| **Clinical Study Report Synopsis** | |
|---|---|
| Drug Substance | Dapagliflozin |
| Study Code | D169EC00001 |
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| NCT Number | NCT03877224 |

# An International, Multicentre, Parallel-group, Randomised, Double-blind, Placebo-controlled, Phase III Study Evaluating the effect of Dapagliflozin on Exercise Capacity in Heart Failure Patients with Preserved Ejection Fraction (HFpEF)

# Short Title: DETERMINE-preserved – Dapagliflozin EffecT on ExeRcise capacity using a 6-MINutE walk test in patients with heart failure with preserved ejection fraction

**Study dates:** First subject enrolled: 09 April 2019
Last subject last visit: 09 July 2020
The analyses presented in this report are based on a database lock date of 02 October 2020

**Phase of development:** Therapeutic confirmatory (III)

**International Co-ordinating Investigator:**
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

### Study centres

This study was conducted at 102 participating sites in 12 countries.

### Publications

None at the time of writing this report.

### Objectives and criteria for evaluation

Table S1 describes all study objectives and endpoints. This report addresses all endpoints except for the exploratory pharmacokinetic and genetic testing endpoints.

**Table S1 Objectives and outcome variables**

| Objective | | Outcome variable |
|---|---|---|
| **Priority/ Type** | **Description** | **Description** |
| Primary/ Efficacy | To determine whether dapagliflozin is superior to placebo in patients with chronic HF NYHA Functional Class II-IV and preserved ejection fraction (LVEF > 40%) [HFpEF] in:<br>• reducing patient-reported HF symptoms<br>• reducing patient-reported physical limitation<br>• improving exercise capacity | Family of primary endpoints:<br>• Change from baseline in the KCCQ-TSS at Week 16.<br>• Change from baseline in the KCCQ-PLS at Week 16.<br>• Change from baseline in 6MWD at Week 16. |
| Secondary/ Efficacy | To determine whether dapagliflozin is superior to placebo in increasing time spent non-sedentary, evaluated in a subset of at least 100 patients | Change from baseline at the end of the study in total time spent in light to vigorous physical activity, as assessed using a wearable activity monitor (accelerometer). |
| Safety | To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients with HFpEF | • AEs<br>• SAEs<br>• DAEs<br>• AEs leading to amputation<br>• Potential risk-factor AEs for amputations affecting lower limbs<br>• Laboratory tests<br>• Vital signs |
| Exploratory/ Efficacy | To determine whether dapagliflozin is superior to placebo in increasing total physical activity, evaluated in a subset of at least 100 patients | Change from baseline at end of study in total activity measured by vector magnitude units per minute, as assessed using a wearable activity monitor (accelerometer). |
| | To determine whether dapagliflozin is superior to placebo in reducing serum NT-proBNP | Change from baseline in serum NT-proBNP at Week 16. |

**Table S1 Objectives and outcome variables**

| Objective | | Outcome variable |
|---|---|---|
| **Priority/ Type** | **Description** | **Description** |
| | To determine whether dapagliflozin is superior to placebo in increasing the exercise capacity during daily life, evaluated in a subset of at least 100 patients | Change from baseline at end of study in movement intensity during walking, as assessed using a wearable activity monitor (accelerometer). |
| | To determine whether dapagliflozin is superior to placebo in reducing the proportion of patients with worsened NYHA Functional Classification | Proportion of patients with worsened NYHA Functional Classification at Week 16. |
| | To compare the effect of dapagliflozin versus placebo on physical activity, evaluated in a subset of at least 100 patients | Change from baseline at end of study for exploratory endpoints assessed using wearable activity monitors (accelerometers), in amount, duration, and intensity. |
| | To compare the effect of dapagliflozin versus placebo on health status as assessed by EQ-5D-5L | Change from baseline in health status utilities as measured by EQ-5D-5L at Week 16. |
| | To compare the effect of dapagliflozin versus placebo on patient reported dyspnoea and fatigue | Change from baseline in dyspnoea at Week 16.<br>Change from baseline in fatigue at Week 16. |
| | To assess the patients' overall evaluation of net treatment benefit | Distribution of patients' assessment of benefit of study drug. |
| | To explore whether dapagliflozin compared to placebo improves symptom frequency, symptom burden, symptom stability, social limitation, and QoL | Changes from baseline in the following KCCQ domains at Week 16:<br>• TSS domains: symptom burden and symptom frequency<br>• Overall summary score<br>• Symptom stability domain<br>• Self-efficacy domain<br>• Social limitation domain<br>• QoL domain |
| | To assess change in oxygen saturation after 6MWT | Change from baseline in oxygen saturation difference after 6MWT at Week 16. |
| | To determine whether dapagliflozin compared with placebo has an effect on systolic BP | Change from baseline in systolic BP at Week 16. |
| | To determine whether dapagliflozin compared with placebo has an effect on body weight | Change from baseline in body weight at Week 16. |
| | To determine whether dapagliflozin compared with placebo has an effect on eGFR. | Change from baseline in eGFR at Week 16. |

