1)	6855 (80.0)	13976 (81.5)
>36	6878 (80.2)	6556 (76.5)	13434 (78.4)
>42	6300 (73.5)	5984 (69.8)	12284 (71.7)
>48	4413 (51.5)	4119 (48.1)	8532 (49.8)
>54	1173 (13.7)	1075 (12.5)	2248 (13.1)
>60	38 (0.4)	37 (0.4)	75 (0.4)

Extent of exposure (months) = (last dosing date - first dosing date + 1)/30 rounded to one decimal, regardless of interruptions.

Dapa Dapagliflozin; Max Maximum; Min Minimum; N Number of patients per treatment group; n Number of patients with information; Q1 1st quartile; Q3 3rd quartile; SAS Safety analysis set; SD Standard deviation

Adverse events

Analysis of adverse events

The SAS is considered the primary analysis set for malignancies, amputations, and fractures, while the OT-SAS is considered the primary analysis set for all other safety variables. Data for the primary analysis sets for each variable are presented below, except for overall AEs, deaths, SAEs, and DAEs, for which both analysis sets are presented.

Common adverse events

An overall summary of AEs is shown in Table 12. The numbers of patients with SAEs were balanced between treatment groups, while there were more patients with DAEs in the dapagliflozin group compared with the placebo group.

There were fewer patients with renal events or major hypoglycaemic events in the dapagliflozin group compared with the placebo group. Definite DKA events were rare overall, but there were more in the dapagliflozin group compared with the placebo group. There were more patients with SAEs/DAEs of genital infections in the dapagliflozin group compared with the placebo group; the difference was driven by non-serious genital infection DAEs. The occurrence of amputations and all other AEoSIs was balanced between treatment groups. The findings were generally consistent when analysed by baseline CV risk category, with no specific pattern to event occurrence related to baseline CV risk category.

Only AEs belonging to the categories described in the introduction were collected in the study, and therefore, analyses of the most common PTs overall were not performed. All SAEs were collected in the study; for the most common PTs for SAEs, refer to Table 13.

Table 12 Overall summary of adverse events (SAS and OT-SAS)

Adverse event[a]	Number (%) of patients			
	Dapa 10 mg		Placebo	
	SAS (N=8574)	OT-SAS (N=8574)	SAS (N=8569)	OT-SAS (N=8569)
Number of patients with:				
AE leading to death	527 (6.1)	392 (4.6)	566 (6.6)	390 (4.6)
At least 1 SAE	3205 (37.4)	2925 (34.1)	3418 (39.9)	3100 (36.2)
At least 1 study drug-related SAE[b]	132 (1.5)	131 (1.5)	153 (1.8)	148 (1.7)
Any AE leading to premature permanent discontinuation of study drug	693 (8.1)	693 (8.1)	592 (6.9)	592 (6.9)
Any SAE leading to premature permanent discontinuation of study drug	255 (3.0)	255 (3.0)	303 (3.5)	303 (3.5)
At least 1 adjudicated malignancy[c]	481 (5.6)	418 (4.9)	486 (5.7)	414 (4.8)
At least 1 hepatic event with causality to IP adjudicated as definite or highly likely[d]	0	0	0	0
At least 1 event of fracture[c]	457 (5.3)	401 (4.7)	440 (5.1)	378 (4.4)
At least 1 event of symptoms suggestive of volume depletion[c]	250 (2.9)	213 (2.5)	256 (3.0)	207 (2.4)
At least 1 SAE/DAE of hypersensitivity reaction[c]	36 (0.4)	32 (0.4)	40 (0.5)	36 (0.4)
At least 1 SAE/DAE of urinary tract infection[c]	145 (1.7)	127 (1.5)	156 (1.8)	133 (1.6)
At least 1 SAE/DAE of genital infection[c]	76 (0.9)	76 (0.9)	10 (0.1)	9 (0.1)
At least 1 renal event[c]	494 (5.8)	422 (4.9)	614 (7.2)	526 (6.1)
At least 1 major hypoglycaemic event	66 (0.8)	58 (0.7)	98 (1.1)	83 (1.0)
At least 1 event of surgical or spontaneous/non-surgical amputation	120 (1.4)	102 (1.2)	113 (1.3)	93 (1.1)
At least 1 event of definite diabetic ketoacidosis	23 (0.3)	20 (0.2)	11 (0.1)	9 (0.1)
At least one embolic or thrombotic event AND marked abnormality in haematocrit or haemoglobin		24 (0.3)		6 (<0.1)
At least 1 SAE/DAE of pancreatitis	30 (0.3)	24 (0.3)	29 (0.3)	25 (0.3)

Table 12 Overall summary of adverse events (SAS and OT-SAS)

Adverse event[a]	Number (%) of patients			
	Dapa 10 mg		Placebo	
	SAS (N=8574)	OT-SAS (N=8574)	SAS (N=8569)	OT-SAS (N=8569)
At least 1 event of Fournier's gangrene[d]	2 (<0.1)	1 (<0.1)	8 (<0.1)	5 (<0.1)

[a] Includes SAE, DAE, AE leading to death, malignancies, adjudicated related hepatic events, fractures, symptoms suggestive of volume depletion, SAEs/DAEs of hypersensitivity reactions, SAEs/DAEs of urinary tract infection, SAEs/DAEs of genital infections, renal events, major hypoglycaemic events, events of surgical or spontaneous/non-surgical amputation, and event of definite diabetic ketoacidosis

[b] Study drug related AE/SAE as assessed by investigator.

[c] AEs are based on pre-defined preferred term list.

[d] Includes events assessed as Fournier's gangrene by TIMI and AstraZeneca prior to database lock and treatment allocation unblinding.

AEs were coded according the MedDRA version 21.0. Patients with events in more than 1 category are counted in each category. SAS includes events that occurred after the first dose of study drug up to the Closing Visit. On-treatment SAS includes events that occurred after the first dose of study drug to the earlier of on or before 30 (for SAE/adjudicated events/amputation/major hypoglycaemia) or 7 (for non-SAE) days after last dose of study drug or the Closing Visit.

AE Adverse event; Dapa Dapagliflozin; DAE Adverse event leading to discontinuation of study drug; IP Investigational product; MedDRA Medical Dictionary for Regulatory Activities; N Number of patients per treatment group; OT On-treatment; SAE Serious adverse event; SAS Safety analysis set

Serious adverse event/deaths/other significant events

Serious adverse events

The numbers of patients with SAEs were balanced between treatment groups: 37.4% in the dapagliflozin group and 39.9% in the placebo group in the SAS, and 34.1% in the dapagliflozin group and 36.2% in the placebo group in the OT-SAS. The SOCs and PTs of the most commonly reported SAEs were similar between treatment groups. The most common PTs for SAEs in the OT-SAS were Angina unstable, Acute myocardial infarction, and Pneumonia in both treatment groups (Table 13).

Table 13 Most common serious adverse events by preferred term (SAS and OT-SAS)

Preferred term[a]	Number (%) of patients			
	Dapa 10 mg		Placebo	
	SAS (N=8574)	OT-SAS (N=8574)	SAS (N=8569)	OT-SAS (N=8569)
Patients with at least 1 SAE	3205 (37.4)	2925 (34.1)	3418 (39.9)	3100 (36.2)
Angina unstable	271 (3.2)	243 (2.8)	269 (3.1)	238 (2.8)
Acute myocardial infarction	265 (3.1)	228 (2.7)	233 (2.7)	195 (2.3)
Pneumonia	194 (2.3)	163 (1.9)	219 (2.6)	183 (2.1)
Angina pectoris	154 (1.8)	138 (1.6)	159 (1.9)	146 (1.7)
Cardiac failure	147 (1.7)	120 (1.4)	188 (2.2)	165 (1.9)
Cardiac failure congestive	121 (1.4)	89 (1.0)	147 (1.7)	122 (1.4)
Atrial fibrillation	117 (1.4)	94 (1.1)	139 (1.6)	121 (1.4)
Coronary artery disease	106 (1.2)	94 (1.1)	84 (1.0)	69 (0.8)
Osteoarthritis	103 (1.2)	91 (1.1)	92 (1.1)	76 (0.9)
Cerebrovascular accident	102 (1.2)	89 (1.0)	88 (1.0)	71 (0.8)
Ischaemic stroke	97 (1.1)	85 (1.0)	90 (1.1)	79 (0.9)
Myocardial infarction	96 (1.1)	84 (1.0)	108 (1.3)	96 (1.1)
Acute kidney injury	94 (1.1)	67 (0.8)	127 (1.5)	101 (1.2)
Non-cardiac chest pain	93 (1.1)	82 (1.0)	107 (1.2)	85 (1.0)
Cellulitis	84 (1.0)	76 (0.9)	93 (1.1)	80 (0.9)
Death	81 (0.9)	40 (0.5)	89 (1.0)	43 (0.5)
Sepsis	77 (0.9)	53 (0.6)	70 (0.8)	49 (0.6)
Hypoglycaemia	69 (0.8)	61 (0.7)	86 (1.0)	73 (0.9)
Prostate cancer	69 (0.8)	62 (0.7)	55 (0.6)	53 (0.6)
Transient ischaemic attack	68 (0.8)	63 (0.7)	54 (0.6)	46 (0.5)
Chronic obstructive pulmonary disease	54 (0.6)	45 (0.5)	54 (0.6)	48 (0.6)
Urinary tract infection	49 (0.6)	37 (0.4)	67 (0.8)	51 (0.6)
Myocardial ischaemia	47 (0.5)	37 (0.4)	54 (0.6)	51 (0.6)
Peripheral arterial occlusive disease	43 (0.5)	41 (0.5)	49 (0.6)	47 (0.5)
Acute respiratory failure	37 (0.4)	26 (0.3)	43 (0.5)	34 (0.4)
Hyperglycaemia	37 (0.4)	27 (0.3)	55 (0.6)	46 (0.5)
Syncope	37 (0.4)	28 (0.3)	41 (0.5)	30 (0.4)
Osteomyelitis	26 (0.3)	21 (0.2)	39 (0.5)	30 (0.4)

[a] Patients with events in more than 1 category are counted in each category. Patients with multiple events in the same category are counted only once in that category. Only PTs with a frequency of ≥0.5% (rounded) in a single treatment group are displayed in the table.

SAS includes SAEs that occurred after the first dose of study drug up to the Closing Visit. OT-SAS includes SAEs that occurred after the first dose of study drug to the earlier of 30 days after last dose of study drug or the Closing Visit. AE coded using MedDRA version 21.0.

AEs are sorted based on frequencies in Dapa 10 mg group in SAS by decreasing frequency of PT.

AE Adverse event; Dapa Dapagliflozin; MedDRA Medical Dictionary for Regulatory Activities; N Number of patients per treatment group; OT On-treatment; PT Preferred term; SAE Serious adverse event; SAS Safety analysis set

Deaths

In the SAS, there were 527 patients (6.1%) in the dapagliflozin group and 566 patients (6.6%) in the placebo group who died. In the OT-SAS, there were 392 patients (4.6%) in the dapagliflozin group and 390 patients (4.6%) in the placebo group who died. The SOCs and PTs of deaths were generally balanced between treatment groups. Most deaths in both treatment groups occurred in the SOC Cardiac and vascular disorders.

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

Analysis of adverse events by organ system or syndrome

AEoSI: malignancies

No overall imbalances in malignancies have been observed between dapagliflozin and comparator in the original dapagliflozin clinical development programme (All Phase IIb/III Pool). When examining tumours in different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumour locations and below 1 for others. The frequencies of bladder cancer, breast cancer, and prostate cancer were higher in dapagliflozin-treated patients than comparator-treated patients, however, event numbers were small: 9 (0.14 events per 100 p-y) and 1 (0.03 events per 100 p-y) for bladder cancer, 12 (0.40 events per 100 p-y) and 3 (0.19 events per 100 p-y) for breast cancer, and 11 (0.30 events per 100 p-y) and 6 (0.26 events per 100 p-y) for prostate cancer in the dapagliflozin and comparator groups, respectively. No causality has been established.

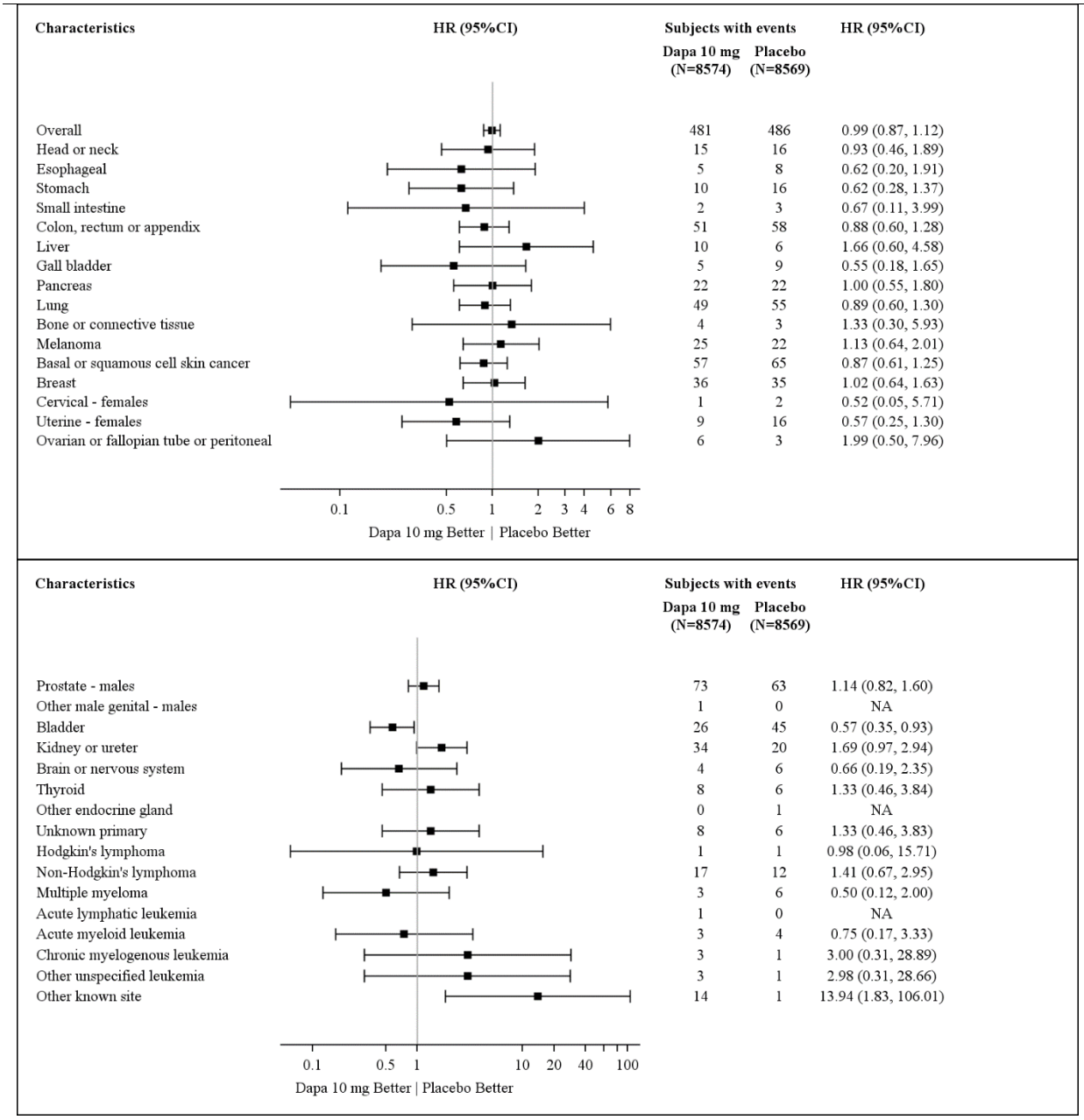
Evaluating bladder cancer, breast cancer, and prostate cancer was an EU post-marketing assessment measure (PAM). In addition, interim monitoring for bladder cancers in DECLARE was conducted regularly to be able to communicate potential signals with regulatory authorities.

