Clinical Study Report Synopsis	
Drug Substance	Dapagliflozin
Study Code	D169CC00001
Edition Number	1
Date	17 June 2022
EudraCT Number	2018-000802-46
NCT Number	NCT03619213

An International, Double-blind, Randomised, Placebo-Controlled Phase III Study to Evaluate the Effect of Dapagliflozin on Reducing Cardiovascular Death or Worsening Heart Failure in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)

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

Study dates: First subject enrolled: 27 August 2018
Last subject last visit: 27 March 2022
The analyses presented in this report are based on a clinical data lock date of 22 April 2022

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator: PPD PPD PPD PPD PPD PPD PPD

Sponsor's Responsible Medical Officer: PPD PPD PPD

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study Centre

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

Publications

Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN et al; Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail. 2021; 23(7):1217-25.

Solomon SD, Vaduganathan M, Claggett BL, de Boer RA, DeMets D, Hernandez AF et al, Baseline Characteristics of Patients With HF With Mildly Reduced and Preserved Ejection Fraction: DELIVER Trial. J Am Coll Cardiol Heart Failure. 2022;10(3):184-97.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function in • full study population • subpopulation with LVEF < 60%	Time to the first occurrence of any of the components of this composite: 1. CV death 2. Hospitalisation for HF 3. Urgent HF visit (eg, emergency department or outpatient visit)
Secondary	Efficacy	To determine whether dapagliflozin is superior to placebo in reducing the total number of HF events (hospitalisation for HF or urgent HF visit) and CV death in • full study population • subpopulation with LVEF < 60%	Total number of HF events (first and recurrent) and CV death
Secondary	Efficacy	To determine whether dapagliflozin is superior to placebo in improving Patient Reported Outcomes measured by KCCQ	Change from baseline in the TSS of the KCCQ at 8 months
Secondary	Efficacy	To determine whether dapagliflozin is superior to placebo in reducing CV death	Time to the occurrence of CV death
Secondary	Efficacy	To determine whether dapagliflozin is superior to placebo in reducing all-cause mortality	Time to the occurrence of death from any cause
-	Safety	To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients with HFpEF	SAEs, DAEs, amputations, AEs leading to amputation and potential risk factor AEs for amputations affecting lower limbs

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory		To determine whether dapagliflozin is superior to placebo in reducing all-cause hospitalisation [a]	Time to the first occurrence of hospitalisation from any cause
Exploratory		To determine whether dapagliflozin is superior to placebo in reducing the proportion of patients with worsened NYHA class [a]	Proportion of patients with worsened NYHA class from baseline to 8 months
Exploratory		To describe health status assessed by EuroQol five-dimensional five-level questionnaire to support health economic analysis and health technology assessment [a]	Results will be reported separately in a health economic report
Exploratory		To determine whether dapagliflozin compared with placebo will have an effect on systolic BP [a]	Change in systolic BP from baseline
Exploratory		To determine whether dapagliflozin compared with placebo will have an effect on body weight [a]	Change in body weight from baseline
Exploratory		To determine whether dapagliflozin compared with placebo will have an effect on eGFR [a]	Change in eGFR from baseline
Exploratory		To explore whether dapagliflozin compared to placebo improves KCCQ summary scores, subscores of TSS (symptom frequency and symptom burden) and domains [a]	Change in clinical summary score, TSS subscores, overall summary score, QoL score
Exploratory		To collect and store blood samples for future exploratory genetic research [a]	Not applicable. Results will be reported separately.

[a] Data only reported in Section 14 of the clinical study report.
AE, adverse event; BP, blood pressure; CV, cardiovascular; DAEs, discontinuation of investigation product due to an AE; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, HF with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QoL, quality of life; SAE, serious AE; TSS, total symptom score.