**Table S1 Objectives and outcome variables**

| Objective | | Outcome variable |
|---|---|---|
| **Priority/ Type** | **Description** | **Description** |
| | To collect and store blood samples for PK assessment | Explore dapagliflozin exposure-response relationship for efficacy and safety endpoints. The results will be analysed and reported in a separate report. |
| | To collect and store blood samples for future exploratory genetic samples | Not applicable. Results will be analysed and reported separately. |

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; AE, Adverse event; BP, Blood pressure; DAE, Adverse event leading to discontinuation of investigational product; eGFR, Estimated glomerular filtration rate; EQ-5D-5L, European Quality of Life 5-dimensional 5-level health status questionnaire; HF, Heart failure; HFpEF, Heart failure with preserved ejection fraction; IP, Investigational product; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, Left ventricular ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PK, Pharmacokinetic; PLS, Physical limitation score; QoL, Quality of Life; SAE, Serious adverse event; TSS, Total symptom score

## Study design

This was an international, randomised, multi-centre, double-blind, placebo-controlled, parallel-group, phase III study in heart failure (HF) with preserved ejection fraction (HFpEF) patients evaluating the effect of dapagliflozin 10 mg versus placebo given once daily on change in HF symptoms as measured by the Kansas City Cardiomyopathy Questionnaire – Total Symptom Score (KCCQ-TSS), physical limitation as measured by the KCCQ – Physical Limitation Score (KCCQ-PLS), and exercise capacity as measured by 6-minute walk distance (6MWD). During the study all patients were to be treated according to local guidelines on standard of care treatment for patients with HFpEF, including treatment as needed with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual. Treatment of diabetes was to follow established guidelines.

## Target subject population and sample size

The target population was adult patients with chronic HFpEF (defined in this study as left ventricular ejection fraction [LVEF] > 40% and evidence of structural heart disease) and New York Heart Association (NYHA) Functional Class II-IV, aged ≥ 40 years who met the all of the inclusion criteria and none of the exclusion criteria. It was estimated that approximately 1000 patients would need to be enrolled to reach the target of approximately 500 patients randomised 1:1 to receive either dapagliflozin 10 mg or matching placebo.

The study population included patients with baseline estimated glomerular filtration rate ≥ 25 mL/min/1.73m$^2$ both with type 2 diabetes mellitus (T2DM) and without diabetes, as the beneficial haemodynamic effects of dapagliflozin appear to be independent of the glycaemic effect and could therefore be expected in both groups. Enrolment in the study was capped on a study level based on the proportion of patients with T2DM and the proportion of patients with

an LVEF value above 40% and below 50%, and the proportion of patients with atrial fibrillation/flutter (AF) status was monitored to ensure they were representative.

**Investigational product and comparator(s): dosage, mode of administration, and batch numbers**

Treatment was once-daily oral doses of dapagliflozin 10 mg film coated tablets compared to matching placebo. The dapagliflozin batch number was L006289/HN0485 and the matching placebo batch number was L005127/166074.