<u>DECLARE results</u>

In the DECLARE study, malignancies were analysed overall and by location. All potential malignancies/suspect neoplasms except non-melanoma skin cancers were sent for adjudication. Potential malignancies adjudicated to be malignancies are summarised below.

The numbers of patients with adjudicated malignancies were balanced between treatment groups: 481 (5.6%) and 486 (5.7%) in the dapagliflozin and placebo groups, respectively, corresponding to incidence rates of 14.32 and 14.52 events per 1000 p-y (SAS). The relative risk associated with dapagliflozin was above 1 for some tumour locations and below 1 for others (Figure 15). The location of events with relative risk above 1 for dapagliflozin was not consistent between DECLARE and what was observed in the original dapagliflozin clinical programme. The results were consistent when analysed using the OT-SAS.

Figure 15 Forest plot of malignancies by location (SAS)



Only adjudicated events with event date on or after date of randomisation are included.

CI Confidence interval; Dapa Dapagliflozin; HR Hazard ratio; N Number of patients per treatment group; NA Not analysed; SAS Safety analysis set

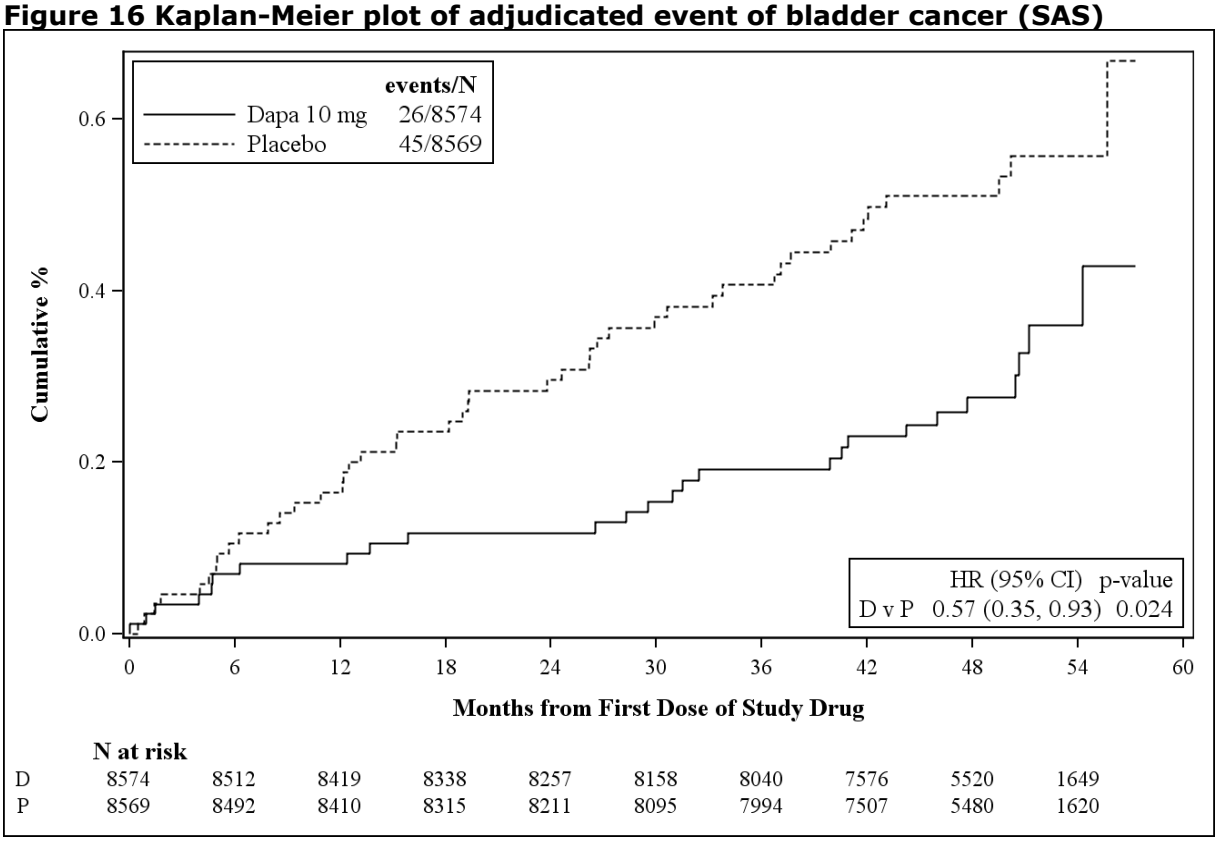
Malignancies were categorised as "Other known site" when the other prespecified locations were not applicable. There was no pattern to the localisation of the "Other known site" malignancies.

Results for bladder cancer, breast cancer, and prostate cancer are presented below.

Bladder cancer

There were fewer patients with adjudicated bladder cancer in the dapagliflozin group compared with the placebo group: 26 (0.3%) and 45 (0.5%), respectively (SAS), corresponding to incidence rates of 0.76 and 1.32 per 1000 p-y and an incidence rate ratio of 0.58 (95% CI: 0.34, 0.95) for dapagliflozin vs placebo (Figure 16).

Figure 16 Kaplan-Meier plot of adjudicated event of bladder cancer (SAS)



N at risk is the number of patients at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p-value is displayed. Events are adjudicated and confirmed as malign. Analysis of time from first dose of study drug to first occurrence of event or censoring.

HR, CI and p-value are from Cox proportional hazard model.

CI Confidence interval; D Dapaglifozin 10 mg; Dapa Dapagliflozin; HR Hazard ratio; N Number of patients per treatment group; P Placebo; SAS Safety analysis set; v Versus

Breast cancer

The numbers of patients with adjudicated breast cancer were balanced between the treatment groups: 36 (0.4%) in the dapagliflozin group and 35 (0.4%) in the placebo group (SAS).

Prostate cancer

The numbers of patients with adjudicated prostate cancer were balanced between the treatment groups: 73 (1.4% of male patients) in the dapagliflozin group and 63 (1.2% of male patients) in the placebo group (SAS).

AEoSI: hepatic events

One case of drug-induced hepatitis and a subsequent diagnosis of autoimmune hepatitis was reported in a dapagliflozin-treated patient in study D1690C00004, described in the 30-MSU. The MAH considered the event not likely to be related to study drug. In the original dapagliflozin clinical development programme, no imbalances in liver AEs or marked liver abnormalities have been observed between dapagliflozin and comparator treatment.

Evaluating liver injury in DECLARE was an EU PAM.

DECLARE results

Hepatic events were adjudicated for study drug causality. There were no hepatic events for which study drug causality was assessed as 'definite' or 'highly likely' by the adjudication committee in either treatment group. There were no events in the dapagliflozin group and 1 event in the placebo group for which study drug causality was adjudicated as 'probable' (OT-SAS).

AEoSI: fractures

Increased rates of fractures were observed in patients treated with the sodium-glucose cotransporter 2 (SGLT2) inhibitor canagliflozin in the CANVAS Program (Neal et al 2017). However, no increased risk of fractures has been observed in the EMPA-REG study of empagliflozin (Zinman et al 2015) or in the overall dapagliflozin clinical development programme (30-MSU All Phase IIb/III Pool), and in a dedicated study (D1690C00012), dapagliflozin had no effect on markers of bone formation and resorption or bone mineral density in patients with T2DM after 102 weeks of treatment. These data suggest that the increased incidence of fractures observed in the CANVAS Program is not a class effect of SGLT2 inhibitors.

Evaluating bone fractures in DECLARE was an EU PAM.

DECLARE results

The numbers of patients with fractures were balanced between treatment groups: 457 (5.3%) and 440 (5.1%) in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 13.6 and 13.2 events per 1000 p-y (SAS). There were fewer patients with osteoporotic fractures in the dapagliflozin group compared with the placebo group.

AEoSI: adverse events suggestive of volume depletion

In the original dapagliflozin clinical development programme, the frequency of AEs suggestive of volume depletion was low but slightly higher in dapagliflozin-treated patients compared with placebo-treated patients (27 [1.1%] vs 17 [0.7%] in the Placebo-Controlled Pool); however, there were very few serious events, and the small number of events did not allow for a complete evaluation of serious volume depletion events.

DECLARE results

The numbers of patients with AEs suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 7.0 and 7.0 events per 1000 p-y (OT-SAS). There were 81 (0.9%) and 70 (0.8%) patients with SAEs suggestive of volume depletion in the dapagliflozin and placebo groups, respectively. There were very few patients who had AEs suggestive of volume depletion that led to study drug discontinuation in both treatment groups.

AEoSI: hypersensitivity reactions (SAEs/DAEs)

There have been spontaneous post-marketing reports of serious hypersensitivity reactions in dapagliflozin-treated patients. In the original dapagliflozin clinical development programme, the incidence of serious hypersensitivity reactions was low and generally similar between patients treated with dapagliflozin and with comparator (All Phase IIb/III Pool). The small number of events did not allow for a complete evaluation of serious hypersensitivity reactions.

DECLARE results

There were 15 (0.2%) and 26 (0.3%) patients with SAEs of hypersensitivity reactions in the dapagliflozin and placebo groups, respectively (OT-SAS). There were 19 (0.2%) and 11 (0.1%) patients with DAEs of hypersensitivity reactions in the dapagliflozin and placebo groups, respectively (OT-SAS).

AEoSI: urinary tract infections (SAEs/DAEs)

In the original dapagliflozin clinical development programme, the frequency of UTIs was slightly higher in dapagliflozin-treated patients than in patients receiving placebo (110 [4.7%] vs 81 [3.5%] in the Placebo-Controlled Pool). There were very few serious events, and the small number of events did not allow for a complete evaluation of serious UTI events.

DECLARE results

The numbers of patients with UTI SAEs/DAEs were balanced between treatment groups: 127 (1.5%) and 133 (1.6%) in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 4.1 and 4.5 events per 1000 p-y (OT-SAS). There were fewer patients with UTI SAEs in the dapagliflozin group compared with the placebo group: 79 (0.9%) and 109 (1.3%), respectively (OT-SAS). SAEs of urosepsis were balanced between treatment groups, and there were fewer SAEs of pyelonephritis in the dapagliflozin group compared with the placebo group. There were more patients with UTI DAEs in the dapagliflozin group compared with the placebo group: 61 (0.7%) and 35 (0.4%), respectively (OT-SAS). Most patients had only 1 UTI.

AEoSI: genital infections (SAEs/DAEs)

In the original dapagliflozin clinical development programme, the frequency of genital infections was higher in dapagliflozin-treated patients compared with patients receiving placebo (Placebo-Controlled Pool). There were very few serious events, and the small number of events did not allow for a complete evaluation of serious genital infections.

DECLARE results

There were more patients with genital infections SAEs/DAEs in the dapagliflozin group compared with the placebo group: 76 (0.9%) and 9 (0.1%), respectively, corresponding to event rates of 2.5 and 0.3 events per 1000 p-y (OT-SAS). The difference was driven by non-serious DAEs of genital infection: there were 74 (0.9%) and 7 (<0.1%) non-serious DAEs of genital infection in the dapagliflozin group and placebo group, respectively (OT-SAS). There were only 2 SAEs of genital infection in each treatment group (OT-SAS).

AEoSI: renal events

In the original dapagliflozin clinical development programme, events of renal impairment or failure were more common in dapagliflozin-treated patients compared with patients receiving placebo (76 [3.2%] vs 42 [1.8%] in the Placebo-Controlled Pool). SAEs of renal impairment or failure were few in both treatment groups.

Evaluating renal impairment/failure in DECLARE was an EU PAM.

DECLARE results

There were fewer patients with renal events in the dapagliflozin group compared with the placebo group: 422 (4.9%) and 526 (6.1%), respectively, corresponding to event rates of 14.0 and 18.0 events per 1000 p-y (OT-SAS). There were fewer patients with events reported as acute kidney injury in the dapagliflozin group compared with the placebo group: 125 (1.5%) and 175 (2.0%), respectively, of which 67 and 101 were reported as SAEs (OT-SAS). There were fewer patients with SAEs of renal events in the dapagliflozin group compared with the placebo group: 80 (0.9%) and 136 (1.6%), respectively (OT-SAS). There were 55 (0.6%) and 61 (0.7%) patients with renal events reported as DAEs in the dapagliflozin and placebo groups, respectively (OT-SAS).

There were fewer patients with events of acute impairment of renal function in the dapagliflozin group compared with the placebo group: 293 (3.4%) and 376 (4.4%) in the dapagliflozin and placebo groups, respectively, corresponding to event rates of 9.7 and 12.8 events per 1000 p-y (OT-SAS). Most events of acute impairment of renal function were reported as non-serious AEs: 219 (2.6%) and 254 (3.0%) in the dapagliflozin and placebo groups, respectively.

AEoSI: major hypoglycaemic events

Dapagliflozin reduces blood glucose in a manner dependent on blood glucose concentration. This mechanism of action in combination with clinical experience in patients with T2DM suggests that dapagliflozin has a low intrinsic risk of hypoglycaemia. However, in patients taking insulin or sulfonylureas (SUs) in the original dapagliflozin clinical development programme, hypoglycaemic events were more common overall and more common in dapagliflozin-treated patients compared with patients receiving placebo (Placebo-Controlled Pool).