Study Design

DELIVER (D169CC00001) was an international, multi-centre, parallel-group, event-driven, randomised, double-blind, placebo-controlled Phase III study in patients with heart failure (HF) and left ventricular ejection fraction (LVEF) > 40%, evaluating the effect of dapagliflozin 10 mg compared with placebo, given once daily, in reducing the composite of cardiovascular (CV) death, hospitalisation for HF or an urgent HF visit (hospitalisation for HF or an urgent HF visit are hereafter jointly referred to as an HF event). Eligible patients were randomly assigned dapagliflozin 10 mg or placebo (1:1) using an interactive voice or web response system, and stratified according to their type 2 diabetes mellitus (T2DM) status. Patient recruitment was continuously monitored, with the possibility of capping to ensure

representative proportions of patients with T2DM and without diabetes. In addition, patient recruitment was continuously monitored to ensure that the study population was representative of patients with HF and LVEF > 40% with the possibility of capping based on patient's LVEF category, NYHA (New York Heart Association) class, atrial fibrillation status, subacute status (subacute status defined as randomised during hospitalisation or within 30 days of discharge), and geographic region. A pre-planned interim analysis was carried out after the accrual of 70.9% (792 events) of the final target number of 1117 primary events; the study continued after the interim analysis. Study closure procedures were initiated after the predetermined number of adjudicated primary events (n = 1117) were predicted to have occurred, ie, the primary analysis censoring date (PACD).

Target Population and Sample Size

To be eligible in the study, patients had to be male or female, aged ≥ 40 years, with a documented diagnosis of symptomatic HF (NYHA class II to IV) with LVEF > 40% and evidence of structural heart disease. Patients were required to have an elevated NT-proBNP (N-terminal pro b-type natriuretic peptide) concentration at enrolment: ≥ 300 pg/mL in patients with no ongoing atrial fibrillation or flutter and ≥ 600 pg/mL in patients with ongoing atrial fibrillation or flutter. Patients could be ambulatory or hospitalised (subacute status); patients must be off intravenous HF treatment (including diuretics) for at least 12 hours prior to enrolment and 24 hours prior to randomisation. Key exclusion criteria lowered the risk of enrolling patients with alternative conditions that could account for the patient's HF symptoms and signs. Hence, patients with anaemia, hypothyroidism, and primary pulmonary hypertension, or severe pulmonary disease were not eligible to participate in the study.

This study was event-driven with a target number of 1117 patients with an adjudicated primary endpoint. The primary endpoint was tested simultaneously in the full study population and in the subpopulation with LVEF < 60%, with alpha allocated to each test. It was anticipated that at least 70% of the events (ie, approximately 780 events) would be available for the subpopulation with LVEF < 60%. Assuming a true hazard ratio (HR) of 0.80, a two-sided alpha of 2.4% and of 3.7% allocated to the subpopulation with LVEF < 60% would result in a power of 80% and 85% to detect a treatment difference, respectively, whereas an alpha allocation of 1.5% to the full study population would result in 90% power. This was based on an overall 1:1 allocation between dapagliflozin and placebo. Approximately 6100 patients were estimated to provide the required target number of 1117 patients with a primary event in the full study population, based on an anticipated recruitment period of 26 months and a minimum follow-up period of 13.5 months. Overall, 6263 patients were analysed (3131 patients in the dapagliflozin group and 3132 patients in the placebo group) having 1122 adjudicated primary endpoints.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

Details of investigational products (IPs) are shown below.

Investigational Product	Dapagliflozin	Placebo
Dosage form and strength	10 mg (green, diamond-shaped, film-coated tablets)	Matching 10 mg placebo (green, diamond-shaped, film-coated tablets)
Batch numbers	AAR1429 HN0485 KF0352 KF0352/L010077	166074 189096 215963/L015362
Route of administration	Oral	Oral
Dosing instructions	Once daily	Once daily
Packaging and labelling	Investigational products were provided in bottles. Each bottle was labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements.	
Provider	Manufactured by AstraZeneca, whilst packaged and distributed to study sites by Fisher Clinical Services.	
Excipient	The tablets contain lactose, in quantities not likely to cause discomfort in lactose-intolerant individuals.	

Duration of Treatment

DELIVER was event-driven with an anticipated duration of 39 months. The median time in study until PACD was 28.0 months (range 0.1 to 42.1 months).

Statistical Methods

All patients who were randomised to IP were included in the full analysis set (FAS), irrespective of their protocol adherence and continued participation in the study. The primary variable was the time to first event included in the composite of CV death or an HF event, which was tested simultaneously in the full study population and in the subpopulation with LVEF < 60%. The primary analysis was based on the intention-to-treat principle using the FAS, including events with onset on or prior to PACD, adjudicated and confirmed by the Clinical Event Adjudication Committee. In the analysis of the primary composite endpoint, dapagliflozin versus placebo was compared using a Cox proportional hazards model with a factor for treatment group, stratified by T2DM status at randomisation.