**Duration of treatment**

The study included 5 scheduled visits (4 on-site visits and 1 telephone contact) over an initial enrolment/screening visit and a 16-week treatment and assessment period. There was no follow-up visit.

**Statistical methods**

The primary endpoints in this study were change from baseline in each of KCCQ-TSS, KCCQ-PLS, and 6MWD at Week 16. The secondary endpoint was change from baseline in total time spent in light to vigorous physical activity (LVPA), as assessed using a wearable activity monitor (accelerometer) at the end of the study. The primary and secondary efficacy endpoints were evaluated under a combined treatment policy (intent-to-treat) and composite variable strategy estimand, including differences between the 2 treatment groups in outcomes at the end of the 16-week treatment period/end of study. The intent-to-treat approach was employed to reflect the effect of the initially assigned randomised study drug, irrespective of exposure to study drug and concomitant treatment as well as subsequent treatment after discontinuation of study drug. A composite variable strategy approach was employed to account for deaths occurring during the follow-up period.

Each primary endpoint was analysed based on a rank analysis of covariance (ANCOVA) model with rank-based change from baseline at Week 16 as the outcome. The rank-based baseline value was included as a covariate along with the stratification factor used in the randomisation. The main estimation of magnitude of treatment effect was based on the Hodges-Lehmann median difference. Sensitivity analyses were performed to assess the robustness of the treatment effect from the handling of missing data.

As this study was ongoing at the time of onset of the COVID-19 pandemic, and the objective of the study was to evaluate the efficacy of dapagliflozin in a world where there is not an ongoing COVID-19 pandemic, adjustments were made to the originally-planned analyses. KCCQ-TSS and KCCQ-PLS results were expected to be influenced by pandemic-related impacts on patients' lifestyle and behaviour. To account for these impacts, for the rank ANCOVA a categorical covariate variable quantifying the number of weeks impacted by the COVID-19 pandemic was introduced in the hypothesis tests of the KCCQ-TSS and KCCQ-

PLS endpoints, and the Hodges-Lehmann estimate of the median difference and the supportive responder analysis of these endpoints used data collected prior to the onset date of COVID-19 at each site, imputing any data collected or missing after the onset date of COVID-19 at each site, assuming missing at random based on pre-COVID-19 data only (under the original efficacy estimand). This approach was applied to all main estimations of the magnitude of treatment effect, to preserve the original efficacy estimand.

To account for multiplicity to test the primary and secondary efficacy endpoints, a prespecified testing strategy was followed to control the overall type I error rate. The testing was performed according to a gatekeeping procedure: the 3 tests of KCCQ-TSS, KCCQ-PLS, and 6MWD at the family-wise error rate of 0.05 (2-sided) were conducted first. The 0.05 was divided among the 3 primary efficacy endpoints using a weighted Bonferroni method, with 0.04990 assigned to KCCQ-TSS, 0.00005 to KCCQ-PLS, and 0.00005 to 6MWD. The secondary efficacy endpoint, total time spent in LVPA, was not to be tested unless the test of 6MWD was significant. As the testing procedure progressed, if a test was significant its assigned alpha was to be preserved and considered as unused and passed along fully or partially to the other tests in the primary endpoint family. The passed-along alpha was to be added to the originally assigned alpha to test the other endpoints. The test of secondary endpoint was to only use the unused alpha from the primary efficacy endpoints family.

**Subject population**

In total, 946 patients were enrolled, 504 were randomised and 491 completed the study. All 504 randomised patients were included in the full analysis set and 501 patients were included in the safety analysis set. In total, 465 patients completed the study on study drug. Few patients discontinued study drug: 20 (7.9%) and 16 (6.4%) in the dapagliflozin and placebo groups, respectively.

Few patients (5.4%; n = 27) included in the full analysis set had an important protocol deviation. Important protocol deviations were generally balanced between treatment groups in terms of both frequency and type.