DECLARE results

Major hypoglycaemia was defined as an event where all the following were true: (1) the patient experienced symptoms of severe impairment in consciousness or behaviour; (2) the patient needed external assistance; (3) intervention was needed to treat the hypoglycaemia; and (4) there was prompt recovery of acute symptoms following the intervention.

There were fewer patients with major hypoglycaemic events in the dapagliflozin group compared with the placebo group: 58 (0.7%) and 83 (1.0%), respectively, corresponding to event rates of 1.9 and 2.8 events per 1000 p-y (OT-SAS). Most patients with major hypoglycaemia events in both treatment groups were using insulin at the time of the event. In patients using insulin or SUs at the time of the event, there were also fewer major hypoglycaemic events in the dapagliflozin group compared with the placebo group (OT-SAS).

Other safety event: amputations

Increased rates of lower-limb amputations were observed in patients treated with the SGLT2 inhibitor canagliflozin in the CANVAS Program (Neal et al 2017). However, no increased risk of lower-limb amputations has been observed in the overall dapagliflozin clinical development programme or in the EMPA-REG study of empagliflozin (Zinman et al 2015).

Evaluating amputations in DECLARE was an EU PAM and was requested during the study.

DECLARE results

The numbers of patients with amputations (surgical and spontaneous/non-surgical) were balanced between treatment groups: 123 (1.4%) and 113 (1.3%) in the dapagliflozin and placebo groups, respectively (SAS) (Table 14). Most amputations were reported as SAEs. There were 2 and 4 patients with amputations reported as DAEs in the dapagliflozin and placebo groups, respectively (SAS).

Table 14 Amputations by type of event and location (SAS)

Category	Number (%) of patients	
	Dapa 10 mg	Placebo
	SAS (N=8574)	SAS (N=8569)
Patients with amputation	123 (1.4)	113 (1.3)
1 amputation	78 (0.9)	83 (1.0)
2 amputations	31 (0.4)	21 (0.2)
3 amputations	10 (0.1)	6 (<0.1)

Table 14 Amputations by type of event and location (SAS)

Category	Number (%) of patients	
	Dapa 10 mg	Placebo
	SAS (N=8574)	SAS (N=8569)
>3 amputations	4 (<0.1)	3 (<0.1)
Type of event		
Trauma by accident	3 (<0.1)	0
Surgical amputation	115 (1.3)	113 (1.3)
Spontaneous/non-surgical amputation	6 (<0.1)	1 (<0.1)
Anatomic localisation for surgical or spontaneous/non-surgical amputation		
Lower limb amputation	117 (1.4)	110 (1.3)
Event rate per 1000 subject years	3.4	3.2
Big toe	32 (0.4)	38 (0.4)
Index toe	33 (0.4)	27 (0.3)
Middle toe	23 (0.3)	25 (0.3)
Fourth toe	16 (0.2)	16 (0.2)
Little toe	23 (0.3)	21 (0.2)
Trans metatarsal	16 (0.2)	13 (0.2)
Foot	4 (<0.1)	1 (<0.1)
Below knee	26 (0.3)	17 (0.2)
Above knee	20 (0.2)	13 (0.2)
Other	5 (<0.1)	2 (<0.1)
Upper limb amputation	3 (<0.1)	3 (<0.1)
Event rate per 1000 subject years	0.1	0.1
Thumb	0	1 (<0.1)
Index finger	0	1 (<0.1)
Middle finger	1 (<0.1)	1 (<0.1)
Ring finger	3 (<0.1)	0
Little finger	0	0
Hand	0	0
Below elbow	0	0
Above elbow	0	0

SAS includes amputations that occurred after the first dose of study drug up to the Closing Visit.

Location not recorded for trauma by accident. Amputations at the same hospitalisation will be counted as 2 amputations in case of different anatomical laterality.

Dapa Dapagliflozin; N Number of patients per treatment group; SAS Safety analysis set

Most amputations in both treatment groups were lower-limb amputations. The most common AEs leading to amputation were gangrene, osteomyelitis, and diabetic foot in both treatment groups. The most

common condition triggering lower-limb amputations was infection in both treatment groups. The most common contributing factors to lower-limb amputations were chronic limb ischaemia and neuropathy in both treatment groups.

Other safety event: diabetic ketoacidosis

There have been post-marketing reports of ketoacidosis, including DKA, in patients with T2DM taking dapagliflozin and other SGLT2 inhibitors, although a causal relationship has not been established.

Evaluating DKA in DECLARE was an EU PAM.

DECLARE results

Potential DKA events were adjudicated and assigned a likelihood of being DKA. Events adjudicated as definite DKA or probable DKA are discussed below.

Definite DKA was defined in the adjudication charter as an event in a clinical setting consistent with DKA (history, symptoms, and physical exam), for which no alternative diagnosis was considered a more likely primary cause of presentation, and with the following biochemical data:

- Ketonaemia ≥3.0 mmol/L and/or significant ketonuria (more than 2+ on standard urine sticks), **and**
- At least one of the following criteria suggesting high anion gap metabolic acidosis:
  - Arterial or venous pH ≤7.3
  - Serum bicarbonate ≤18 mEq/L
  - Anion gap [Na – (Cl + HCO3)] >10

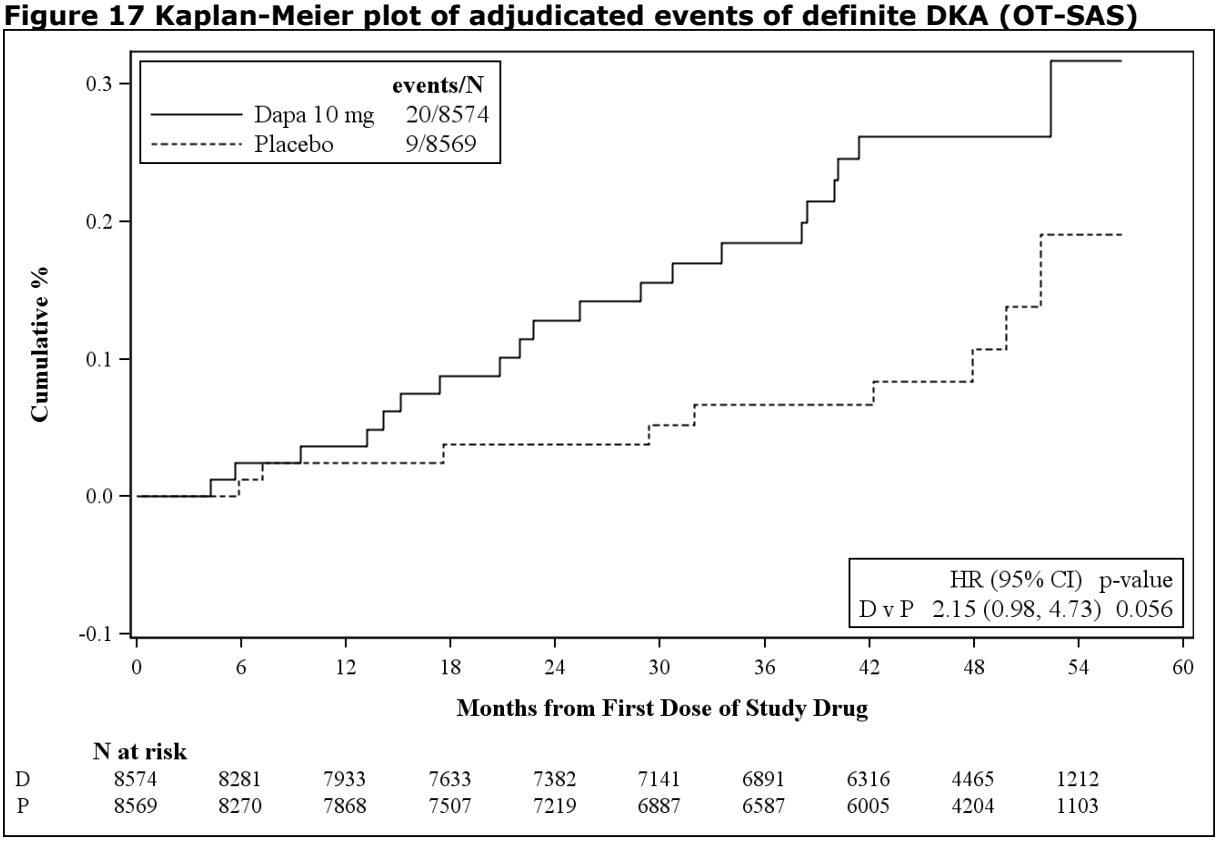
Probable DKA was defined in the adjudication charter as an event that does not meet strict criteria for definite DKA due to incomplete biochemical workup, but for which the clinical setting (history, symptoms, and physical exam) is consistent with DKA and there are no alternative diagnoses thought to be the primary cause of presentation. Probable was indicated when the adjudicators judged DKA to be the most likely clinical diagnosis based on available data.

There were 71 and 73 potential DKA events sent for adjudication in the dapagliflozin and placebo groups, respectively. Events adjudicated as definite or probable DKA were rare overall. There were more patients with events of definite or probable DKA in the dapagliflozin group compared with the placebo group: 27 (0.3%) and 12 (0.1%), respectively, corresponding to event rates of 0.9 and 0.4 events per 1000 p-y[1] (OT-SAS). There were 20 (0.2%) and 9 (0.1%) patients with events of definite DKA and 7 (<0.1%) and 3 (<0.1%) patients with events of probable DKA in the dapagliflozin group and the placebo group, respectively (OT-SAS).

Events of definite DKA were evenly distributed over time in both treatment groups, and no timepoint was identified at which the risk of definite DKA was particularly high (Figure 17).

[1] Event rate per 1000 p-y of events adjudicated as definite or probable DKA is calculated as number of events * 1000/p-y in study: 1000*(21+8)/30623=0.9 in the dapagliflozin group and 1000*(9+3)/29749=0.4 in the placebo group.

Figure 17 Kaplan-Meier plot of adjudicated events of definite DKA (OT-SAS)



N at risk is the number of patients at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p-value is displayed. Analysis of time from first dose of study drug to first occurrence of event or censoring.

CI Confidence interval; D Dapa 10 mg; DKA Diabetic ketoacidosis; HR Hazard ratio; N Number of patients; P Placebo; OT-SAS On-treatment safety analysis set

The most common contributing factors to definite and probable DKA events were as expected in this population and similar between treatment groups (e.g. illness/severe illness, infection, changed or missed insulin dose or underdose of insulin, and poor intake of food and/or drink). The most common signs and symptoms (as reported by the Investigator) of definite and probable DKA events were as expected for DKA events and similar between treatment groups, e.g. abdominal pain, confusion, fatigue, fever sign, frequent urination, thirst, fruity scented breath, loss of consciousness, nausea, malaise, vomiting, shortness of breath, weakness (OT-SAS).

Most patients in the dapagliflozin group had concomitant insulin treatment at the time of the DKA event (16 of 20 patients with definite DKA and 6 of 7 patients with probable DKA). All patients in the placebo group with definite or probable DKA events had concomitant insulin treatment at the time of the DKA event. Three patients in the dapagliflozin group with definite DKA had T1DM; none of the patients in the placebo group who had definite DKA had T1DM (OT-SAS).

There were 4 patients in the dapagliflozin group and 2 patients in the placebo group who died and who had definite DKA events occurring in conjunction with the events leading to death. There were 2 patients in the dapagliflozin group and 1 patient in the placebo group who died and who had probable DKA events occurring in conjunction with the events leading to death. Among these patients, DKA was reported as the primary cause of death in 1 patient in the placebo group and as the secondary cause of death in 2 patients in the dapagliflozin group. The remaining patients did not have DKA reported as a cause of death.

Additional safety analyses

Pancreatitis

Evaluating pancreatitis in DECLARE was an EU PAM.

DECLARE results

The numbers of patients with events of pancreatitis SAEs/DAEs were balanced between treatment groups: 24 (0.3%) in the dapagliflozin group and 25 (0.3%) in the placebo group (Table 15). All events were reported as SAEs. None of the events in the dapagliflozin group led to discontinuation of study drug.

Table 15 Pancreatitis SAE/DAEs by preferred term (OT-SAS)

Preferred term[a]	Number (%) of patients	
	Dapa 10 mg	Placebo
	OT-SAS (N=8574)	OT-SAS (N=8569)
Subjects with at least 1 Pancreatitis event	24 (0.3)	25 (0.3)
Event rate per 1000 subject years	0.8	0.8
Pancreatitis acute	12 (0.1)	12 (0.1)
Pancreatitis	10 (0.1)	10 (0.1)
Pancreatic pseudocyst	2 (<0.1)	1 (<0.1)
Pancreatitis chronic	1 (<0.1)	1 (<0.1)
Pancreatitis necrotising	1 (<0.1)	0
Pancreatic necrosis	1 (<0.1)	0
Pancreatitis relapsing	0	1 (<0.1)
Pancreatic abscess	0	1 (<0.1)

[a] Patients with events in more than 1 category are counted in each category. Patients with multiple events in the same category are counted only once in that category.

On-treatment SAS includes events that occurred after the first dose of study drug to the earlier of 30 (for serious AE) or 7 (for non-serious AE) days after last dose of study drug or the Closing Visit. AEs are based on pre-defined PT lists. AEs coded using MedDRA version 21.0.

AEs are sorted based on frequencies in Dapa 10 mg group in SAS by decreasing frequency of PT

AE Adverse event; Dapa Dapagliflozin; MedDRA Medical Dictionary for Regulatory Activities; N Number of patients per treatment group; OT On-treatment; PT Preferred term; SAS Safety analysis set

Clinical consequences of increased haematocrit

In the original dapagliflozin clinical development programme, small mean increases from baseline were observed in haematocrit and haemoglobin in dapagliflozin-treated patients (Placebo-Controlled Pool). Marked abnormalities of increased haemoglobin or haematocrit generally occurred in the absence of adverse clinical events.

Evaluating clinical consequences of increased haematocrit was an EU PAM.

DECLARE results

There were 202 patients in the dapagliflozin group and 64 patients in the placebo group who had marked abnormalities of haematocrit (>55%) or haemoglobin (>18 g/dL). Haematocrit and haemoglobin values were recorded every 12 months during the study. There were 681 patients in the dapagliflozin group and

618 patients in the placebo group who had an embolic or thrombotic event (standardised MedDRA query *Embolic and thrombotic events*).

There were 24 patients in the dapagliflozin group and 6 patients in the placebo group who had both marked abnormalities of haematocrit or haemoglobin and an embolic or thrombotic event reported at any time during the study (Table 16). Review of event narratives suggested that the marked abnormality and the event did not occur at the same time during the study in most patients. There were 8 patients in the dapagliflozin group and 3 patients in the placebo group who had marked abnormalities of haematocrit or haemoglobin reported at the study visit closest in time (9 to 282 days) to an embolic or thrombotic event. Most of the events were arterial thrombotic or embolic events, and most of the patients had risk factors or a medical history of thrombotic or embolic events.