The primary and the secondary endpoints were tested in a hierarchical sequence. Statistical significance was assessed in 2 branches in the prespecified order of the endpoints and populations. To control the overall type I error rate at 5% two-sided, the significance level was adjusted for a pre-planned interim analysis of efficacy, resulting in a significance level

of 4.8% for the final analysis. The total significance level was split for the dual primary analysis, allocating α_1 to test the subpopulation with LVEF < 60% and α_2 to test the full study population.

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

Study Population

Overall, 10418 patients were enrolled at 353 sites in 20 countries to randomise a total of 6263 patients: 3131 in the dapagliflozin group and 3132 in the placebo group. A total of 886 patients (14.1%) prematurely discontinued IP: 444 (14.2 %) in the dapagliflozin group and 442 (14.1%) in the placebo group. Of the 6263 randomised patients, 6211 patients (99.2%) had complete follow-up of the primary composite endpoint.

Demographic and other baseline patient characteristics were balanced between treatment groups in the full study population. Overall, 44.8% of patients had T2DM at baseline. Median LVEF was 54.0%, median NT-proBNP was 1011.0 pg/mL, mean eGFR was 61.0 mL/min/1.73 m^2, and median systolic BP was 128.0 mmHg.

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

The study population was representative of the general HF population with LVEF > 40%.

Summary of Efficacy Results

Treatment with dapagliflozin was superior to placebo in reducing the incidence of primary composite endpoint of CV death or an HF event in the full study population (HR 0.82 [95% Confidence Interval (CI) 0.73, 0.92], p = 0.0008). All components individually contributed to the treatment effect. The treatment benefit of dapagliflozin was supported by the total number of HF events (first and recurrent) and CV death (hereafter referred to as the composite of CV death and recurrent HF events) (rate ratio 0.77 [95% CI 0.67, 0.89], p = 0.0003). Further, dapagliflozin was superior to placebo in providing symptom benefit as measured by KCCQ-TSS (Kansas City Cardiomyopathy Questionnaire-total symptom score) (win ratio

1.11 [95% CI 1.03, 1.21], p = 0.0086). There were fewer CV deaths in the dapagliflozin group compared with the placebo group, not reaching statistical significance. There was no difference in all-cause mortality between treatment groups.

The treatment benefit on primary composite endpoint was consistent across the key prespecified subgroups, including those defined by baseline LVEF (≤ 49%, 50% to 59%, ≥ 60%), age, and sex.

A consistent treatment benefit of dapagliflozin was observed on the primary composite endpoint and the secondary composite endpoint of CV death and recurrent HF events in the subpopulation with LVEF < 60%.

The overall impact of the COVID-19 pandemic on the efficacy evaluation was assessed as low and the COVID-19 pandemic was judged not to have meaningfully impacted the interpretation of results.

Summary of Safety Results

In total, there were 6426 patient-years of exposure to dapagliflozin in the study. The median duration of exposure to IP was similar between treatment groups: 26.9 months in the dapagliflozin group and 27.0 months in the placebo group.

Treatment with dapagliflozin 10 mg once daily was well-tolerated in patients with HF and LVE > 40%, with no new safety concern identified. The proportions of patients with SAEs and patients with an AE with outcome of death were balanced between treatment groups. The number of patients with DAEs were low and balanced between treatment groups. The number of patients with interruptions of IP were balanced between treatment groups. The proportions of patients with SAEs suggestive of volume depletion were low and balanced between treatment groups. DAEs suggestive of volume depletion were few and numerically higher in the dapagliflozin group. SAEs and DAEs of renal events were balanced between treatment groups. There were 2 patients with DKA events, both had T2DM and were in the dapagliflozin group. The proportions of patients with major hypoglycaemic events were low and balanced between treatment groups. The proportions of patients with amputations were balanced between treatment groups. The proportions of patients with cardiac ischaemic events and strokes were balanced between treatment groups. There were no cases of Fournier's gangrene.

Despite the COVID-19 pandemic, the ability to monitor and manage patients' safety during the conduct of the study was maintained. The COVID-19 pandemic did not appear to have a meaningful impact on the interpretation of the safety results.

Conclusion(s)

DELIVER demonstrated that treatment with dapagliflozin had a statistically significant and clinically meaningful benefit in reducing the incidence of CV death or an HF event in patients with HF and LVEF > 40%, with no heterogeneity by LVEF.

Dapagliflozin was well-tolerated, the established safety profile of dapagliflozin was confirmed in patients with HF and LVEF > 40%.