The treatment groups were generally balanced with respect to demographic characteristics, specific disease history, and HF-related baseline characteristics. The mean age of patients in the study was 71.8 years and 46.0% of patients were ≥ 75 years of age. Most patients were male (63.5%) and White (73.4%); 43.7% of patients had T2DM at randomisation and 52.0% had AF. Mean LVEF was 53.1%, median N-terminal pro b-type natriuretic peptide (NT-proBNP) was 776.0 pg/mL, and most patients (83.7%) were NYHA class II. Overall, 6.7% of patients had a history of either implantable cardioverter defibrillator or cardiac resynchronisation therapy (CRT) defibrillator and 3.0% had a history of CRT-pacemaker or CRT-defibrillator.

The study population was appropriately treated with background local standard of care for HFpEF. Use of concomitant HF medications at baseline was high and similar between the treatment groups: 71.6% of patients were treated with a beta blocker in combination with at least one of an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or angiotensin receptor-neprilysin inhibitor, 39.7% with a mineralocorticoid receptor antagonist, and 85.5% with a diuretic, most commonly a loop diuretic.

**Summary of efficacy results**

Treatment with dapagliflozin did not demonstrate superiority to placebo in reducing patient-reported HF symptoms in adults with HFpEF as measured by KCCQ-TSS. There was a numerical improvement from baseline at Week 16 in the dapagliflozin group compared with the placebo group in KCCQ-TSS, in adults with HFpEF, but the improvement was not statistically significant: p = 0.07905 (rank ANCOVA). The Hodges-Lehmann estimate of median difference in the dapagliflozin group vs. placebo was 3.16 points (95% confidence interval [CI] 0.36, 6.01).

Treatment with dapagliflozin did not demonstrate superiority to placebo in reducing patient-reported physical limitation due to HF in adults with HFpEF as measured by KCCQ-PLS. The Hodges-Lehmann estimate of median difference in the dapagliflozin group vs. placebo was 3.12 points (95% CI -0.09, 5.37).

Treatment with dapagliflozin did not demonstrate superiority to placebo in improving exercise capacity in adults with HFpEF as measured by 6MWD. The Hodges-Lehmann estimate of median difference in the dapagliflozin group vs. placebo was 1.6 metres (95% CI -5.9, 9.0).

For the secondary endpoint, there was little change from baseline in total time spent non-sedentary (ie, total time spent in LVPA) in either treatment group.

**Summary of safety results**

Median exposure to study drug was 113 days in each treatment group.

Treatment with dapagliflozin 10 mg once daily was well-tolerated in patients with HFpEF and no new safety concerns were identified. Similar proportions of patients in the dapagliflozin and placebo groups had adverse events (AEs) (38.9% vs. 35.3%, respectively), serious AEs (10.3% vs. 7.6%), and AEs leading to discontinuation of study drug (3.6% vs. 2.4%). There were few deaths: 3 (1.2%) and 2 (0.8%) in the dapagliflozin and placebo groups, respectively. No patient had an AE leading to amputation. Potential risk-factor AEs for amputations affecting lower limbs (‘preceding events’) were few (9 [1.8%]) and balanced between the treatment groups. Assessments of clinical laboratory and chemistry values, vital signs, and physical findings did not identify any safety concerns.

## Conclusions

- DETERMINE-preserved was impacted by the COVID-19 pandemic. Adjustments were made to mitigate the impact and overall the study was well-conducted, with high treatment compliance, low discontinuation rates, and few important protocol deviations.
- The study population was appropriately treated with background local standard of care for HFpEF.
- Treatment with dapagliflozin 10 mg once daily did not demonstrate superiority to placebo in reducing patient-reported HF symptoms, as measured by change from baseline at Week 16 in KCCQ-TSS, in reducing patient-reported physical limitation, as measured by change from baseline at Week 16 in KCCQ-PLS, or in improving exercise capacity, as measured by change from baseline at Week 16 in 6MWD, in adults with HFpEF.
- Treatment with dapagliflozin was well-tolerated and no new safety concerns were identified.