There was no increased risk of stroke in dapagliflozin-treated patients in DECLARE, and there were numerically fewer events of MI in the dapagliflozin group.

Because only 8 of the 202 patients in the dapagliflozin group with marked abnormalities of haematocrit or haemoglobin had thrombotic or embolic events reported at the study visit closest in time to the reporting of the abnormality (compared with 3 out of 64 patients in the placebo group), there is no indication that the small increases in haematocrit or haemoglobin observed during dapagliflozin treatment are associated with an increased risk of thrombotic or embolic events.

Table 16 Clinical consequences of increased haematocrit (OT-SAS)

	Dapagliflozin 10 mg (N=8574)	**Placebo (N=8569)**
Number of patients (%)		
Embolic or thrombotic event OR marked abnormality in haematocrit or haemoglobin (%)	859 (10.0)	676 (7.9)
Embolic or thrombotic event (%)[a]	681 (7.9)	618 (7.2)
Marked abnormality in haematocrit or haemoglobin (%)[b]	202 (2.4)	64 (0.7)
Embolic or thrombotic event AND marked abnormality in haematocrit or haemoglobin (%)[c]	24 (0.3)	6 (<0.1)

[a] AE indicating any patient with an AE coded to a PT included in the SMQ Embolic and thrombotic events

[b] Lab indicating any patient with a marked abnormality in elevated haematocrit (>55%) or haemoglobin (>18 g/dL)

[c] Combination of [a] and [b]

AE Adverse event; N Number of patients per treatment group; OT On-treatment; PT Preferred term; SAS Safety analysis set; SMQ Standardised Medical Dictionary for Regulatory Activities query

Fournier's gangrene

The FDA identified a signal of Fournier's gangrene (necrotizing fasciitis of the genital and perineal area) with SGLT2 inhibitors based on post-marketing reports of Fournier's gangrene in patients treated with SGLT2 inhibitors, including dapagliflozin. Most of the reports of Fournier's gangrene in patients treated with dapagliflozin contained limited information or included known risk factors for Fournier's gangrene (eg, T2DM and obesity). No cases of Fournier's gangrene have been identified in dapagliflozin-treated patients in MAH-sponsored clinical studies completed before 30 August 2018.

DECLARE results

Following communications with the FDA, prior to database lock and treatment allocation unblinding, the DECLARE database was broadly searched by PTs indicating genital area infections or necrotizing fasciitis (see footnote to Table 17 for the list of PTs). The events were then medically assessed to identify cases of Fournier's gangrene.

There were 18 patients with events with PTs indicating genital area infections or necrotizing fasciitis: 8 (<0.1%) and 10 (0.1%) the dapagliflozin and placebo group, respectively (OT-SAS) (Table 17).

Table 17 SAE/DAEs indicating genital area infections or necrotizing fasciitis by preferred term (SAS and OT-SAS)

Preferred term[a]	Number (%) of patients			
	Dapagliflozin 10 mg		Placebo	
	SAS (N=8574)	OT-SAS (N=8574)	SAS (N=8569)	OT-SAS (N=8569)
Patients with at least 1 event	9 (0.1)	8 (<0.1)	13 (0.2)	10 (0.1)
Necrotising fasciitis	4 (<0.1)	4 (<0.1)	5 (<0.1)	5 (<0.1)
Rectal abscess	2 (<0.1)	2 (<0.1)	3 (<0.1)	2 (<0.1)
Penile infection	1 (<0.1)	1 (<0.1)	0	0
Perineal abscess	1 (<0.1)	0	1 (<0.1)	0
Scrotal abscess	1 (<0.1)	1 (<0.1)	4 (<0.1)	3 (<0.1)

[a] Patients with events in more than 1 category are counted in each category. Patients with multiple events in the same category are counted only once in that category.

SAS includes events that occurred after the first dose of study drug up to the Closing Visit. On-treatment SAS includes events that occurred after the first dose of study drug to the earlier of 30 (for serious AE) or 7 (for non-serious AE) days after last dose of study drug or the Closing Visit.

AEs are based on a pre-defined PT list. PTs included were: Necrotising fasciitis, Necrotising fasciitis fungal, Necrotising fasciitis streptococcal, Necrotising fasciitis staphylococcal, Scrotal gangrene, Perineal abscess, Perineal cellulitis, Perineal infection, Necrotising soft tissue infection, Penile abscess, Penile infection, Scrotal abscess, Scrotal infection, Clitoris abscess, Vulval abscess, Rectal abscess, Fascial infection, Perineal necrosis, Myofascitis. AEs coded using MedDRA version 21.0. AEs are sorted based on frequencies in dapagliflozin 10 mg group in SAS by decreasing frequency of PT.

MedDRA Medical Dictionary for Regulatory Activities; N Number of patients per treatment group; OT On-treatment; PT Preferred term; SAS Safety analysis set

Prior to database lock and treatment allocation unblinding for DECLARE, the events were separately evaluated by the MAH and the Thrombolysis in Myocardial Infarction (TIMI) Study Group. Ten events were jointly assessed by the MAH and the TIMI Study Group as being Fournier's gangrene (SAS); 6 of these events were on-treatment (OT-SAS). Following unblinding of the DECLARE data, it was determined that 2 of the events were in the dapagliflozin group and 8 of the events were in the placebo group (SAS); of these, 1 event in the dapagliflozin group and 5 events in the placebo group were on-treatment (OT-SAS) (Table 18).

All patients with Fournier's gangrene were men with T2DM, the group at highest risk for this event. Most of the patients had additional risk factors for Fournier's gangrene (e.g. obesity).

Table 18 Listing of patients with Fournier's gangrene (OT-SAS)

Ecode	Treat-ment	Age/Sex /BMI	AE verbatim/ preferred term	Time to onset (days)	Start date AE	Stop date AE	On IP at time of event/ Permanent stop IP	Action taken (IP interrupted dates)	Outcome
[redacted]	Dapa 10	[redacted]/[redacted]/ [redacted]	Fourniers gangrene/ NECROTISING FASCIITIS	279	[redacted]	[redacted]	Yes [redacted]	Dose Not Changed	Recovered/ Resolved

Table 18 Listing of patients with Fournier's gangrene (OT-SAS)

Ecode	Treat-ment	Age/Sex /BMI	AE verbatim/ preferred term	Time to onset (days)	Start date AE	Stop date AE	On IP at time of event/ Permanent stop IP	Action taken (IP interrupted dates)	Outcome
[redacted]	Placebo	[redacted]	Fournier's gangrene/ NECROTISING FASCIITIS	1263	[redacted]	[redacted]	Yes [redacted]	Dose Not Changed	Recovered/ Resolved
[redacted]	Placebo	[redacted]	Necrotising fasciitis/ NECROTISING FASCIITIS	1159	[redacted]	[redacted]	Yes [redacted]	Drug interrupted	Recovered/ Resolved
[redacted]	Placebo	[redacted]	Fournier's gangrene/ NECROTISING FASCIITIS	408	[redacted]	[redacted]	Yes [redacted]	Drug Interrupted	Recovered/ Resolved with sequelae
[redacted]	Placebo	[redacted]	Fournier's gangrene/ NECROTISING FASCIITIS	741	[redacted]	[redacted]	Yes [redacted]	Drug permanently discontinued	Recovered/ Resolved
[redacted]	Placebo	[redacted]	Fournier's gangrene/ NECROTISING FASCIITIS	1129	[redacted]	[redacted]	Yes [redacted]	Drug interrupted	Recovered/ Resolved with sequelae

AE Adverse event; BMI Body mass index; Dapa Dapagliflozin; IP Investigational product (study drug); M Male; OT On-treatment; SAS Safety analysis set

It has been suggested that an increased risk of genitourinary infections associated with SGLT2 inhibitors could increase the risk of Fournier's gangrene. In DECLARE, there was no imbalance in serious genital infections or UTIs between treatment groups: there were only 2 SAEs of genital infections in each treatment group, and there were fewer SAEs of UTI in the dapagliflozin group compared with the placebo group (79 and 109, respectively). For the 6 cases of Fournier's gangrene in DECLARE (OT-SAS), no events of genital infections or UTIs were recorded proximate, or at any time prior, to the Fournier's gangrene event. Non-SAEs/DAEs of genital infections or UTIs were not to be reported in DECLARE.

Laboratory findings

Clinical laboratory evaluations

Haematology

Mean haematocrit and haemoglobin levels initially increased in the dapagliflozin group compared with the placebo group and then plateaued. The increases were not considered clinically relevant.

Clinical chemistry

Changes in blood chemistry values over time

There were no clinically relevant changes in blood alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), or alkaline phosphatase in either treatment group. Serum

creatinine increased slightly in both treatment groups. There were mean decreases in creatinine clearance that were similar between treatment groups. eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower in the dapagliflozin group compared with the placebo group, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group. Blood glucose decreased from baseline in the dapagliflozin group over time and remained unchanged in the placebo group.

Changes in blood lipids over time

There were no clinically relevant changes in total cholesterol, low-density lipoprotein, high-density lipoprotein, or triglycerides in either treatment group.

Elevations in alanine aminotransferase or aspartate aminotransferase accompanied by elevations in total bilirubin

Any patient with AST or ALT ≥3x upper limit of normal and TBL ≥2x upper limit of normal at any point during the study was to have their study drug discontinued and the event reported as an SAE. There were 24 (0.3%) patients in the dapagliflozin group and 20 (0.2%) patients in the placebo group meeting these criteria. None of the events in the dapagliflozin group had study drug causality assessed as 'definite', 'highly likely', or 'probable' by the adjudication committee.

Other marked laboratory abnormalities

There were fewer patients with marked abnormalities of creatinine, creatinine clearance, eGFR, and urine albumin-to-creatinine ratio in the dapagliflozin group compared with the placebo group. There were fewer patients with marked abnormalities of hyperkalaemia in the dapagliflozin group compared with the placebo group. There were more patients with marked abnormalities of haematocrit and haemoglobin in the dapagliflozin group compared with the placebo group.

Urinalysis

Urine albumin, urine creatinine, and urine albumin-to-creatinine ratio were lower in the dapagliflozin group compared with the placebo group at 4 years.

Vital signs, physical findings, and other observations related to safety

Systolic blood pressure decreased in the dapagliflozin group compared with the placebo group. There were no clinically relevant changes in diastolic blood pressure or pulse rate in either treatment group.

Safety in special populations

Intrinsic factors

Effect of sex

Malignancies, fractures and osteoporotic fractures, UTI SAEs/DAEs, genital infection SAEs/DAEs, and AEs leading to amputations were analysed by sex. Key findings in the sex subgroup analyses were:

- Malignancies, fractures and osteoporotic fractures, and AEs leading to amputations were balanced between treatment groups in both the male and female subgroups.
- There were 40 (0.7%) and 61 (1.1%) males and 39 (1.2%) and 48 (1.5%) females with UTI SAEs in the dapagliflozin and placebo groups, respectively (OT-SAS). There were 23 (0.4%) and 9 (0.2%) males and 38 (1.2%) and 26 (0.8%) females with UTI DAEs in the dapagliflozin and placebo groups, respectively (OT-SAS).

- There were more patients with genital infection DAEs in the dapagliflozin group compared with the placebo group in both the male and female subgroups. In males, there were 2 SAEs of genital infection in each treatment group, and in females, there were no SAEs of genital infection (OT-SAS).
- There were fewer patients with renal events in the dapagliflozin group compared with the placebo group in both the male and female subgroups.

Effect of age

Exposure and overall AEs in patients ≥75 years of age

A total of 1092 patients in the study were ≥75 years of age. The median duration of exposure to study drug in patients ≥75 years of age was 47 months in both treatment groups.

An overall summary of AEs in patients ≥75 years of age is shown in Table 19; refer to Table 12 for the results in the overall population.

Table 19 Overall summary of adverse events in patients ≥75 years of age (SAS and OT-SAS)

Adverse event[a]	Number (%) of patients			
	Dapa 10 mg		Placebo	
	SAS (N=537)	OT-SAS (N=537)	SAS (N=555)	OT-SAS (N=555)
Number of patients with:				
AE leading to death	71 (13.2)	46 (8.6)	73 (13.2)	44 (7.9)
At least 1 SAE	287 (53.4)	260 (48.4)	304 (54.8)	264 (47.6)
At least 1 study drug-related SAE[b]	18 (3.4)	18 (3.4)	15 (2.7)	15 (2.7)
Any AE leading to premature permanent discontinuation of study drug	83 (15.5)	83 (15.5)	76 (13.7)	76 (13.7)
Any SAE leading to premature permanent discontinuation of study drug	40 (7.4)	40 (7.4)	40 (7.2)	40 (7.2)
At least 1 adjudicated malignancy[c]	54 (10.1)	49 (9.1)	60 (10.8)	50 (9.0)
At least 1 hepatic event with causality to IP adjudicated as definite or highly likely[d]	0	0	0	0
At least 1 event of fracture[c]	40 (7.4)	32 (6.0)	32 (5.8)	24 (4.3)
At least 1 event of symptoms suggestive of volume depletion[c]	24 (4.5)	21 (3.9)	35 (6.3)	31 (5.6)
At least 1 SAE/DAE of hypersensitivity reaction[c]	5 (0.9)	4 (0.7)	5 (0.9)	4 (0.7)
At least 1 SAE/DAE of urinary tract infection[c]	18 (3.4)	16 (3.0)	13 (2.3)	10 (1.8)
At least 1 SAE/DAE of genital infection[c]	4 (0.7)	4 (0.7)	2 (0.4)	2 (0.4)
At least 1 renal event[c]	56 (10.4)	48 (8.9)	73 (13.2)	62 (11.2)
At least 1 major hypoglycaemic event	9 (1.7)	9 (1.7)	16 (2.9)	14 (2.5)
At least 1 event of surgical or spontaneous/non-surgical amputation	7 (1.3)	5 (0.9)	8 (1.4)	5 (0.9)
At least 1 event of definite diabetic ketoacidosis	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)

[a] Includes SAE, DAE, AE leading to death, malignancies, adjudicated related hepatic events, fractures, symptoms suggestive of volume depletion, SAEs/DAEs of hypersensitivity reactions, SAEs/DAEs of urinary tract infection, SAEs/DAEs of genital infections, renal events, major hypoglycaemic events, events of surgical or spontaneous/non-surgical amputation, and event of definite diabetic ketoacidosis.

[b] Study drug related AE/SAE as assessed by investigator.
[c] AEs are based on pre-defined preferred term list.
[d] AEs are based on pre-defined preferred term list and pre-defined laboratory criteria.
AEs were coded according to MedDRA version 21.0. Patients with events in more than 1 category are counted in each category. SAS includes events that occurred after the first dose of study drug up to the Closing Visit. On-treatment SAS includes events that occurred after the first dose of study drug to the earlier of on or before 30 (for SAE/adjudicated events/amputation/major hypoglycaemia) or 7 (for non-SAE) days after last dose of study drug or the Closing Visit.
AE Adverse event; DAE Adverse event leading to discontinuation of study drug; Dapa Dapagliflozin; MedDRA Medical Dictionary for Regulatory Activities; N Number of patients per treatment group; OT On-treatment; SAE Serious adverse event; SAS Safety analysis set

Key findings in patients ≥75 years of age were:

- The incidence of SAEs and DAEs were balanced between treatment groups.
- Malignancies were balanced between treatment groups.
- There were 40 (7.4%) and 32 (5.8%) patients with fracture events in the dapagliflozin and placebo groups, respectively (SAS).
- AEs suggestive of volume depletion were balanced between treatment groups.
  - AEs suggestive of volume depletion were reported for 21 (3.9%) and 31 (5.6%) patients ≥75 years of age in the dapagliflozin and placebo groups, respectively (OT-SAS).
  - SAEs suggestive of volume depletion were reported for 11 (2.0%) and 16 (2.9%) patients ≥75 years of age in the dapagliflozin and placebo groups, respectively (OT-SAS) (see Table 8.18).
- UTI SAEs were reported for 11 (2.0%) and 8 (1.4%) patients ≥75 years of age in the dapagliflozin and placebo groups, respectively (OT-SAS) (see Table 8.18).
- UTI DAEs were reported for 9 (1.7%) and 2 (0.4%) patients ≥75 years of age in the dapagliflozin and placebo groups, respectively (OT-SAS) (see Table 8.18).
- There were fewer renal events in the dapagliflozin group compared with the placebo group.
  - Renal AEs were reported for 48 (8.9%) and 62 (11.2 %) patients ≥75 years of age in the dapagliflozin and placebo groups, respectively (OT-SAS).
  - Renal SAEs were reported for 7 (1.3%) and 18 (3.2%) of patients ≥75 years of age in the dapagliflozin and placebo groups, respectively (OT-SAS) (see Table 8.18).
- Amputations were balanced between treatment groups.

Results of subgroup analyses of patients ≥75 years of age indicate that the safety profile of dapagliflozin in patients ≥75 years of age is consistent with the safety profile of dapagliflozin in the overall population.

Analyses of AEoSIs in <65 and ≥ 65-year age subgroups

Malignancies, fractures and osteoporotic fractures, symptoms suggestive of volume depletion, UTI SAEs/DAEs, genital infection SAEs/DAEs, renal events, and AEs leading to amputations were analysed for patients <65 and ≥65 years of age. Key findings in the <65 and ≥65-year age subgroups were:

- Malignancies were balanced between treatment groups in both the <65 and ≥65-year age subgroups.
- Fractures were balanced between treatment groups in both the <65 and ≥65-year age subgroups. There were fewer osteoporotic fractures in the dapagliflozin group compared with the placebo group in both the <65 and ≥65-year age subgroups.
- AEs suggestive of volume depletion were generally balanced between treatment groups in both the <65 and ≥65-year age subgroups.
  - AEs suggestive of volume depletion were reported for 96 (2.1%) and 86 (1.9%) patients <65 years of age and 117 (3.0%) and 121 (3.1%) patients ≥65 years of age in the dapagliflozin and placebo groups, respectively (OT-SAS).
  - SAEs suggestive of volume depletion were reported for 30 (0.6%) and 26 (0.6%) patients <65 years of age and for 51 (1.3%) and 44 (1.1%) patients ≥65 years of age in the dapagliflozin and placebo groups, respectively (OT-SAS).

- There were fewer UTI SAEs and more UTI DAEs in the dapagliflozin group compared with the placebo group in both the <65 and ≥65-year age subgroups.
- There were more patients with non-serious DAEs of genital infection in the dapagliflozin group compared with the placebo group in both the <65 and ≥65-year age subgroups.
- There were fewer renal events in the dapagliflozin group compared with the placebo group in both the <65 and ≥65-year age subgroups.
  - Renal AEs were reported for 176 (3.8%) and 215 (4.7%) patients <65 years of age and 246 (6.2%) and 311 (7.9%) patients ≥65 years of age in the dapagliflozin and placebo groups, respectively (OT-SAS).
  - Renal SAEs were reported for 34 (0.7%) and 54 (1.2%) of patients <65 years of age and 46 (1.2%) and 82 (2.1%) of patients ≥65 years of age in the dapagliflozin and placebo groups, respectively (OT-SAS).
- AEs leading to amputations were balanced between treatment groups in both the <65 and ≥65-year age subgroups.

Results of age subgroup analyses indicate that the safety profile of dapagliflozin is consistent between patients <65 and ≥65 years of age.

Effect of renal function

There were 1 262 patients in total who had baseline eGFR <60 mL/min/1.73 m^2 and 15 880 patients in total who had baseline eGFR ≥60 mL/min/1.73 m^2 (OT-SAS).

The proportion of patients with events of sustained confirmed eGFR decrease ≥40% was analysed for patients with baseline eGFR <60 mL/min/1.73 m^2. Among these patients, there were fewer patients in the dapagliflozin group with events of sustained confirmed eGFR decrease ≥40% compared with the placebo group.

Fractures and osteoporotic fractures, symptoms suggestive of volume depletion, renal events, and AEs leading to amputations were analysed by baseline eGFR (<60 mL/min/1.73 m^2, 60 to <90 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2 [EPI-CKD]). Key findings in eGFR subgroups were:

- Fractures and osteoporotic fractures and AEs leading to amputations were balanced between treatment groups across eGFR subgroups.
- AEs suggestive of volume depletion were balanced between treatment groups across eGFR subgroups, except that there were more patients with SAEs suggestive of volume depletion in the dapagliflozin group with eGFR <60 mL/min/1.73 m^2 at baseline compared with the placebo group (19 and 13 events, respectively).
- There were fewer renal events in the dapagliflozin group compared with the placebo group across eGFR subgroups.

Renal events were also analysed by albumin/creatinine ratio (<30 mg/g, ≥30 to ≤300 mg/g, >300 mg/g). There were fewer renal events in the dapagliflozin group compared with the placebo group across albumin/creatinine ratio subgroups.

Results of these subgroup analyses indicate that the safety profile of dapagliflozin is generally consistent regardless of renal function.

Other intrinsic factors

Additional subgroup analyses included analyses of AEs suggestive of volume depletion and renal events by systolic and diastolic blood pressure at baseline; analyses of renal events and AEs leading to amputations by diabetes duration; and analysis of AEs leading to amputations by peripheral arterial disease at baseline. The results of these subgroup analyses were generally consistent with the overall analyses.

There were more patients with AEs leading to amputations in patients with peripheral arterial disease at baseline in the dapagliflozin group compared with the placebo group (43 and 28 patients, respectively), and fewer AEs leading to amputations in patients without peripheral arterial disease at baseline in the dapagliflozin group compared with the placebo group (75 and 85 patients, respectively). There was no consistent pattern to the occurrence of AEs leading to amputations across the subgroups analysed, suggesting the variability is due to the small subgroup sizes.

Extrinsic factors

AEs suggestive of volume depletion and renal events were analysed by diuretic use at baseline and angiotensin-converting-enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) use at baseline. AEs suggestive of volume depletion were also analysed by loop diuretic use at baseline. AEs leading to amputations were analysed by diuretic and loop diuretic use at baseline. Key findings in these subgroup analyses were:

- AEs suggestive of volume depletion were balanced between treatment groups across subgroups with and without baseline diuretic, loop diuretic, or ACEi/ARB use.
- There were fewer renal events and fewer serious events of acute impairment of renal function in the dapagliflozin group compared with the placebo group across subgroups with and without baseline diuretic or ACEi/ARB use.
- AEs leading to amputations were balanced between treatment groups across subgroups with and without baseline diuretic or loop diuretic use.

Safety related to drug-drug interactions and other interactions

No new information is available on the potential impact on safety of such interactions in patients with T2DM and CV risk factors or established CV disease.

Discontinuation due to adverse events

There were more patients with DAEs in the dapagliflozin group compared with the placebo group: 8.1% and 6.9% of patients, respectively (OT-SAS). The most common PTs for DAEs in the dapagliflozin group were Urinary tract infection, Balanoposthitis, and Pollakiuria, which were more common in the dapagliflozin group compared with the placebo group (OT-SAS). The most common PTs for DAEs in the placebo group were Urinary tract infection, Bladder cancer, and Acute kidney injury (OT-SAS) (Table 20).

Table 20 Most common adverse events leading to discontinuation of study drug (frequency ≥0.2% for either treatment) by preferred term (SAS and OT-SAS)

Preferred term[a]	Number (%) of patients			
	Dapa 10 mg		Placebo	
	SAS (N=8574)	OT-SAS (N=8574)	SAS (N=8569)	OT-SAS (N=8569)
Patients with at least 1 DAE	693 (8.1)	693 (8.1)	592 (6.9)	592 (6.9)
Urinary tract infection	42 (0.5)	42 (0.5)	22 (0.3)	22 (0.3)
Balanoposthitis	27 (0.3)	27 (0.3)	2 (<0.1)	2 (<0.1)
Pollakiuria	20 (0.2)	20 (0.2)	13 (0.2)	13 (0.2)
Bladder cancer	11 (0.1)	11 (0.1)	21 (0.2)	21 (0.2)
Acute kidney injury	8 (<0.1)	8 (<0.1)	19 (0.2)	19 (0.2)

[a] Patients with events in more than 1 category are counted in each category. Patients with multiple events in the same category are counted only once in that category.

SAS and On-treatment SAS include events leading to discontinuation of study drug that occurred after the first dose of study drug up to the Closing Visit. AEs coded using MedDRA version 21.0.

AEs are sorted based on frequencies in Dapa 10 mg group in SAS by decreasing frequency of PT.

AE Adverse event; DAE Adverse event leading to discontinuation of study drug; Dapa Dapagliflozin; MedDRA Medical Dictionary for Regulatory Activities; N Number of patients per treatment group; OT On-treatment; SAS Safety analysis set

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 90 countries. Post-marketing experience in the approved T2DM indication is summarised in regular periodic benefit-risk evaluation reports (PBRERs) that are submitted to regulatory authorities worldwide. The most recent PBRER, with a data lock of 04 October 2018 and including approximately 4 856 324 p-y of post-marketing exposure globally (cumulative until 30 September 2018), concluded that a comprehensive review of clinical studies and post-marketing experience revealed no new information to alter the overall positive benefit-risk profile for dapagliflozin in the approved indication.

2.5.1. Discussion on clinical safety

The safety and tolerability of dapagliflozin were investigated and documented in the original submission for approval of dapagliflozin for treatment of type 2 diabetes mellitus (T2DM). The original T2DM submission has been supplemented over time with updated information on the safety and tolerability of dapagliflozin, notably with data from a 30-month safety update (30-MSU) cut-off relative to the original data cut and with post-marketing data. The original dapagliflozin clinical development programme included 21 active- and placebo-controlled studies and 9 885 years of exposure (6 247 p-y in the dapagliflozin group and 3638 p-y in the comparator group), and the placebo-controlled pool, which included 13 placebo-controlled studies and 4 682 p-y of exposure (2 438 p-y in the dapagliflozin group and 2 244 p-y in the placebo group); these were documented in the 30-MSU. With this submission the exposure data have been substantially extended. Most importantly, patients have been followed for a median of 50 months. The data from DECLARE has not been pooled with data from previous studies. This is acceptable due to the differences in the study designs and the collection of safety data.

DECLARE is included in the RMP for dapagliflozin a Category 3 PASS, in order to further study safety concerns identified at the time of the MAA but also identified after the launch of the product. As opposed to the studies in the MAA, only selected (non-serious) AEs were collected in addition to SAEs and DAEs. Adjudication of important safety variables were performed.

The DECLARE study provides long-term exposure data in a large number of patients, with more than 4 000 patients followed for four years and some patients followed up to five years. Although drop-out rates were slightly higher in the placebo group, the numbers still remained comparable up to EOT. Patients with HF NYHA class I-III, previously not included in the clinical study program, were eligible for inclusion in the study. Overall, 1724 patients (10% of the total population) were included in the study. In total 56% of patients with HF were in NYHA class II and 7.3% (125 patients) were in NYHA class III. There was no imbalance between treatment groups.

SAEs and AEoSIs were generally balanced between treatment groups. Genital infections, DKA and embolic or thrombotic events AND marked abnormality in haematocrit or haemoglobin were the only AEoSI with a higher reporting in the dapagliflozin groups, whereas renal events, hypoglycaemias and

Fournier's gangrene was more commonly reported in the placebo group. The pattern was consistent for both the SAS and the OT-SAS.

SAEs were generally well balanced, with less than an 0.2% difference between treatment groups for most PTs. HF and acute kidney injury were somewhat more common in the placebo group, in line with the data presented in the efficacy part of this report. The occurrence of death was balanced between groups and in both analysis populations. All-cause mortality and CV death are further discussed in the efficacy part of this report.

During the study, patients were to be treated according to local guidelines and practices in order to achieve glycaemic goals, although some medications (pioglitazone, rosiglitazone and SGLT2 inhibitors) were prohibited. In spite of measures taken, 113 patients in the dapagliflozin treated group were treated with dual SGLT2i. The majority (86 out of 113) however stopped dual treatment within 3 months. Thus, the exposure is limited, but no unexpected safety issues emerged in this small population.

During the assessment of the original MAA, imbalances in the occurrence of bladder cancer, breast cancer, and prostate cancer were observed which led to concerns on that dapagliflozin could carry an increased risk of malignancies, although the overall incidence did not differ from comparators. The data from DECLARE, which has a considerably longer follow-up (up to 5 years) and includes a large number of patients, the overall incidence rates of malignancies did not differ between dapagliflozin and placebo (14.32 and 14.52 events per 1000 p-y). The relative risks varied around 1 but CIs were wide and included 1 for all types of cancer except bladder cancer (in favour of dapagliflozin) and "Other known site" (in favour of placebo).

In DECLARE, the relative risk of bladder cancer was lower with dapagliflozin than with placebo (HR 0.57 [95% CI: 0.35, 0.93]), the number of breast cancer cases was similar in both groups (36 (0.4%) vs 35 (0.4%)) and a higher number of prostate cancer cases were observed in the dapagliflozin group (73 (1.4% of male patients) vs 63 (1.2% of male patients)).

Although 3 to 5 years of exposure is not sufficient to rule out a cancerogenic effect, no overall imbalance was observed in the overall incidence in the original studies and there are no non-clinical findings suggestive of a genotoxic effect of dapagliflozin. The additional data obtained with DECLARE have not strengthened but rather weakened the pattern observed in the MAA with e.g. a lower incidence of bladder cancer.

Concerns were raised during the original MAA on the risk of hepatic events with dapagliflozin, based on one case of autoimmune hepatitis. In DECLARE, no hepatic events assessed as definite or highly likely to be caused by dapagliflozin was observed.

Due to findings in the CANVAS program for another SGLT2 inhibitor (canagliflozin), and the fact that in the initial data provided with the MAA for dapagliflozin, concerns were raised that treatment with dapagliflozin may be associated with an increased risk of fractures, evaluation of bone fractures was included in DECLARE as a PAM. Data from the CVOT for another SGLT2 inhibitor (empagliflozin), have not shown an increased risk. Data from the dedicated dapagliflozin study D1690C00012 have not shown any negative effect on bone markers or BMD. In the DECLARE study, the number of patients with fractures were balanced between treatment groups (5.3% vs 5.1%). Thus, there was no evidence for an increased risk of fractures with the use of dapagliflozin.

AEs suggestive of volume depletion were somewhat more common in the dapagliflozin group in the clinical development program. In DECLARE, the AEs suggestive of volume depletion included e.g. hypotension, syncope and shock. These events were balanced between treatment groups (213 (2.5%) and 207 (2.4%)). Thus, these data concerning events suggestive of volume depletions appear reassuring but are not considered sufficient to remove warnings regarding the risk of volume depletion on an

individual basis. Volume depletion should however also be considered in relation to the data on haematocrit and thromboembolic events.

The MAH investigated the clinical consequences of increased haematocrit as requested. There was an imbalance between treatment groups with a higher reporting of both embolic and thrombotic events (7.9% with dapagliflozin and 7.2% with placebo) and the reporting of marked abnormalities in haematocrit or haemoglobin with dapagliflozin (2.4%) compared to placebo (0.7%). In patients experiencing both events, there was however no clear temporal association between the occurrence of abnormal haematocrit and a thromboembolic event. An association can however not be entirely ruled out and since the change in haematocrit is most likely due to volume depletion, this is still considered to be a risk with dapagliflozin treatment, especially in vulnerable patients.

Overall the incidence of serious hypersensitivity reactions was lower with dapagliflozin than with placebo (15 (0.2%) and 26 (0.3%)), although there were more patients with DAEs of hypersensitivity reactions in the dapagliflozin group.

Non-serious UTIs are a known side effect of dapagliflozin. The results from DECLARE indicated that dapagliflozin is associated with UTI DAEs, but there is no evidence that dapagliflozin is associated with an increased risk of serious UTIs, including urosepsis and pyelonephritis, as there were fewer patients with UTI SAEs in the dapagliflozin group (79 (0.9%) and 109 (1.3%)).

There were more patients with genital infections SAEs/DAEs in the dapagliflozin group compared with the placebo group: 76 (0.9%) and 9 (0.1%), respectively, corresponding to event rates of 2.5 and 0.3 events per 1000 p-y (OT-SAS). The difference was driven by non-serious DAEs of genital infection, thus the data does not indicate that dapagliflozin is associated with an increased risk of serious genital infections.

There were fewer patients with renal events in the dapagliflozin group compared with the placebo group (422 (4.9%) and 526 (6.1%)). The same pattern was observed for acute kidney injury, SAEs and DAEs. Thus, these data do not indicate that the use of dapagliflozin is associated with an increased risk of renal events. The effect of dapagliflozin on renal function is also presented in the efficacy part of this report.

In DECLARE only major hypoglycaemic events were collected. Previous data from the placebo-controlled studies have indicated an increased risk of hypoglycaemias in patients on concomitant treatment with dapagliflozin and insulin or SU compared to patients on placebo (and insulin or SU). In DECLARE, major hypoglycaemic events were few (58 (0.7%) and 83 (1.0%), dapagliflozin and placebo, respectively) especially taking the size and duration of the study into account. The number of events was lower for dapagliflozin, both in the overall population and in the subgroup using insulin or SU.

Amputations was introduced as an AEoSI during the course of the study due to a signal raised based on data for another SGLT2 inhibitor, canagliflozin. The amendment that included amputations as an AEoSI was made in September 2016, i.e. two years before the study was closed. The MAH has provided data that show that there was no change in the reporting rate with the introduction of the amendment. The data presented does not indicate any apparent increased risk of amputations with dapagliflozin compared to placebo (123 (1.4%) and 113 (1.3%)). It is however noted that there were more patients in the dapagliflozin groups who had more than 1 amputation (45 vs 30) and also more patients with amputations below and above the knee (46 vs 30).

When analysed by subgroups based on risk factors for amputations, the overall point estimate favours placebo, but events are few and the confidence intervals are wide. As a result, no statistically significant differences between treatments are observed for any of the subgroups. Notably the point estimates are in favour of dapagliflozin for the most vulnerable groups whereas the point estimates are in favour of placebo for subgroups theoretically at lower risk. The only exception from this observation is in patients with a history of PAD where the point estimate is 1.49 (0.93 to 2.39).

Overall, the data do not support an increased risk of amputation or more complicated amputation with dapagliflozin treatment. However, taking the diuretic effect of dapagliflozin into account (that may jeopardise the peripheral circulation) as well as the observation for canagliflozin, the class warning regarding a potential risk in vulnerable patients should remain in section 4.4.

The large size of the DECLARE study population allowed for a clinically meaningful evaluation of DKA, a rare event in patients with T2DM, in dapagliflozin-treated patients compared with previously available data. The amendment by which DKA was included as an AEoSI was introduced in September 2016, i.e. two years before the closure of the study. The MAH has clarified that no measures to prevent DKA was introduced during the study. There was no change in the reporting rate of DKA with the introduction of the amendment. The DECLARE results showed that there is a reasonable possibility of a causal relation between dapagliflozin and DKA, although DKA events were rare overall. The clinical presentation, risk factors, and contributing factors of DKA events in dapagliflozin-treated patients are similar to what is generally observed for DKA events. As observed for the T1DM population, the events were evenly distributed over time.

Events of pancreatitis were also collected. There was no difference in the number or type of events between treatment groups (24 (0.3%) with dapagliflozin and 25 (0.3%) with placebo). Thus, the data give no indication of an increased risk of pancreatitis with dapagliflozin treatment.

Following the signal of Fournier's gangrene with the use of SGLT2 inhibitors, but prior to database lock and unblinding, the DECLARE safety database was retrospectively searched for events suggestive of Fournier's gangrene. There were 18 patients with events with PTs indicating genital area infections or necrotizing fasciitis: 8 (<0.1%) and 10 (0.1%) the dapagliflozin and placebo group, respectively. Ten of these cases were adjudicated as Fournier's gangrene, out of which 2 were treated with dapagliflozin. The data provided does not indicate an increased risk of Fournier's gangrene with dapagliflozin treatment, although it should be taken into account that data was retrospectively collected in a database where only SAEs were routinely reported.

Apart for the data on haematocrit (see above), there were no remarkable findings with regards to laboratory values. As noted in the efficacy part of this report, eGFR was lower in the dapagliflozin group than in the placebo group after 1 year whereas eGFR was higher than for placebo after 4 years. Although numerically slightly more patients showed increased AST, ALT or total bilirubin levels in the dapagliflozin group compared to placebo, this was not reflected as an increase in hepatic events.

When the safety was assessed by sex, the only apparent difference observed was a higher reporting of UTI SAEs in females in both treatment groups and the reporting was lower in the dapagliflozin group than in the placebo group. UTI DAEs were more common in the dapagliflozin groups than in the placebo groups and more common in females than in males.

DECLARE included 1092 patients ≥75 years of age out of which 537 were treated with dapagliflozin. The overall reporting of SAEs and AEoSIs was about twice as high in the population ≥75 years of age compared to the overall population, but the reporting was balanced between groups. The overall safety profile was comparable to that of the overall population. When analysed by an age cut-off of 65 years, a slightly higher reporting of AEs was observed in the older age group, but the safety profile did not differ in the older age group compared to the younger age group.

Effect of renal function on the safety profile was also evaluated. Apart from events suggestive of volume depletion, that were more common in patients with eGFR <60 treated with dapagliflozin than in those on placebo, there were no indication of a worsening of the safety profile with declining renal function. Furthermore, as discussed in the efficacy part of the report, renal events were less common in the dapagliflozin group compared to placebo.

AEs suggestive of volume depletion, renal events and amputations were analysed by extrinsic factors, such as use of ACEi/ARB and loop diuretics at baseline. These analyses could not identify any influence on these events by the extrinsic factors tested.

There were somewhat more patients with DAEs in the dapagliflozin group (8.1%) than in the placebo group (6.9%). Among the most common DAEs the largest numerical imbalance was observed for UTI, Balanoposthitis, and Pollakiuria which were more common in the dapagliflozin group. Numerically more patients on placebo reported DAEs Bladder cancer or Acute kidney injury.

No new safety concerns have arisen since the signal on Fournier's gangrene was evoked for the class of SGLT2 inhibitors.

2.5.2. Conclusions on clinical safety

The DECLARE study provides long-term data in a large number of patients treated with dapagliflozin and was designed to address a number of safety concerns raised in the assessment of the documentation for the MAA. No new safety concerns arise from the data provided.

The study included a substantial number of elderly subjects (≥75 years of age) with no indication of a different safety profile compared to placebo, supporting the proposed changes to the SmPC for this population. Relevant numbers of patients with HF (NYHA Class I-III) were also included. The data provided does not raise any safety concerns with the use of dapagliflozin in patients with HF (NYHA class I-III) and supports the removal of the warning on lack of experience in this patient group from section 4.4.

Data have also been provided on the following safety concerns listed in the RMP: volume depletion, clinical consequences of increased haematocrit, bone fracture, serious hypersensitivity reactions and pancreatitis, and for which no other PhV activities than DECLARE are ongoing. In addition, data on malignancies and specifically bladder cancer, breast cancer, prostate cancer, has been provided. No new safety concerns arise from the data provided.

Concerning volume depletion and clinical consequences of increased haematocrit, there are still uncertainties with regards to the risk with dapagliflozin use, but the SmPC contains adequate information. With regards to the potential risk of amputations the data does not indicate an increased risk with dapagliflozin use, but the class warning should remain in the SmPC.

The data from DECLARE is considered sufficient to conclude that dapagliflozin treatment is not associated with an increased risk of bone fracture, serious hypersensitivity reactions or pancreatitis.

The safety information in the SmPC has been updated based on the submitted data. The proposed changes to the RMP are further discussed in section 2.6 of this report.

2.5.3. PSUR cycle

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

2.6. Risk management plan

2.6.1. Risk management plan for dapagliflozin

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

The PRAC considered that the risk management plan version 17.3 for dapagliflozin is acceptable.

In addition, a revision of the RMP is recommended to be taken into account with the next RMP update as such: the MAH is requested to reinstate the category 3 study on "Knowledge and understanding of additional RMM for DKA in Health Care Professionals and Patients", in the pharmacovigilance plan of the dapagliflozin RMP (please see further information under the Pharmacovigilance Plan subsection below).

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 17.3 with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	Urinary tract infection Renal impairment Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	Liver injury Bladder cancer Breast cancer Prostate cancer Lower limb amputation
Missing information	None

Pharmacovigilance plan

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Retrospective Cohort Study on the Risk of Diabetic Ketoacidosis (DKA). (planned)	Determine the effectiveness of additional risk minimization measures in place for DKA in Europe by assessing the impact of the RMMs on the risk of DKA in T1DM patients who are treated with	diabetic ketoacidosis in T1DM	Protocol submission Feasibility assessment Populations	June 24, 2019 June 24, 2019

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
	dapagliflozin in Europe.		size update Submission of interim report(s) Submission of final data	Annual Q4 2023 (estimated) Q4 2025 (estimated) Q4 2026 (estimated)
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
MB102103 (D1690R00008)- Observational study: Complications of UTI in Patients on Dapagliflozin Ongoing	Assess the incidence of hospitalization or emergency department visit for severe complications of UTI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Severe complications of UTI	Submission of interim data Submission of final data	2016,2019 2020
MB102104 (D1690R00005) - Observational study: Acute Liver Injury in Patients on Dapagliflozin Ongoing	To assess the incidence of hospitalization for ALI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Risk of acute hepatic failure	Submission of Interim data Submission of final data	2016,2019 2020
MB102110 (D1690R00004) - Observational study: Acute Kidney Injury in Patients on Dapagliflozin and Other Antidiabetic Medications Ongoing	To assess the incidence of hospitalization for AKI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Risk of AKI	Submission of Interim data Submission of final data	2016,2019 2020
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,	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	lipolysis, and ketogenesis following insulin withdrawal in subjects with diabetes mellitus and absolute or relative endogenous insulin deficiency, when treated with dapagliflozin.			
Meta-analysis across studies D1690C00018, D1690C00019, and D1693C00001 (DECLARE). Planned	Determine the incidence of amputation and relevant preceding AEs over time by showing the cumulative proportion of subjects with events and numbers of subjects at risk at relevant time points.	Lower limb amputation	Protocol submission Submission of final data	Q1 2018 Q3 2020

In dapagliflozin RMP version 17.3, the MAH removed the planned study on "Knowledge and understanding of additional RMM for DKA in Health Care Professionals and Patients". This study was included in the previous dapagliflozin RMP version 17. The MAH is therefore requested to reinstate at a next regulatory opportunity impacting the RMP this study in the pharmacovigilance plan of the dapagliflozin RMP. This study should include the following milestones:

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
Knowledge and Understanding evaluation of additional RMM for DKA in Health Care Professionals and Patients. (planned)	Determine the effectiveness of additional risk minimisation measures in place for DKA in Europe by assessment of health care provider and patient knowledge, understanding and behaviour regarding DKA and how to minimise its risk in T1DM patients treated with dapagliflozin. Other objectives include evaluation of differences	diabetic ketoacidosis in T1DM	Protocol submission Submission of final data	Q2 2019 Q4 2021 (estimated)

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
	across countries, patients and prescriber characteristics.			

Risk minimisation measures

Safety concern	Risk minimisation measures
Urinary tract infection	Routine risk minimisation measures: SmPC section: 4.8 PL section: 4
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/m2 should not be

Safety concern	Risk minimisation measures
	initiated on dapagliflozin. Additional risk minimisation measures: Educational materials for HCPs and patients/carers. Additional risk minimisation measures: Educational materials for HCPs and patients/carers.
Renal impairment	Routine risk minimisation measures: Guidance is provided on monitoring renal function (SmPC section 4.4 and PL section 2).
Liver injury	No risk minimisation measures.
Bladder cancer	No risk minimisation measures.
Breast cancer	No risk minimisation measures.
Prostate cancer	No risk minimisation measures.
Lower limb amputation	No risk minimisation measures.

2.6.2. Risk management plan for dapagliflozin + Metformin

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

The PRAC considered that the risk management plan version 11.3 for dapagliflozin/metformin is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 11.3 with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	Urinary tract infection (dapagliflozin) Lactic acidosis (metformin) Renal impairment (dapagliflozin) Diabetic Ketoacidosis including events with atypical presentation (dapagliflozin)
Important potential risks	Liver injury (dapagliflozin) Bladder cancer (dapagliflozin) Breast cancer (dapagliflozin) Prostate cancer (dapagliflozin) Lower limb amputation (dapagliflozin)
Missing information	None

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
MB102103 (D1690R00008)- Observational study: Complications of UTI in Patients on Dapagliflozin Ongoing	Assess the incidence of hospitalization or emergency department visit for severe complications of UTI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs	Severe complications of UTI	Submission of interim data Submission of final data	2016, 2019 2020
MB102104 (D1690R00005) - Observational study: Acute Liver Injury in Patients on Dapagliflozin Ongoing	To assess the incidence of hospitalization for ALI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs	Risk of acute hepatic failure	Submission of Interim data Submission of final data	2016, 2019 2020
MB102110 (D1690R00004) - Observational study: Acute Kidney Injury in Patients on Dapagliflozin and Other Antidiabetic Medications Ongoing	To assess the incidence of hospitalization for AKI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs	Risk of AKI	Submission of Interim data Submission of final data	2016, 2019 2020

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
MB102118 (D1690R00007)[a] - 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	Interim data Final data	2016, 2019, 2021, 2023 2025
Nonclinical mechanistic model studies relating to diabetic ketoacidosis Ongoing	Research aiming to elucidate impact on cellular processes where presence of dapagliflozin may impact acid balance.	Ketoacidosis	Submission of final data	When available
Meta-analysis across studies D1690C00018, D1690C00019, and D1693C00001 (DECLARE). Planned	Determine the incidence of amputation and relevant preceding AEs over time by showing the cumulative proportion of subjects with events and numbers of subjects at risk at relevant time points.	Lower limb amputation	Protocol submission Submission of final data	Q1 2018 Q3 2020

Risk minimisation measures

Safety concern	Risk minimisation measures
Urinary tract infection	Routine risk minimisation measures: SmPC section 4.8. PL section 4.
Lactic acidosis	Routine risk minimisation measures: SmPC sections 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Symptoms of lactic acidosis included, and direction to assess patients immediately if these symptoms occur. Avoidance of excessive alcohol intake. Information included that Xigduo should be interrupted in relation to dehydration or conditions that could lead to hypoxia. In case of suspected symptoms, the patient should stop taking Xigduo and seek immediate medical

Safety concern	Risk minimisation measures
	attention. Discontinuation prior to intravascular administration of iodinated contrast agents due to risk of lactic acidosis. Laboratory abnormalities or clinical illness should be evaluated promptly and if evidence of acidosis, treatment must be stopped immediately. In the case of uncontrolled diabetes, Xigduo should not be taken (SmPC section 4.4, PL section 2). Xigduo is contraindicated in any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis) (SmPC section 4.3). Information on how to detect symptoms of lactic acidosis and instructions to seek medical attention (PL section 2, 4).
Diabetic Ketoacidosis including events with atypical presentation	Routine risk minimisations measures: SmPC sections 4.4, 4.8. PL sections 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Symptoms of DKA included, and direction to assess patients immediately, regardless of blood glucose level, if these symptoms occur. Information included that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected. (SmPC section 4.4, PL section 2). Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. (SmPC section 4.4). Information on how to detect symptoms of DKA and instructions to seek medical attention (PL section 2, 4).
Renal impairment	Routine risk minimisations measures: SmPC section 4.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance is provided on monitoring renal function, and dosage adjustment (SmPC section 4.2, 4.4 and PL section 2). Contraindication in patients with severe renal failure or acute conditions with the potential to alter renal function (GFR < 30 mL/min) (SmPC section 4.3 and PL section 2).
Liver injury	No risk minimisation measures.
Bladder cancer	None
Breast cancer	None
Prostate cancer	None

Safety concern	Risk minimisation measures
Lower limb amputation	No risk minimisation measures.

2.7. Update of the Product Information

As a result of this variation, section 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC has been updated based on the data obtained with the DECLARE study. The Package Leaflet (PL) is updated accordingly.

Please refer to the full text of the Product Information.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA. However, the changes to the package leaflet are limited and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication is changed as shown here:

"Forxiga is indicated in adults for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.**"**

T2DM is associated with CV and renal complications. There is increasing recognition of the overlap in CV and renal disease; primary dysfunction in either the heart or kidneys often results in secondary dysfunction or injury in the other organ. For example, kidney damage is more strongly associated with development of CV disease, and in particular HF and CV death, than traditional CV risk factors such as hypertension and dyslipidaemia. This confluence of cardiac and renal disease, often referred to as cardio-renal syndrome, is accentuated by T2DM resulting in a vicious circle consisting of T2DM, HF, and chronic renal disease.

The estimated prevalence of CV disease in patients with T2DM ranges from 14.8% to 40.5% depending on age and region with HF more prevalent than history of myocardial infarction (MI) or stroke. CV disease is the most common cause of death in patients with T2DM, with at least 50% of T2DM patients globally dying from CV disease.

3.1.2. Available therapies and unmet medical need

As a result of the FDA requirements to exclude an increased CV risk associated with products intended for the treatment of patients with T2DM, several CVOTs have been or are being performed.

DECLARE evaluated the effect of dapagliflozin compared to placebo on cardiovascular (CV) and renal outcomes in a broad T2DM population with or without established CV disease. In the EU DECLARE was a post-authorisation safety study (PASS); the PASS requirement was that DECLARE be designed to evaluate bladder cancer. Other potential safety concerns that the European Medicines Agency (EMA) requested be assessed were clinical consequences of increased haematocrit, renal impairment/failure, bone fracture, liver injury, breast cancer, prostate cancer, diabetic ketoacidosis (DKA), amputations, and pancreatitis. Some of these requests were made while the study was ongoing.

Some of these CVOT studies have shown a (modest) superior effect compared to placebo in prevention of CV events while others have reported a neutral effect. The vast majority of these studies have mainly included patients with established CV disease.

3.1.3. Main clinical study

The DECLARE study, was a post-marketing study that evaluated the effect of dapagliflozin on CV events with the aim to exclude increased CV risk and evaluating a potential CV benefit. The primary endpoint was the composite of CV death, MI and ischemic stroke (MACE). A composite of heart failure hospitalisation and CV death was added as an additional primary efficacy variable while the study was ongoing. The secondary objective of the study was to determine the effect on renal events and all-cause mortality. The renal composite endpoint was defined as confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15ml/min/1.73m^2) and/or renal or CV death (time to first event).

DECLARE included 17160 randomised and assessed T2DM patients, including both patients with established CV disease (6974; 40.6%) and without established CV disease (10186; 59.4%) who were followed for a median of 4.2 years.

3.2. Favourable effects

The primary safety endpoint was met as the upper CI for MACE (CV death, MI and ischaemic stroke) was well within the non-inferiority margin of 1.3; HR 0.93 [95%CI 0.84-1.03].

Dapagliflozin was found to be superior to placebo for the additional primary efficacy endpoint of hospitalisation for HF/CV death (HR 0.83 [95%CI 0.73, 0.95]).

For the composite endpoint of hospitalisation for HF and CV death, the outcome was driven by the reduction in hospitalisations for HF (HR 0.73 [95%CI 0.61, 0.88]) and there was no difference in the incidence of CV death.

The outcome of the secondary endpoint, renal events, was not formally tested. For the composite endpoint a HR of 0.76 [95% CI 0.67 to 0.87], was observed, mainly driven by the reduction of sustained GFR decrease and ESRD events.

A number of exploratory endpoints evaluated the effect of dapagliflozin on eGFR and albuminuria. eGFR measurements over time show that in the dapagliflozin group there was an initial drop in eGFR during the first 6 months after which the decrease in eGFR slowed down. From 6 months and onward the decrease in

eGFR was slower in the dapagliflozin group, resulting in a higher mean eGFR at 4 years compared to placebo.

The increase in the albumin to creatinine ratio from baseline was slower in the dapagliflozin treated group compared to the placebo group and new onset of macroalbuminuria was delayed in the dapagliflozin group compared to the placebo group. Regression in severity of albuminuria in patients with pre-existing macroalbuminuria was greater with dapagliflozin than with placebo. Notably, improvements were also observed in the placebo group.

The HR for all-cause mortality was 0.93 [95% CI 0.82-1.04]

In the dapagliflozin group, a mean decrease of -0.7% in HbA1c was observed at 6 months. After that time-point, HbA1c slowly increased and the mean change from baseline was -0.4% at 4 years. In the placebo group a mean decrease of -0.2% was observed at 4 years.

Subgroup analyses for the composite of hospitalisation for HF and CV death, the composite of MACE and for the renal composite variables showed consistent findings across the subgroups tested.

3.3. Uncertainties and limitations about favourable effects

The trial showed non-inferiority of dapagliflozin to placebo on the primary outcome MACE whereas superiority was not shown. However, the point estimate is rather similar as for other products in the class albeit that the upper CI was just above 1 (HR (CI)0.93 (0.84, 1.03)).

3.4. Unfavourable effects

DECLARE is included in the RMP for dapagliflozin a Category 3 PASS, in order to further study safety concerns identified at the time of the MAA but also identified after the launch of the product. As opposed to the studies in the MAA, only selected (non-serious) AEs were collected in addition to SAEs and DAEs. Adjudication of important safety variables were performed.

The DECLARE study provides long-term exposure data with more than 4 000 patients followed for four years and some patients followed up to five years.

SAEs and AEoSIs were generally balanced between treatment groups. Genital infections, DKA and embolic or thrombotic events and marked abnormality in haematocrit or haemoglobin were the only AEoSI with a higher reporting in the dapagliflozin groups, whereas renal events, hypoglycaemias and Fournier's gangrene was more commonly reported in the placebo group.

SAEs were generally well balanced, with less than an 0.2% difference between treatment groups for most PTs. HF and acute kidney injury were somewhat more common in the placebo group. The occurrence of death was balanced between groups and in both analysis populations.

Patients with HF NYHA class I-III, previously not included in the clinical study program, were eligible for inclusion in the study. Overall, 1724 patients (10% of the total population) were included in the study. In total 56% of patients with HF were in NYHA class II and only 7.3% (125 patients) were in NYHA class III. There was no imbalance between treatment groups. The data provided does not raise any safety concerns with the use of dapagliflozin in patients with HF (NYHA class I-III) and supports the removal of the warning on lack of experience in this patient group from section 4.4.

During the assessment of the original MAA, imbalances in the occurrence of bladder cancer, breast cancer, and prostate cancer were observed which led to concerns on that dapagliflozin could carry an increased risk of malignancies, although the overall incidence did not differ from comparators. The data from DECLARE, which has a considerably longer follow-up (up to 5 years) and includes a large number of patients, the overall incidence rates of malignancies did not differ between dapagliflozin and placebo (14.32 and 14.52 events per 1000 p-y). The relative risks varied around 1 but CIs were wide and included 1 for all types of cancer except bladder cancer (in favour of dapagliflozin) and "Other known site" (in favour of placebo).

In DECLARE, the relative risk of bladder cancer was lower with dapagliflozin than with placebo (HR 0.57 [95% CI: 0.35, 0.93]), the number of breast cancer cases was similar in both groups (36 (0.4%) vs 35 (0.4%)) and a higher number of prostate cancer cases were observed in the dapagliflozin group (73 (1.4% of male patients) vs 63 (1.2% of male patients)).

In DECLARE, no hepatic events assessed as definite or highly likely to be caused by dapagliflozin was observed.

Evaluation of bone fractures was included in DECLARE as a PAM. In the DECLARE study, the number of patients with fractures were balanced between treatment groups (5.3% vs 5.1%).

AEs suggestive of volume depletion were somewhat more common in the dapagliflozin group in the preapproval clinical development program. In DECLARE, the AEs suggestive of volume depletion included e.g. hypotension, syncope and shock. These events were balanced between treatment groups (213 (2.5%) and 207 (2.4%)).

The clinical consequences of increased haematocrit were evaluated. There was an imbalance between treatment groups with a higher reporting of both embolic and thrombotic events (7.9% with dapagliflozin and 7.2% with placebo) and the reporting of marked abnormalities in haematocrit or haemoglobin with dapagliflozin (2.4%) compared to placebo (0.7%). In patients experiencing both events, there was however no clear temporal association between the occurrence of abnormal haematocrit and a thromboembolic event.

Overall the incidence of serious hypersensitivity reactions was lower with dapagliflozin than with placebo (15 (0.2%) and 26 (0.3%)), although there were more patients with DAEs of hypersensitivity reactions in the dapagliflozin group.

Non-serious UTIs are a known side effect of dapagliflozin. The results from DECLARE indicated that dapagliflozin is associated with UTI DAEs, but there is no evidence that dapagliflozin is associated with an increased risk of serious UTIs, including urosepsis and pyelonephritis, as there were fewer patients with UTI SAEs in the dapagliflozin group (79 (0.9%) and 109 (1.3%)).

There were more patients with genital infections SAEs/DAEs in the dapagliflozin group compared with the placebo group: 76 (0.9%) and 9 (0.1%), respectively, corresponding to event rates of 2.5 and 0.3 events per 1000 p-y (OT-SAS). The difference was driven by non-serious DAEs of genital infection, thus the data does not indicate that dapagliflozin is associated with an increased risk of serious genital infections.

There were fewer patients with renal events in the dapagliflozin group compared with the placebo group (422 (4.9%) and 526 (6.1%)). The same pattern was observed for acute kidney injury, SAEs and DAEs.

In DECLARE only major hypoglycaemic events were collected. These events were few (58 (0.7%) and 83 (1.0%), dapagliflozin and placebo, respectively) especially taking the size and duration of the study into account. The number of events was lower for dapagliflozin, both in the overall population and in the subgroup using insulin or SU.

The data on amputations presented does not indicate any apparent increased risk of amputations with dapagliflozin compared to placebo (123 (1.4%) and 113 (1.3%)). It is however noted that there were more patients in the dapagliflozin groups who had more than 1 amputation (45 vs 30) and also more patients with amputations below and above the knee (46 vs 30). In the subgroup of patients with peripheral arterial disease at baseline, more patients in the dapagliflozin groups experienced an amputation than in the placebo group (43 and 28 patients, respectively), whereas the opposite was observed in patients without peripheral arterial disease at baseline.

The DECLARE results showed that there is a reasonable possibility of a causal relation between dapagliflozin and DKA in patients with T2DM, although DKA events were rare overall. The clinical presentation, risk factors, and contributing factors of DKA events in dapagliflozin-treated patients are similar to what is generally observed for DKA events. As observed for the T1DM population, the events were evenly distributed over time.

Events of pancreatitis were also collected. There was no difference in the number or type of events between treatment groups (24 (0.3%) with dapagliflozin and 25 (0.3%) with placebo).

Following the signal of Fournier's gangrene with the use of SGLT2 inhibitors, the DECLARE safety database was retrospectively searched for events suggestive of Fournier's gangrene. There were 18 patients with events with PTs indicating genital area infections or necrotizing fasciitis: 8 (<0.1%) and 10 (0.1%) the dapagliflozin and placebo group, respectively. Ten of these cases were adjudicated as Fournier's gangrene, out of which 2 were treated with dapagliflozin.

Apart for the data on haematocrit (see above), there were no remarkable findings with regards to laboratory values. As noted in the efficacy part of this report, eGFR was lower in the dapagliflozin group than in the placebo group after 1 year whereas eGFR was higher than for placebo after 4 years. Although numerically slightly more patients showed increased AST, ALT or total bilirubin levels in the dapagliflozin group compared to placebo, this was not reflected as an increase in hepatic events.

When the safety was assessed by sex, the only apparent difference observed was a higher reporting of UTI SAEs in females in both treatment groups and the reporting was lower in the dapagliflozin group than in the placebo group. UTI DAEs were more common in the dapagliflozin groups than in the placebo groups and more common in females than in males.

DECLARE included 1092 patients ≥75 years of age out of which 537 were treated with dapagliflozin. The overall reporting of SAEs and AEoSIs was about twice as high in the population ≥75 years of age compared to the overall population, but the reporting was balanced between groups. The overall safety profile was comparable to that of the overall population.

Effect of renal function on the safety profile was also evaluated. Apart from events suggestive of volume depletion, that were more common in patients with eGFR <60 treated with dapagliflozin than in those on placebo, there were no indication of a worsening of the safety profile with declining renal function.

AEs suggestive of volume depletion, renal events and amputations were analysed by extrinsic factors, such as use of ACEi/ARB and loop diuretics at baseline. These analyses could not identify any influence on these events by the extrinsic factors tested.

There were somewhat more patients with DAEs in the dapagliflozin group (8.1%) than in the placebo group (6.9%). Among the most common DAEs the largest numerical imbalance was observed for UTI, Balanoposthitis, and Pollakiuria which were more common in the dapagliflozin group. Numerically more patients on placebo reported DAEs Bladder cancer or Acute kidney injury.

3.5. Uncertainties and limitations about unfavourable effects

Although the data concerning events suggestive of volume depletion appear reassuring they are not considered sufficient to remove warnings regarding the risk of volume depletion on an individual basis. Volume depletion should also be considered in relation to the data on haematocrit and thromboembolic events. An association cannot be entirely ruled out and since the change in haematocrit is most likely due to volume depletion, this is still considered to be a risk with dapagliflozin treatment, especially in vulnerable patients.

Data on amputations was collected throughout the course of the study. The data provided does not indicate an increased risk of amputations with dapagliflozin use (HR 1.06; 95% CI 0.82, 1.37). However, due to the observations made for another SGLT2i, as well as the known diuretic effect of dapagliflozin that may jeopardise the microcirculation, the class warning in section 4.4 of the SmPC should remain.

The data provided does not indicate an increased risk of Fournier's gangrene with dapagliflozin treatment, although it should be taken into account that data was retrospectively collected in a database where only SAEs were routinely reported.

3.6. Effects Table

Table 1. Effects Table for dapagliflozin in the treatment of T2DM (data cut-off: 16 September 2018)

Effect	Short description	Unit	Dapa-gliflozin	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
MACE	The composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke	n (%)	756 (8.8)	803 (9.4)	HR (CI) 0.93 (0.84, 1.03) p-value <0.001 (non-inferiority) p-value 0.172 (superiority)	DECLARE
HF/CV death	The composite endpoint of hospitalization for heart failure or CV death	n (%)	417 (4.9)	496 (5.8)	HR (CI) 0.83 (0.73, 0.95) p-value 0.005	DECLARE
HF	Hospitalization for heart failure	n (%)	212 (2.5)	286 (3.3)	HR (CI) 0.73 (0.61, 0.88) p-value <0.001	DECLARE
CV death	CV death	n (%)	245 (2.9)	249 (2.9)	HR (CI) 0.98 (0.82, 1.17) p-value 0.830	DECLARE
Renal	Confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m^2 and/or ESRD and/or renal or CV death	n (%)	370 (4.3)	480 (5.6)	HR (CI) 0.76 (0.67, 0.87) p-value <0.001	DECLARE
All-cause mortality		n (%)	529 (6.2)	570 (6.6)	HR (CI) 0.93 (0.82, 1.04)	DECLARE

Effect	Short description	Unit	Dapa-gliflozin	Placebo	Uncertainties / Strength of evidence	References
					p-value 0.198	
HbA1c	Change from baseline at • Month 6 • 4 years	% (SD)	-0.72 (1.11) -0.43 (1.36)	-0.14 (1.17) -0.19 (1.46)	Exploratory variable, no statistical testing performed	DECLARE
Unfavourable Effects						
Malignancies	Overall incidence	n (%)	481 (5.6)	486 (5.7)	HR (CI) 0.99 (0.87, 1.12)	DECLARE
	Bladder ca	n (%)	26 (0.3)	45 (0.5)	HR (CI) 0.57 (0.35, 0.93)	DECLARE
	Breast ca	n (%)	36 (0.4)	35 (0.4)	HR (CI) 1.02 (0.64, 1.63)	DECLARE
	Prostate ca	n (% of males)	73 (1.4)	63 (1.2)	HR (CI) 1.14 (0.82, 1.60)	DECLARE
Hepatic events	Events positively adjudicated for study drug causality	n (%)	0	1		DECLARE
Fractures		n (%)	457 (5.3)	440 (5.1)		DECLARE
Volume depletion	E.g. hypotension, syncope and shock	n (%)	213 (2.5)	207 (2.4)		DECLARE
Hyper-sensitivity	SAEs on-treatment DAEs on-treatment	n (%)	15 (0.2) 19 (0.2)	26 (0.3) 11 (0.1)		DECLARE
UTI	SAEs on-treatment DAEs on-treatment	n (%)	79 (0.9) 61 (0.7%)	109 (1.3) 35 (0.4%)		DECLARE
Genital inf	SAEs on-treatment DAEs on-treatment	n (%)	2 74 (0.9)	2 7 (<0.1)		DECLARE
Renal events	SAEs on-treatment DAEs on-treatment	n (%)	80 (0.9) 55 (0.6)	136 (1.6) 61 (0.7)		DECLARE
Major hypo-glycaemia		n (%)	58 (0.7)	83 (1.0)		DECLARE
Amputations	Overall	n (%)	123 (1.4)	113 (1.3)	Partly retrospectively collected data	DECLARE
	> 1 amp	n	45	30		
	Patient with PAD at baseline	n	43	28		
DKA	Definite or probable DKA	n (%)	27 (0.3)	12 (0.1)	Partly retrospectively collected data	DECLARE
Pancreatitis		n (%)	24 (0.3)	25 (0.3)		DECLARE
Clinical con-sequences of increased haematocrit	Marked abnormality in haematocrit or haemoglobin	n (%)	202 (2.4)	64 (0.7)		DECLARE
	Embolic or thrombotic event	n (%)	681 (7.9)	618 (7.2)		DECLARE
	Embolic or thrombotic event AND marked abnormality in haematocrit or haemoglobin	n (%)	24 (0.3)	6 (<0.1)	No clear temporal relationship	DECLARE
Fournier's gangrene	On-treatment	n (%)	8 (<0.1)	10 (0.1)	Retrospectively collected data	DECLARE

Abbreviations: PAD - peripheral arterial disease; DKA – Diabetic ketoacidosis

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

DECLARE was a well-designed and well-conducted trial, conducted to investigate the impact of dapagliflozin treatment on CV risk in patients with T2DM. The trial showed non-inferiority of dapagliflozin to placebo on the primary outcome MACE whereas superiority was not shown. However, the point estimate is rather similar as for other products in the class albeit that the upper CI was just above 1.

One difference compared to other CVOTs, e.g. the EMPA-REG study, is the higher proportion of patients without established CV disease included in the DECLARE study; 59% compared to 0.5% in EMPA-REG. Thus, the study population of DECLARE is reflecting a broader population with T2DM.

A statistically significant lower risk of hospitalisations due to HF compared to placebo was observed, whereas no difference compared to placebo could be shown on CV death or all-cause mortality. A lower risk (of the same magnitude) of hospitalisation for HF has also been documented for other products in the class and is not unexpected considering the diuretic effect. The majority (90%) of the included patients in DECLARE did not have HF at the time of inclusion in the study and the data is therefore mainly relevant for patients without HF. The relative risk reduction for hospitalisation due to HF was 27% while the absolute reduction was only 0.8%.

The impact on renal events was investigated and the data indicate that progression of nephropathy was slower in the dapagliflozin group compared to the placebo group. Thus, the data provided give no indication of a negative effect on renal function. Similar results with respect to renal events were seen in the EMPA-REG study. It should be noted that even if the incidence of renal events was lower in the dapagliflozin group (relative risk reduction 24%, absolute risk reduction 1.3%) compared to placebo, there was still a mean reduction in eGFR during the study also in the dapa-group.

The MAH originally proposed to update the indication to include "prevention of new or worsening HF or CV death" and "prevention of new or worsening nephropathy" in the indication wording. This was not accepted by the CHMP and the MAH withdrew this proposal for SmPC section 4.1. The data from DECLARE on HF, other CV outcomes and nephropathy are of interest for the prescribers and are reflected in section 5.1 of the SmPC. In consistency with previous procedures on outcome studies with SGLT-2 inhibitors, a cross-reference to study results on cardiovascular events has been added in SmPC 4.1. With regards to the indication as initially claimed by the MAH, the CHMP is of the view that the patient population eligible for treatment with dapagliflozin should be mentioned, i.e. patients with T2DM, without mentioning any goal of treatment, i.e. neither improvement of glycaemic control, nor prevention of clinical outcomes. This means that the wording of the indication will refer to the patient population for whom treatment with dapagliflozin is intended, i.e. patients with T2DM, and the information on the DECLARE study, will be included in section 5.1. The CHMP considers both improvement of glycaemic control and reduction of other outcomes such as cardiovascular morbidity and mortality an integral part of the treatment of T2DM, which could best be expressed in a single indication for the treatment of T2DM. Therefore, separate prevention indications were not considered approvable. However, the CHMP considered the strengthening of the wording of the indication in section 4.1 of the SmPC by deleting "improvement of glycaemic control" from section 4.1 of the SmPC (as this restriction does no longer adequately reflect the demonstrated effects for dapagliflozin) together with the description of the benefits with dapagliflozin regarding microvascular events and heart failure, as assessed in this application, in section 5.1 of the SmPC. The wording "treatment of T2DM" is considered more relevant as it encompasses both glycaemic control and results on clinical outcomes.

The DECLARE study provides long-term data in a large number of patients treated with dapagliflozin and was designed to address a number of safety concerns raised in the assessment of the documentation for the MAA. No new safety concerns arise from the data provided.

The study included a substantial number of elderly subjects (≥75 years of age) with no indication of a different safety profile compared to placebo, supporting the proposed changes to the SmPC for this population. Relevant numbers of patients with HF (NYHA Class I-III) were also included. The data provided does not raise any safety concerns with the use of dapagliflozin in patients with HF (NYHA class I-III) and supports the removal of the warning on lack of experience in this patient group from section 4.4.

Data have also been provided on the following safety concerns listed in the RMP: volume depletion, clinical consequences of increased haematocrit, bone fracture, serious hypersensitivity reactions and pancreatitis, and for which no other PhV activities than DECLARE are ongoing. In addition, data on malignancies and specifically bladder cancer, breast cancer, prostate cancer was provided.

Although 3 to 5 years of exposure is not sufficient to completely rule out a cancerogenic effect, no imbalance was observed in the overall incidence in the original studies and there are no non-clinical findings suggestive of a genotoxic effect of dapagliflozin. The additional data obtained with DECLARE does not support the imbalance in e.g. bladder cancer documented in the data supporting the MAA.

Concerning volume depletion and clinical consequences of increased haematocrit, there are still uncertainties with regards to the risk with dapagliflozin use, but the SmPC contains adequate information. This also relates to the potential risk of amputations.

The data from DECLARE is considered sufficient to conclude that dapagliflozin treatment is not associated with an increased risk of bone fracture, serious hypersensitivity reactions or pancreatitis.

The safety information of the SmPC has been updated based on the submitted data.

3.7.2. Balance of benefits and risks

The DECLARE study provides important information concerning the long-term safety of dapagliflozin as well as the effect on cardiovascular and renal outcomes. The indication in section 4.1 of the SmPC has been modified to reflect the glycaemic and CV benefits of dapagliflozin by removing the reference to the surrogate goal "to improve glycaemic control" and by inserting a cross reference to the results of the DECLARE study presented in section 5.1

3.8. Conclusions

The overall B/R of dapagliflozin is positive.

4. Recommendations

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

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

Update of sections 4.1 , 4.2, 4.4, 4.8, and 5.1 of the SmPC of Forxiga, Edistride, Xigduo and Ebymect to modify the indication and to reflect new data based on final results from study D1693C00001 (DECLARE). This was a multi-centre, randomised, double-blind, placebo-controlled study to evaluate the effect of dapagliflozin on cardiovascular (CV) and renal outcomes in patients with T2DM with or without established CV disease.

The Package Leaflets (PL) are updated accordingly. The dapagliflozin Risk Management Plan (RMP) and dapagliflozin/metformin RMP have also been updated to version 17 and version 11 respectively.

The Worksharing applicant took the opportunity to make editorial changes and bring the PI in line with the updated excipient guideline (lactose wording in SmPC section 4.4) .

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan.