CLINICAL STUDY PROTOCOL
VERSION 5.0

A Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Trial to Evaluate the Effect of In-Hospital Initiation of Dapagliflozin on Clinical Outcomes in Patients Who Have Been Stabilized During Hospitalization for Acute Heart Failure

Dapagliflozin and Effect on Cardiovascular Events in Acute Heart Failure - Thrombolysis in Myocardial Infarction 68 (DAPA ACT HF-TIMI 68)

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1. Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AHF	Acute heart failure
AE	Adverse event
AEOSI	Adverse event of special interest
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
BNP	B-type natriuretic peptide
CEC	Clinical Events Committee
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
CRT	Cardiac resynchronization therapy
CSP	Clinical study protocol
CSS	Clinical summary score
CV	Cardiovascular
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Record Form
eGFR	Estimated glomerular filtration rate
GCP	Good Clinical Practice
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICH	International Conference on Harmonization
IND	Investigational new drug
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
RRR	Relative risk reduction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SGLT2	Sodium-glucose cotransporter-2
T2DM	Type 2 diabetes mellitus
TIMI	Thrombolysis in Myocardial Infarction
TSS	Total symptom score
UP	Unanticipated problem
WOCBP	Women of child-bearing potential

2. Protocol Synopsis

Study sites and number of subjects planned

The study will be conducted at approximately 150-250 sites in North America and Europe. It is estimated that approximately 2400 patients will be enrolled during a recruitment period of approximately 30 months.

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2020	3b/4
Estimated date of last subject completed	Q2 2023	

Study Design

This is an international, multicenter, parallel-group, randomized, double-blind, placebo-controlled trial in patients who have been stabilized during hospitalization for acute heart failure, evaluating the effect of in-hospital initiation of dapagliflozin versus placebo on the clinical outcome of cardiovascular death or worsening heart failure.

Study Objectives

Primary Objective:	Outcome Measure:
To assess the effect of in-hospital initiation of dapagliflozin, as compared with placebo, on the clinical outcome of cardiovascular death or worsening heart failure in patients who have been stabilized during hospitalization for acute heart failure.	Time to first occurrence of cardiovascular death or worsening heart failure defined as: 1. Worsening HF during the index admission requiring at least one of the following: a) initiation or re-initiation of inotropic therapy for ≥24 hours b) mechanical circulatory support c) invasive ventilatory support for heart failure d) heart transplantation 2. Readmission for worsening heart failure 3. Worsening heart failure leading to an urgent visit with administration of intravenous diuretic therapy (e.g., outpatient setting, emergency department) without associated hospital admission

Safety Objective:	Outcome Measure:
To evaluate the safety and tolerability of in-hospital initiation of dapagliflozin in this patient population.	• Symptomatic hypotension leading to hospitalization or study drug discontinuation • Worsening renal function that results in at least a doubling of serum creatinine, hospitalization, study drug discontinuation, dialysis, or renal death

Target Population

Patients who have been stabilized during hospitalization for acute heart failure.

Investigational Product, Dosage, and Mode of Administration

Dapagliflozin 10 mg administered orally once daily for 2 months.

Comparator Product, Dosage, and Mode of Administration

Matching placebo administered orally once daily for 2 months.

Statistical Methods

The primary efficacy assessment will involve an intention-to-treat (ITT) comparison of the effect of allocation to dapagliflozin versus placebo on the primary efficacy outcome through the 2-month follow-up period. Cumulative clinical event rates will be calculated according to the Kaplan–Meier method. Differences in clinical outcomes between the two treatment groups will be assessed using the log-rank test. Hazard ratios and 95% confidence intervals will be calculated with a Cox proportional-hazards model stratified by history of heart failure (established vs. de novo) and T2DM (yes vs. no) status at baseline.

With a 2-sided alpha of 0.05, a 16% event rate in the control arm, and a 0.5% dropout rate, approximately 2400 AHF patients should provide at least 320 events and therefore at least 80% power to detect a 27% relative risk reduction (RRR) in the primary endpoint.

3. Study Background & Rationale

Acute heart failure (AHF) is the most common cardiovascular reason for hospital admission, accounting for approximately one million hospitalizations in the United States annually.[1] Patients admitted for AHF are at high risk for cardiovascular death and re-hospitalization for heart failure (HF), and are thus an important target population for decreasing overall heart failure morbidity and mortality.[2, 3] In addition, HF hospitalization is an ideal time to implement evidence-based therapies for HF, as multiple studies have shown that initiation and adherence

are enhanced when these agents are prescribed prior to hospital discharge.[4, 5] The heightened risk of patients with AHF and the important opportunity for intervention support novel treatment strategies initiated prior to hospital discharge to improve the outcomes of patients with HF.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors induce glycosuria and natriuresis through pharmacologic inhibition of SGLT2 in the renal proximal tubule. In multiple large, well-powered, cardiovascular outcomes trials, members of this class, including dapagliflozin, were shown to robustly reduce the risk of hospitalization for HF in patients with type 2 diabetes mellitus (T2DM) and either established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors.[6]

Since few patients in the initial cardiovascular outcomes trials of SGLT2 inhibitors had pre-existing HF,[7] the question of whether SGLT2 inhibitors might also be beneficial in patients with established HF led to the design of multiple dedicated trials enrolling patients with chronic HF and either reduced or preserved ejection fraction (DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved). The first of these trials to be completed was the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial, which demonstrated that dapagliflozin, as compared with placebo, significantly reduced the risk of cardiovascular death, hospitalization for HF, or urgent HF visit in stable patients with chronic HF with reduced ejection fraction (HFrEF).[8] Subsequent data from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial showed that SGLT2 inhibitors can reduce the risk of cardiovascular death or hospitalization for HF in patients with chronic HF with mildly reduced (HFmrEF) and preserved ejection fraction (HFpEF) as well.[9]

Since DAPA-HF tested the effect of SGLT2 inhibition in ambulatory patients with chronic HF and did not randomize patients in the midst of HF hospitalization, an important remaining question is whether it is safe and efficacious to initiate an SGLT2 inhibitor in patients who are hospitalized for AHF. Of note, the subset of stable patients in DAPA-HF who had been hospitalized for HF 1-12 months prior to enrollment were at high risk for rehospitalization for HF or CV death and had robust relative and absolute risk reductions with dapagliflozin.[10] A small pilot study with empagliflozin in AHF also suggested robust clinical benefit.[11] On the other hand, patients with AHF could be more susceptible to therapy-related complications due to active modulation of diuretic therapy, fluctuating renal function, and concomitant dose adjustment of neurohormonal antagonists. Thus, evaluating the initiation of SGLT2 inhibition in the inpatient setting is of critical importance to the field. By analogy, the PIONEER-HF trial demonstrated that sacubitril/valsartan, as compared with enalapril, in patients stabilized during hospitalization for AHF was safe, well-tolerated, and led to a reduction in the clinical composite outcome of rehospitalization for HF or cardiovascular death.[12]

4. Study Objectives

The primary objective of this study is to assess the effect of in-hospital initiation of dapagliflozin, as compared with placebo, on the clinical outcomes of cardiovascular death or worsening heart failure in patients who have been stabilized during hospitalization for acute heart failure.

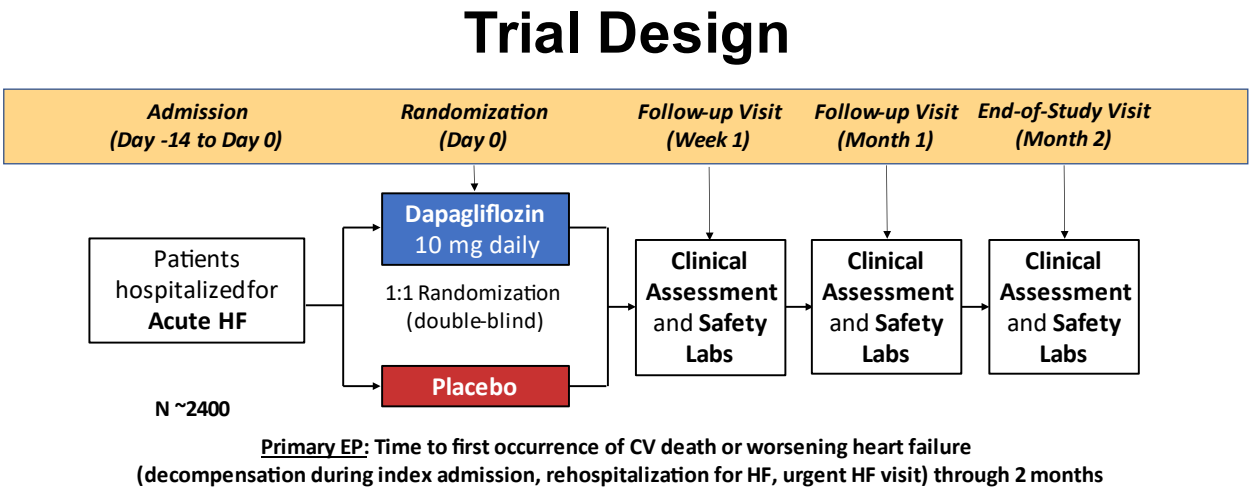
The key safety objectives are to assess the effect of in-hospital initiation of dapagliflozin, as compared with placebo, on the incidence of:

- Symptomatic hypotension leading to hospitalization or study drug discontinuation
- Worsening renal function resulting in at least a doubling of serum creatinine, hospitalization, study drug discontinuation, dialysis, or renal death

See Section 8 (Study Outcomes) for additional secondary and exploratory objectives.

5. Study Design

This is a phase 3b/4, multicenter, parallel-group, randomized, double-blind, placebo-controlled trial. The trial will be conducted in approximately 150-250 sites in North America and Europe. Approximately 2400 patients will be enrolled. Patients will be randomized in a 1:1 allocation ratio to receive either dapagliflozin 10 mg daily or placebo. Randomization will be stratified by history of heart failure (established vs. *de novo*) and T2DM (yes vs. no). Patients will have assessments at 1 week, 1 month, and 2 months. The anticipated enrollment period is approximately 30 months, each patient is followed for a maximum of 2 months, and thus the anticipated total duration of the study is approximately 32 months. The End of Trial is defined as the date when the last patient randomized completes his/her 2-month End-of-Study visit.



6. Study Population

Inclusion Criteria

1. Age ≥18 years (male or female)
2. Currently hospitalized for AHF defined as meeting all the following criteria:
   a) Presentation with worsening symptoms of heart failure (e.g., worsening dyspnea or dyspnea at rest, progressive fatigue, rapid weight gain, worsening edema/abdominal distention/anasarca)
   b) Objective signs or diagnostic testing consistent with volume overload (e.g., jugular venous distension, pulmonary basilar crackles, S3 gallop, ascites, hepatomegaly, peripheral edema, radiological evidence of pulmonary congestion, noninvasive or invasive hemodynamic evidence of elevated filling pressures)
   c) Intensification of AHF therapy during admission defined as at least one of the following:
      i. Augmentation of oral diuretic therapy [e.g., ≥2x outpatient regimen dose, addition of a second diuretic agent, or new initiation of diuretic therapy in a previously naïve patient]
      ii. Initiation of intravenous diuretic therapy
      iii. Initiation of intravenous vasoactive agent (e.g., inotrope or vasodilator)

The majority of enrolled patients should have an established history of heart failure (defined as present for ≥2 months and for which the patient is on treatment). Trial leadership will monitor this proportion and may cap enrollment of patients without an established history of heart failure (i.e., patients presenting with de novo heart failure).

3. Left ventricular ejection fraction (LVEF) measured within the past 12 months (including during the current hospitalization)
4. Elevated NT-proBNP or BNP during current hospitalization:
   a) For patients with LVEF ≤40%: NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL (NT-proBNP ≥2400 pg/mL or BNP ≥600 pg/mL if patient in atrial fibrillation or atrial flutter)
   b) For patients with LVEF >40%: NT-proBNP ≥1200 pg/mL or BNP ≥300 pg/mL (NT-proBNP ≥1800 pg/mL or BNP ≥450 pg/mL if patient in atrial fibrillation or atrial flutter)
5. Eligible patients will be randomized no earlier than 24 hours and up to 14 days after presentation while still hospitalized once they have been stabilized, as defined by:
   a) No increase (i.e., intensification) in the dose of intravenous diuretics during the 12 hours prior to randomization
   b) No use of intravenous vasodilators or inotropes during the 24 hours prior to randomization

   Patients across the spectrum of LVEF are eligible for participation in the trial. Trial leadership will monitor the proportion of patients with various LVEFs and may cap enrollment of certain subgroups to ensure a broad population.

In addition, patients with and without type 2 diabetes are eligible for participation in the trial. Trial leadership will monitor the proportion of patients with and without type 2 diabetes and may cap enrollment of one subgroup to ensure adequate representation of the other.

Exclusion Criteria

1. Symptomatic hypotension in the past 24 hours
2. Concurrent use of two or more intravenous inotropic agents during the index hospitalization
3. eGFR <25 ml/min/1.73 m^2 as measured by the CKD-EPI equation at screening or rapidly progressive renal disease
4. Current use of an SGLT2 inhibitor
5. Prior intolerance of SGLT2 inhibitors
6. Type 1 diabetes mellitus or history of diabetic ketoacidosis
7. (*Only applies to patients with T2DM who are on insulin and/or a sulfonylurea*) History of recurrent major hypoglycemia (i.e., resulting in severe impairment in consciousness or behavior, or requiring emergency external assistance)
8. Implantation of a cardiac resynchronization therapy (CRT) device or valve repair or replacement within 30 days prior to randomization or intent to do so during the trial
9. ST-segment elevation myocardial infarction or coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) within 30 days prior to randomization or intent to undergo coronary revascularization during the trial
10. Untreated sustained ventricular arrhythmias or Mobitz type II or third-degree heart block (i.e., without an ICD or pacemaker, respectively)
11. History of heart transplantation or current transplant listing; mechanical circulatory support use (either durable or temporary) during the index hospitalization
12. History of heart failure due to restrictive or infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy, uncorrected primary valvular disease, complex congenital heart disease, or heart failure felt to be due to a transient process (e.g., stress [takotsubo] cardiomyopathy, tachycardia-induced cardiomyopathy) expected to resolve within 2 months.
13. History of end-stage liver disease
14. Women of child-bearing potential (unless using adequate contraception) or currently breastfeeding
15. Current participation in a clinical trial with an unlicensed drug or device
16. Study staff or their family members
17. Any condition that, in the opinion of the investigator, would make trial participation not in the best interest of the subject, or would compromise compliance with the trial protocol (e.g., active severe infection, active malignancy)

7. Study Intervention

7.1 Investigational Product Information: Dapagliflozin 10 mg tablets and matching placebo tablets will be taken once daily orally in the morning at approximately the same time of day. Both dapagliflozin and placebo will be packaged and labeled in accordance with the US Code of Federal Regulations governing handling of investigational treatments and will be dispensed by the site personnel.

Study drug should be initiated as soon as possible during the index hospitalization once the patient qualifies for the trial.

7.2 Randomized Treatment Assignment: Each participating site will be provided a central supply of numbered bottles of dapagliflozin or matching placebo. Randomization to dapagliflozin vs. placebo will be done via the IRT in balanced blocks by site to ensure approximate balance between the two treatment arms. Patients will be dispensed the entire 2-month supply of study drug at randomization and will be assigned two bottles each containing 35 tablets. Treatment will be provided from the assigned bottle while the patients are in the hospital, and patients will take both bottles home upon discharge. It is possible to dispense an additional bottle of study drug to a patient during the trial in the case that a bottle is lost or damaged. Should this occur, the patient can return to the site to obtain the replacement bottle, or the bottle may be shipped to a patient's home when it is not feasible or advisable for a patient to travel to the clinic due to COVID-19 or other factors.

7.3 Blinding: A double-blind technique will be used. The active tablets and the matching placebo tablets will be identical in size, color, smell, and taste. No member of the study team will have access to the randomization scheme during conduct of the study. Unblinding may be carried out on an emergency basis by the site investigator by using the IRT when knowledge of the treatment allocation could materially influence the immediate medical management. The site investigator should contact the TIMI Hotline beforehand to discuss the planned unblinding.

7.4 Concomitant Medications: Treatment with any SGLT2 inhibitor other than the IP is not permitted for the duration of the study. All therapies for heart failure are at the discretion of the patient's treating physicians. Dapagliflozin does not increase the risk of hypoglycemia when used as monotherapy or in conjunction with drugs that do not increase the risk of hypoglycemia. However, certain diabetes therapies, such as insulin and insulin secretagogues (e.g., sulfonylureas) may cause hypoglycemia, the risk of which could potentially be accentuated by concomitant use of any other glucose-lowering medications, including SGLT2 inhibitors. Therefore, a lower dose of insulin or insulin secretagogues may be required to minimize the risk of hypoglycemia when used in combination with study drug. Reduction of insulin by 10-20% (total daily dose) and sulfonylurea by 25-50% and increased frequency of blood glucose monitoring should be considered in patients receiving insulin and/or a sulfonylurea and with a baseline HbA1c <7%, especially if there is any

history of significant hypoglycemic events. Of note, COVID-19 vaccines may be administered while patients are on study therapy.

7.5 Discontinuation of Study Drug: Patients may voluntarily discontinue study drug for any reason at any time. If adverse events occur that are believed to be due to study drug, or safety events occur that, in the opinion of the investigator, contraindicate further dosing of study drug, study drug may be temporarily interrupted or permanently discontinued. Whenever possible, restarting study drug should be encouraged, so long as the investigator judges that the potential benefit outweighs the risk. Situations that warrant permanent study drug discontinuation include severe non-compliance with the study protocol, diabetic ketoacidosis (DKA), and pregnancy. Refer to the Appendices for treatment guidelines for symptomatic hypotension, worsening renal function, and in patients with diabetes, what to do for hypoglycemia and the prevention and management of DKA. The investigator should contact the TIMI Hotline with any questions regarding study drug discontinuation and must update the IRT with any study drug discontinuation and record it in the eCRF. If a patient permanently discontinues study drug during the 2-month follow-up, an End of Treatment visit should be performed as soon as possible after the last dose of study drug is taken. Discontinuation of study drug does not mean discontinuation of follow-up. All study assessments should be continued even if study drug is discontinued.

7.6 Withdrawal of Consent: Patients are free to completely withdraw from the study at any time (which means permanent discontinuation of IP and all follow-up assessments) without prejudice to further treatment. Withdrawal of consent should only occur if the patient refuses any further assessments or contact whatsoever. Patients who do not want regular in-person follow-up after cessation of IP should be offered alternative methods of follow-up including periodic telephone follow-up, contact at study closure, or assessment of health status via treating physicians or medical records. Such patients would then not be viewed as withdrawals of consent. The investigator must explain to the patient all options for continued participation, and document which options were refused by the patient and the reason for refusal. Withdrawal of consent must be ascertained and documented in writing by the site investigator who must inform the TIMI Hotline and document the withdrawal of consent in the eCRF and medical records. Patients will be asked about the reason(s) for withdrawal of consent. For patients who withdraw from the study, direct ascertainment of health status at the end of the study or vital status via public records will be performed in compliance with local privacy laws/practices. Withdrawn patients will not be replaced.

7.7 Lost to Follow-Up: To prevent patients from being lost to follow-up, their contact details, including next of kin contacts should be collected initially and updated regularly by the site staff or representative. The site investigator should educate the patient on the importance of contact with the study site throughout the study. Repeated attempts will be made to locate and obtain pertinent medical information for patients who are potentially lost to follow-up. A patient will be classified as lost to follow-up at the end of the study only if s/he has failed to return for the required study visits and his/her vital status remains unknown despite multiple attempts to contact him/her via telephone, fax, e-mail, certified letter or

through patient locator agencies. The informed consent forms will include language to grant the option to employ outside companies to assist in obtaining updated contact information or ascertainment of vital status of lost patients using publicly available sources.

8. Study Outcomes

Efficacy outcomes

Primary outcome: Time to first occurrence of CV death or worsening heart failure defined as:

1. Worsening HF during the index admission requiring at least one of the following:
   a) initiation or re-initiation of inotropic therapy for ≥24 hours
   b) mechanical circulatory support
   c) invasive ventilatory support for heart failure
   d) heart transplantation
2. Readmission for worsening heart failure (i.e., rehospitalization for heart failure)
3. Worsening heart failure leading to an urgent visit with administration of intravenous diuretic therapy (e.g., outpatient setting, emergency department) without associated hospital admission

Secondary outcomes

1. Time to first occurrence of composite of CV death, rehospitalization for heart failure, or urgent heart failure visit
2. Time to first occurrence of composite of CV death or rehospitalization for heart failure
3. Time to first occurrence of rehospitalization for heart failure or urgent heart failure visit
4. Time to each individual component of the primary composite outcome
5. Hierarchical composite endpoint composed of: (1) time to CV death, (2) number of worsening HF events, (3) time to first worsening HF event, or (4) change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ)-12 total symptom score (TSS) at 2 months, analyzed using a win ratio approach with hierarchy based on the order of the components listed
6. Time to death

Exploratory outcomes

1. Total number of rehospitalizations for heart failure (first and recurrent) or CV death
2. Total number of days alive and out of the hospital
3. Readmission within 30 days of hospital discharge
4. Readmission within 60 days of hospital discharge
5. Time to composite of CV death or CV rehospitalization
6. Hierarchical composite endpoint composed of: (1) time to CV death during the index hospitalization, (2) time to worsening heart failure (using a hierarchical order of heart transplantation, mechanical circulatory support, invasive ventilatory support for heart

failure, or initiation or re-initiation of inotropic therapy for ≥24 hours) during the index hospitalization, or (3) longer time to discharge from index hospitalization, analyzed using a win ratio approach with hierarchy based on the order of the components listed

7. Health-related quality of life as measured by the KCCQ-12, including:
    a. Change from baseline in KCCQ-12 TSS at 2 months
    b. ≥5-point increase from baseline in KCCQ-12 TSS at 2 months
    c. ≥10-point increase from baseline in KCCQ-12 TSS at 2 months
    d. ≥15-point increase from baseline in KCCQ-12 TSS at 2 months
    e. Change from baseline in KCCQ-12 clinical summary score (CSS) at 2 months
    f. ≥5-point increase from baseline in KCCQ-12 CSS at 2 months
    g. ≥10-point increase from baseline in KCCQ-12 CSS at 2 months
    h. ≥15-point increase from baseline in KCCQ-12 CSS at 2 months
8. Composite congestion score
9. Time to first occurrence of composite of myocardial infarction, ischemic stroke, or CV death
10. New or recurrent atrial fibrillation

<u>Safety outcomes</u>

1. Symptomatic hypotension leading to hospitalization or study drug discontinuation
2. Worsening renal function resulting in at least a doubling of serum creatinine (sCr), hospitalization, study drug discontinuation, dialysis, or renal death

9. Visit Schedule and Assessments

Procedures	Screening (Day -14 to Day 0)*	Visit 1 In-hospital Randomization (Day 0)*	Visit 2 (Week 1)	Visit 3 (Month 1)	Visit 4 End of Study Visit (Month 2)	End of Treatment Visit**
Informed consent	X					
Review of inclusion/exclusion	X					
Medical history	X					
Vital signs (including weight)	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Pregnancy testing (WOCBP)***	X					
Randomization		X				
Dispense treatment		X				
Drug accountability			X	X	X	X
Assess for efficacy & safety events			X	X	X	X
HF signs and symptoms	X	X	X	X	X	X
BNP or NT-proBNP (local)	X					
Creatinine and potassium (local)	X	X	X	X	X	X
KCCQ questionnaire		X			X	

* Screening and randomization visits can be performed concurrently if the patient is fully eligible at the time of screening. If this occurs, it is not necessary to duplicate screening and randomization assessments (e.g., vital signs, creatinine and potassium, HF signs and symptoms), though these combined screening and randomization assessments should be performed on the day of randomization.

** If a patient permanently discontinues study drug during the 2-month follow-up, an End of Treatment (EoT) visit should be performed as soon as possible after the last dose of study drug. Patients should continue all remaining regularly scheduled visits but do not need any additional laboratory testing following the EoT visit.

*** Negative pregnancy test required for WOCBP (Women of Childbearing Potential)

9.1 Visit Windows

All follow-up visits can be scheduled within the following time windows:

- Visit 2: 7 days after randomization (±3 business days)
- Visit 3: 30 days after randomization (±3 business days)
- Visit 4 (End of Study Visit): 60 days after randomization (+5 business days). Visit 4 should not be performed prior to 60 days after randomization.

If scheduled visits cannot be conducted at clinical sites (e.g. due to the COVID-19 pandemic), telehealth visits by study site personnel are permitted in countries where this is logistically feasible and considered acceptable. Arrangements should be made for safety labs (creatinine and potassium) to be obtained as close to the visit date as possible.

Additional details about study procedures and visits can be found in the Manual of Operations.

10. Site Training and Monitoring

10.1 Training of Study Site Personnel: Before enrolling patients into the study, the requirements of the Clinical Study Protocol and related documents will be reviewed with the investigational staff who will be trained in any study-specific procedures. The site principal investigators will ensure that appropriate training relevant to the study is given to all staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The site principal investigator will also maintain a record of all individuals involved in the study.

10.2 Monitoring of Study Sites: Site monitoring will be performed based on the Monitoring Plan. Site visits will occur on a regularly scheduled basis and, as needed, based on site performance and perceived training needs. The purpose of such visits will be to ensure that the study is being conducted in accordance with the protocol, particularly through helping study site staff resolve any local problems and providing extra training focused on specific needs. Particular attention will be given to the effectiveness of strategies to recruit appropriate participants, the completeness of follow-up, the maintenance of participant adherence to study treatment, and the reporting of study outcomes and collection of relevant supporting documentation. A report of each visit will be prepared by the study monitor. If on-site monitoring visits are not possible (e.g. due to the COVID-19 pandemic), remote monitoring visits are permitted in countries where this is logistically feasible and considered acceptable.

11. Data Analysis Plan

Please note further details can be found in the Statistical Analysis Plan.

11.1 Analysis Sets

a) The Full Analysis Set will consist of all randomized patients with the exception of those who were not qualified for randomization and did not receive study drug but were inadvertently randomized into the study. Following the intention-to-treat principle, patients will be analyzed according to the treatment group to which they were assigned at randomization. Efficacy outcomes will be analyzed based on the Full Analysis Set.

b) The Safety Set will consist of all randomized patients who received at least one dose of study drug. Patients will be included in the analysis according to the treatment actually received. The Safety Set will be used for the analyses of safety outcomes.

c) The On-Treatment Analysis Set will consist of all randomized patients who received at least one dose of study drug. However, only those observations collected during treatment with study drug or within 3 days of the last dose of study drug will be part of this analysis set.

11.2 Analyses

The primary efficacy analysis will be performed in the Full Analysis Set. The primary efficacy assessment will involve an intention-to-treat (ITT) comparison of the effect of allocation to dapagliflozin versus placebo on the primary efficacy outcome through the 2-month follow-up period. Cumulative clinical event rates will be calculated according to the Kaplan–Meier method. Differences in clinical outcomes between the two treatment groups will be assessed using the log-rank test. Hazard ratios and 95% confidence intervals will be calculated with a Cox proportional-hazards model stratified by randomization stratification factors.

11.3 Subgroup Analyses

The following subgroups will be analyzed for the primary efficacy outcome:

a) Presence of type 2 diabetes
b) Established vs. newly diagnosed (i.e., *de novo*) heart failure
c) Age
d) Sex
e) Systolic blood pressure
f) LVEF at baseline
g) Estimated GFR at randomization
h) NT-proBNP concentration at randomization
i) BNP concentration at randomization

j) Use of concomitant heart failure therapies both prior to admission and at randomization (beta-blockers vs not; angiotensin receptor-neprilysin inhibitors [ARNI] vs not; inhibitors of the renin-angiotensin system [including ARNI] vs not; mineralocorticoid receptor antagonists [MRA] vs not; loop diuretics vs not)

Further details regarding the analysis sets, analytic periods, and analytic methods can be found in the Statistical Analysis Plan (SAP).

11.4 Sample Size Considerations

With a 2-sided alpha of 0.05, a 16% event rate in the control arm (estimated based on 3 recent trials of AHF patients),[13-15] and a 0.5% dropout rate (i.e., non-cardiovascular death, withdrawal of consent, lost to follow-up), 2400 AHF patients should provide at least 320 events and therefore at least 80% power to detect a 27% relative risk reduction (RRR) in the primary endpoint. In the DAPA-HF study of dapagliflozin in patients with stable, chronic HFrEF, there was a 26% RRR in the primary composite endpoint of cardiovascular death or worsening heart failure;[8] in the subgroup of patients who had been hospitalized for heart failure within the past year, there was a 36% RRR.[10]

Trial leadership will monitor the aggregate event rate during the course of the trial and may consider capping one or more subgroups or expanding the enrollment to ensure accrual of an adequate number of primary endpoint events.

12. Data and Safety Monitoring and Review

12.1 Data Collection

An electronic case record form (eCRF) will be used for data collection and query handling. The site investigator will ensure that data are recorded in the eCRF as specified in the study protocol and in accordance with the instructions provided. The investigator ensures the accuracy, completeness, and timeliness of the data recorded. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site. Data will be validated as defined in the Data Management Plan.

12.2 Safety Monitoring

Dapagliflozin 10 mg daily has been shown to be safe in multiple large cardiovascular outcomes trials and is an approved dose in the United States, Canada, and Europe. This study has received an exemption from the need for an Investigational New Drug (IND). Investigators are required to report: (1) Serious Adverse Events Related to Study Drug, (2) Unanticipated Problems, (3) Adverse Events Leading to Study Drug Discontinuation, (4) Adverse Events of Special Interest, and (5) Non-Heart Failure Hospitalizations.

1. Reporting of Serious Adverse Events Related to Study Drug

A serious adverse event (SAE) related to study drug must meet the following criteria:

a) Be serious, meaning that in the view of either the local investigator or the TIMI Study Group physician, the adverse event results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

b) Be related to study drug, meaning that there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. In making this assessment, there should be consideration, based on the available information, of the probability of an alternative cause, the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and (where appropriate) the response to subsequent re-challenge.

Reports of all such events are to be discussed immediately with a physician on the TIMI Hotline. It will be reviewed for seriousness and relatedness, and any additional information required will be sought (e.g., medical history, treatment before and after randomization). Events that qualify as an SAE related to study drug and occur after the first dose of study drug has been administered (through the end of the study period), should be reported in the eCRF on the appropriate pages and reviewed with the TIMI Hotline physician. SAEs related to study drug must be reported within 24 hours of knowledge of their occurrence. They should be clinically followed until the event has resolved or stabilized. All confirmed SAEs related to study drug will be reported to relevant regulatory authorities, ethics committees, Institutional Review Boards, and investigators in an expedited manner in accordance with regulatory requirements.

2. Reporting of Unanticipated Problems (UPs):

To qualify as a UP, an event must meet all of the following criteria:

a) Be unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
b) Be related or possibly related to participation in the research. "Possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

c) Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

3. Reporting of Adverse Events Leading to Study Drug Discontinuation: All adverse events (AEs) leading to investigational product discontinuation should be reported via the eCRF within 3 working days of knowledge of their occurrence.

4. Reporting of Adverse Events of Special Interest: The following adverse events of special interest (AEOSI) will be reported via the eCRF within 3 working days of knowledge of their occurrence:
   a) Symptomatic hypotension
   b) Worsening renal function resulting in at least a doubling of serum creatinine, hospitalization, study drug discontinuation, dialysis, or renal death
   c) Major hypoglycemia (i.e., resulting in severe impairment in consciousness or behavior, or requiring emergency external assistance)
   d) Diabetic ketoacidosis
   e) COVID-19 diagnosis or treatment

5. Non-Heart Failure Hospitalizations: All non-heart failure hospitalizations should be recorded in the eCRF regardless of whether they qualify as a reportable adverse event.

6. Pregnancy: If any pregnancy occurs during the course of the study, investigators or other site personnel should contact the TIMI Hotline immediately but no later than 24 hours after knowledge of its occurrence. Investigational product should be discontinued immediately. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up (even if after trial completion) and documented on the paper Pregnancy Outcome Report form and sent to the TIMI Safety Desk.

12.3 Data Monitoring Committee (DMC)

An independent DMC will be appointed by the TIMI Study Group. The DMC will be responsible for safeguarding the interests of the patients in the study by assessing the efficacy and safety of the intervention during the trial, and for reviewing the overall conduct of the clinical trial. They will review overall safety in the trial and specifically the incidence of symptomatic hypotension and worsening renal function. The DMC statistician will be able to have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. The DMC Charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data.

12.4 Clinical Events Committee (CEC)

Suspected outcome events in the study including the components of the primary efficacy endpoint will be centrally adjudicated by an independent clinical events committee. Suspected outcome events in the study will be identified either by the site investigator or by electronic review of reported AEs. For all events identified for adjudication, the investigator will complete the appropriate modules of the eCRF and provide source documentation (e.g., discharge summaries, death certificates, autopsy reports, etc).

13. Ethics and Dissemination

13.1 Ethical Conduct of the Study

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the most recent version of the Declaration of Helsinki.

An Ethics Committee (EC) or Institutional Review Board (IRB) will approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to patients.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure).

13.2 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the TIMI Study Group and the IRB prior to implementation.

13.3 Informed Consent Procedures

a) Eligible patients may only be included in the study after providing written informed consent
b) Informed consent must be obtained before conducting any study-specific procedures (i.e., all procedures described in the protocol)

13.4 Publications

The Principal Investigators, in collaboration with the other Steering Committee members, will be responsible for drafting the main report from the trial for publication and for secondary and supplementary analyses.

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15. Appendices

1. Study Organization and Oversight

This study was initiated by independent scientists at the TIMI Study Group at Brigham and Women's Hospital and Harvard Medical School, in collaboration with AstraZeneca. The TIMI Study Group will act as the sponsor for the trial.

TIMI Principal Investigators

The Principal Investigators have overall responsibility for:

a) Design and conduct of the study in collaboration with the Steering Committee;
b) Preparation of the protocol and subsequent revisions;
c) Development of the eCRF;
d) Development of the statistical analysis plan;
e) Interpretation of the final data and reporting of the study.

Steering Committee

The Steering Committee is responsible for:

a) Reviewing and commenting on the final protocol and statistical analysis plans;
b) Reviewing progress of the study and, if necessary, advising on protocol revisions;
c) Reviewing study publications and substudy proposals;
d) Reviewing external new studies that may be of relevance.

Data Monitoring Committee

The indepedendent Data Monitoring Committee is responsible for:

a) Reviewing unblinded data as per the DMC charter;
b) Advising the Principal Investigators if, in its view, the data provide evidence that may warrant modification of the trial protocol or early termination for either efficacy or safety.

Clinical Events Committee

The Clinical Events Committee is responsible for:

a) Independently reviewing, interpreting, and adjudicating potential endpoints that are experienced by the patients. (NB: The precise responsibilities and procedures applicable to the CEC will be detailed in the CEC Charter.)

2. Guidelines for Management of Symptomatic Hypotension

Patients with symptomatic hypotension should have their regular medications reviewed, with consideration given to reducing the dose of, or stopping, concomitant non-essential medications, including diuretics and certain medications that lower blood pressure (e.g., calcium channel blockers, alpha adrenoceptor antagonists). By contrast, efforts should be made to continue all essential evidence-based, disease-modifying treatments (i.e., angiotensin converting enzyme inhibitors [ACEI], angiotensin receptor blockers [ARB], angiotensin receptor-neprilysin inhibitors [ARNI], mineralocorticoid receptor antagonists [MRA], and beta-blockers). The need for conventional diuretics (or the dose of diuretic used) should be re-evaluated in the context of the patient's signs and symptoms; discontinuation of diuretics should be undertaken cautiously.

3. Guidelines for Management of Worsening Renal Function

If an acute decline in kidney function is observed, the patient should be evaluated. Volume depletion, hypotension, intercurrent medical issues, and concomitant medications may cause a decline in kidney function. Urinary tract infection and urinary obstruction should also be considered (the latter especially in men). Several medications may cause a decline in kidney function, especially non-steroidal anti-inflammatory drugs (NSAIDs) and certain antibiotics, such as trimethoprim. If any drug is suspected of causing or contributing to worsening kidney function, its use should be reconsidered.

4. Guidelines for Management of Hypoglycemia

Patients with diabetes who develop severe hypoglycemia should be evaluated immediately. If appropriate, they should be treated with active administration of oral carbohydrates, intravenous dextrose infusion, intramuscular glucagon, and/or other resuscitative actions according to local guidelines. Once patients with severe hypoglycemia have been stabilized, their medications should be carefully reviewed, with consideration given to reducing the dose of the agents responsible for the hypoglycemia, such as insulin or insulin secretagogues (e.g., sulfonylureas). Less stringent HbA1c goals (e.g., 7.5 to 8%) may be appropriate for patients who have had major hypoglycemic episodes.

5. Guidelines for Prevention and Management of Diabetic Ketoacidosis (DKA)

Although rare, diabetic ketoacidosis (DKA), often euglycemic, can be seen in patients with T2DM taking an SGLT2 inhibitor. It is therefore prudent to temporarily interrupt study drug if a patient with T2DM develops a major illness beyond their heart failure (e.g., an acute infectious process) that may predispose them to serious dehydration or prolonged fasting (i.e., routine "sick-day" precautions). Similarly, in anticipation of any major surgery, study drug should be held for 3 days prior to the procedure and resumed once a patient with T2DM is tolerating a normal diet.

Patients with T2DM who present with signs and symptoms consistent with severe metabolic acidosis (e.g., altered mental status, nausea/vomiting, tachypnea, dehydration) should be assessed for ketaoacidosis regardless of presenting blood glucose levels. Patients with diabetic ketoacidosis should be evaluated and treated immediately according to local guidelines, which may involve admission to an intensive care unit for administration of intravenous insulin, intravenous fluids, and carbohydrates. In patients with confirmed diabetic ketoacidosis, study drug should be permanently discontinued.

16. Changes to the Protocol

16.1 Protocol Amendment 1 – December 24, 2020

- Inclusion Criteria
    - The protocol now permits BNP testing in patients who have been treated with an angiotensin receptor neprilysin inhibitor [ARNI] in the 4 weeks prior to randomization to meet inclusion criterion #4
    - Clarification that the higher natriuretic peptide thresholds apply to patients with both atrial fibrillation and atrial flutter
- Exclusion Criteria
    - Clarification that exclusion criterion #2 refers to ***concurrent*** use of two or more inotropic agents during the index hospitalization
    - For clarity, additional emphasis that exclusion criterion #7 only applies to patients with T2DM who are on insulin and/or a sulfonylurea
    - Heart failure felt to be due to a transient process (e.g., stress [takotsubo] cardiomyopathy, tachycardia-induced cardiomyopathy) is added to the list of specific type of conditions that are excluded
    - Clarification that study staff rather than any employee of the hospital system are excluded from participation in the study
- Visit Schedule and Assessments
    - Clarification that the Heart Failure Signs and Symptoms assessment should be performed at each study visit
    - Update to visit windows to include business days only
- Safety Monitoring
    - "COVID-19 diagnosis or treatment" is added as an AE of special interest
    - Clarification that all non-heart failure hospitalizations should be recorded in the eCRF regardless of whether they qualify as a reportable adverse event
- Appendices
    - Clarification that the recommendation to temporarily interrupt study drug if a patient develops a major illness beyond their heart failure that may predispose them to serious dehydration or prolonged fasting (i.e., routine "sick-day" precautions) only applies to patients with T2DM

16.2 Protocol Amendment 2 – June 24, 2021

- Inclusion Criteria
    - For inclusion #5, expansion of the window for enrollment to between 24 hours and 14 days after presentation while still hospitalized
    - For inclusion #5, modification of the definition of clinical stability to indicate that there should be no increase (i.e., intensification) in the dose of intravenous diuretics during the 12 hours (rather than 24 hours) prior to randomization
- Exclusion Criteria
    - Expansion of the renal function eligibility criterion (exclusion #3), namely that patients are only excluded if they have an eGFR <25 ml/min/1.73 m^2 (rather than <30 ml/min/1.73 m^2) as measured by the CKD-EPI equation at screening or have rapidly progressive renal disease
    - Clarification that exclusion #11 only refers to mechanical circulatory support use (either durable or temporary) during the index hospitalization
- Visit Schedule and Assessments
    - Updated Visit Windows for Visit 2 and Visit 3 to be ±3 business days
    - Clarification that the Visit Window for Visit 4 is 60 days after randomization +5 business days

16.3 Protocol Amendment 3 – November 05, 2021

- Inclusion Criteria
    - Modification of inclusion #3 to allow patients to be enrolled with any left ventricular ejection (LVEF)
    - Expansion of the natriuretic peptide eligibility criteria (inclusion #4) for patients with LVEF >40%, namely that these patients must have NT-proBNP ≥1200 pg/mL or BNP ≥300 pg/mL during the current hospitalization (NT-proBNP ≥1800 pg/mL or BNP ≥450 pg/mL if patient in atrial fibrillation or atrial flutter)
- Exclusion Criteria
    - Clarification that exclusion #2 refers to concurrent use of two or more intravenous inotropic agents during the index hospitalization
    - Updated the renal function eligibility criterion (exclusion #3) to be the same in the US and Canada, reflecting current dapagliflozin labeling. Patients are excluded if they have an eGFR <25 ml/min/1.73 m^2 in both the US and Canada.
    - Modification of exclusion #4 to only exclude patients currently on an SGLT2 inhibitor (i.e., use within the last 30 days is no longer an exclusion)

- Modification of exclusion #8 to only exclude patients with implantation of a cardiac resynchronization therapy (CRT) device or valve repair or replacement within 30 days prior to randomization or intent to do so during the trial
- Modification of exclusion #9 to only exclude patients with ST-segment elevation myocardial infarction or coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) within 30 days prior to randomization or intent to undergo coronary revascularization during the trial
- Modification to exclusion #13 to only exclude patients with a history of *end-stage* liver disease

16.4 Protocol Amendment 4 – March 25, 2022

- Study Design
  - Clarification that patients will be enrolled in both North America and Europe across a planned 150-250 sites
- Study Intervention
  - Clarification that a replacement bottle of study drug can be dispensed during the trial if needed
  - Clarification that COVID-19 vaccines may be administered while patients are on study therapy
- Study Outcomes
  - Updated several secondary and exploratory outcomes to align with the language used in the Statistical Analysis Plan (SAP)
- Visit Schedule and Assessments
  - Clarification that when screening and randomization visits are performed on the same day, it is not necessary to duplicate screening and randomization assessments (e.g., vital signs, labs, HF signs and symptoms), but these should be performed on the day of randomization
  - Clarification that a negative pregnancy test is required for WOCBP
  - Clarification that telehealth visits may be performed if a visit cannot be conducted at the clinical site
- Site Training and Monitoring
  - Clarification that remote monitoring visits are permitted if on-site monitoring visits cannot be conducted
- Data Analysis Plan

- Modification of the on-treatment analysis set to include only those observations collected during treatment with study drug or within 3 days of the last dose of study drug (to align with the SAP)
- Updated the list of subgroups to align with the language used in the SAP

- Ethics and Dissemination
  - Clarification that consent cannot be obtained from a legally authorized representative (LAR)

CLINICAL STUDY PROTOCOL
VERSION 6.0
EUROPE

A Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Trial to Evaluate the Effect of In-Hospital Initiation of Dapagliflozin on Clinical Outcomes in Patients Who Have Been Stabilized During Hospitalization for Acute Heart Failure

Dapagliflozin and Effect on Cardiovascular Events in Acute Heart Failure - Thrombolysis in Myocardial Infarction 68 (DAPA ACT HF-TIMI 68)

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Funded By:
AstraZeneca

Protocol Number:
D1690C00078

ClinicalTrials.gov ID:
NCT04363697

Table of Contents

1. Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AHF	Acute heart failure
AE	Adverse event
AEOSI	Adverse event of special interest
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
BNP	B-type natriuretic peptide
CEC	Clinical Events Committee
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
CRT	Cardiac resynchronization therapy
CSP	Clinical study protocol
CSS	Clinical summary score
CV	Cardiovascular
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Record Form
eGFR	Estimated glomerular filtration rate
GCP	Good Clinical Practice
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICH	International Conference on Harmonization
IND	Investigational new drug
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
RRR	Relative risk reduction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SGLT2	Sodium-glucose cotransporter-2
T2DM	Type 2 diabetes mellitus
TIMI	Thrombolysis in Myocardial Infarction
TSS	Total symptom score
UP	Unanticipated problem
WOCBP	Women of child-bearing potential

2. Protocol Synopsis

Study sites and number of subjects planned

The study will be conducted at approximately 150-250 sites in North America and Europe. It is estimated that approximately 2400 patients will be enrolled during a recruitment period of approximately 60 months.

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2020	3b/4
Estimated date of last subject completed	Q2 2025	

Study Design

This is an international, multicenter, parallel-group, randomized, double-blind, placebo-controlled trial in patients who have been stabilized during hospitalization for acute heart failure, evaluating the effect of in-hospital initiation of dapagliflozin versus placebo on the clinical outcome of cardiovascular death or worsening heart failure.

Study Objectives

Primary Objective:	Outcome Measure:
To assess the effect of in-hospital initiation of dapagliflozin, as compared with placebo, on the clinical outcome of cardiovascular death or worsening heart failure in patients who have been stabilized during hospitalization for acute heart failure.	Time to first occurrence of cardiovascular death or worsening heart failure defined as: 1. Worsening HF during the index admission requiring at least one of the following: a) initiation or re-initiation of inotropic therapy for ≥24 hours b) mechanical circulatory support c) invasive ventilatory support for heart failure d) heart transplantation 2. Readmission for worsening heart failure 3. Worsening heart failure leading to an urgent visit with administration of intravenous diuretic therapy (e.g., outpatient setting, emergency department) without associated hospital admission

Safety Objective:	Outcome Measure:
To evaluate the safety and tolerability of in-hospital initiation of dapagliflozin in this patient population.	• Symptomatic hypotension leading to hospitalization or study drug discontinuation • Worsening renal function that results in at least a doubling of serum creatinine, hospitalization, study drug discontinuation, dialysis, or renal death

Target Population

Patients who have been stabilized during hospitalization for acute heart failure.

Investigational Product, Dosage, and Mode of Administration

Dapagliflozin 10 mg administered orally once daily for 2 months.

Comparator Product, Dosage, and Mode of Administration

Matching placebo administered orally once daily for 2 months.

Statistical Methods

The primary efficacy assessment will involve an intention-to-treat (ITT) comparison of the effect of allocation to dapagliflozin versus placebo on the primary efficacy outcome through the 2-month follow-up period. Cumulative clinical event rates will be calculated according to the Kaplan–Meier method. Differences in clinical outcomes between the two treatment groups will be assessed using the log-rank test. Hazard ratios and 95% confidence intervals will be calculated with a Cox proportional-hazards model stratified by history of heart failure (established vs. de novo) and T2DM (yes vs. no) status at baseline.

With a 2-sided alpha of 0.05, a 16% event rate in the control arm, and a 0.5% dropout rate, approximately 2400 AHF patients should provide at least 320 events and therefore at least 80% power to detect a 27% relative risk reduction (RRR) in the primary endpoint.

3. Study Background & Rationale

Acute heart failure (AHF) is the most common cardiovascular reason for hospital admission, accounting for approximately one million hospitalizations in the United States annually.[1] Patients admitted for AHF are at high risk for cardiovascular death and re-hospitalization for heart failure (HF), and are thus an important target population for decreasing overall heart failure morbidity and mortality.[2, 3] In addition, HF hospitalization is an ideal time to implement evidence-based therapies for HF, as multiple studies have shown that initiation and adherence

are enhanced when these agents are prescribed prior to hospital discharge.[4, 5] The heightened risk of patients with AHF and the important opportunity for intervention support novel treatment strategies initiated prior to hospital discharge to improve the outcomes of patients with HF.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors induce glycosuria and natriuresis through pharmacologic inhibition of SGLT2 in the renal proximal tubule. In multiple large, well-powered, cardiovascular outcomes trials, members of this class, including dapagliflozin, were shown to robustly reduce the risk of hospitalization for HF in patients with type 2 diabetes mellitus (T2DM) and either established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors.[6]

Since few patients in the initial cardiovascular outcomes trials of SGLT2 inhibitors had pre-existing HF,[7] the question of whether SGLT2 inhibitors might also be beneficial in patients with established HF led to the design of multiple dedicated trials enrolling patients with chronic HF and either reduced or preserved ejection fraction (DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved). The first of these trials to be completed was the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial, which demonstrated that dapagliflozin, as compared with placebo, significantly reduced the risk of cardiovascular death, hospitalization for HF, or urgent HF visit in stable patients with chronic HF with reduced ejection fraction (HFrEF).[8] Subsequent data from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial showed that SGLT2 inhibitors can reduce the risk of cardiovascular death or hospitalization for HF in patients with chronic HF with mildly reduced (HFmrEF) and preserved ejection fraction (HFpEF) as well.[9]

Since DAPA-HF tested the effect of SGLT2 inhibition in ambulatory patients with chronic HF and did not randomize patients in the midst of HF hospitalization, an important remaining question is whether it is safe and efficacious to initiate an SGLT2 inhibitor in patients who are hospitalized for AHF. Of note, the subset of stable patients in DAPA-HF who had been hospitalized for HF 1-12 months prior to enrollment were at high risk for rehospitalization for HF or CV death and had robust relative and absolute risk reductions with dapagliflozin.[10] A small pilot study with empagliflozin in AHF also suggested robust clinical benefit.[11] On the other hand, patients with AHF could be more susceptible to therapy-related complications due to active modulation of diuretic therapy, fluctuating renal function, and concomitant dose adjustment of neurohormonal antagonists. Thus, evaluating the initiation of SGLT2 inhibition in the inpatient setting is of critical importance to the field. By analogy, the PIONEER-HF trial demonstrated that sacubitril/valsartan, as compared with enalapril, in patients stabilized during hospitalization for AHF was safe, well-tolerated, and led to a reduction in the clinical composite outcome of rehospitalization for HF or cardiovascular death.[12]

4. Study Objectives

The primary objective of this study is to assess the effect of in-hospital initiation of dapagliflozin, as compared with placebo, on the clinical outcomes of cardiovascular death or worsening heart failure in patients who have been stabilized during hospitalization for acute heart failure.

The key safety objectives are to assess the effect of in-hospital initiation of dapagliflozin, as compared with placebo, on the incidence of:

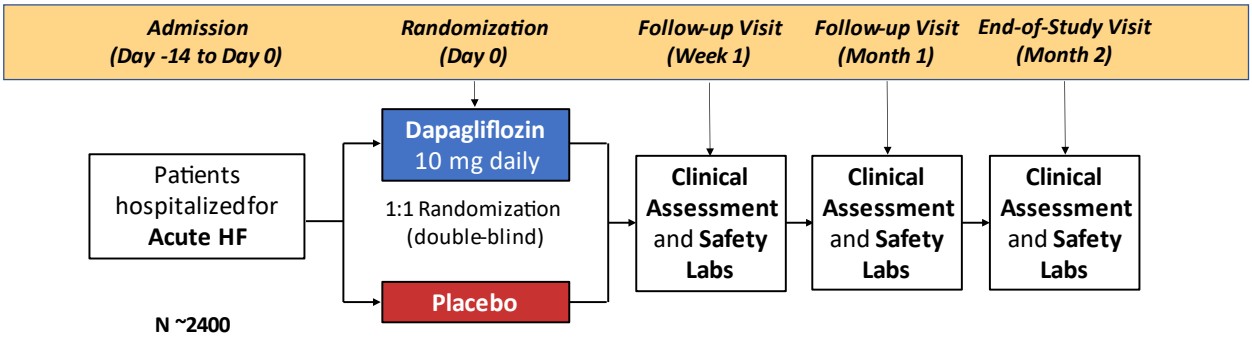
- Symptomatic hypotension leading to hospitalization or study drug discontinuation
- Worsening renal function resulting in at least a doubling of serum creatinine, hospitalization, study drug discontinuation, dialysis, or renal death

See Section 8 (Study Outcomes) for additional secondary and exploratory objectives.

5. Study Design

This is a phase 3b/4, multicenter, parallel-group, randomized, double-blind, placebo-controlled trial. The trial will be conducted in approximately 150-250 sites in North America and Europe. Approximately 2400 patients will be enrolled. Patients will be randomized in a 1:1 allocation ratio to receive either dapagliflozin 10 mg daily or placebo. Randomization will be stratified by history of heart failure (established vs. *de novo*) and T2DM (yes vs. no). Patients will have assessments at 1 week, 1 month, and 2 months. The anticipated enrollment period is approximately 30 months, each patient is followed for a maximum of 2 months, and thus the anticipated total duration of the study is approximately 32 months. The End of Trial is defined as the date when the last patient randomized completes his/her 2-month End-of-Study visit.

Trial Design



Primary EP: Time to first occurrence of CV death or worsening heart failure (decompensation during index admission, rehospitalization for HF, urgent HF visit) through 2 months

6. Study Population

Inclusion Criteria

1. Age ≥18 years (male or female)
2. Currently hospitalized for AHF defined as meeting all the following criteria:
   a) Presentation with worsening symptoms of heart failure (e.g., worsening dyspnea or dyspnea at rest, progressive fatigue, rapid weight gain, worsening edema/abdominal distention/anasarca)
   b) Objective signs or diagnostic testing consistent with volume overload (e.g., jugular venous distension, pulmonary basilar crackles, S3 gallop, ascites, hepatomegaly, peripheral edema, radiological evidence of pulmonary congestion, noninvasive or invasive hemodynamic evidence of elevated filling pressures)
   c) Intensification of AHF therapy during admission defined as at least one of the following:
      i. Augmentation of oral diuretic therapy [e.g., ≥2x outpatient regimen dose, addition of a second diuretic agent, or new initiation of diuretic therapy in a previously naïve patient]
      ii. Initiation of intravenous diuretic therapy
      iii. Initiation of intravenous vasoactive agent (e.g., inotrope or vasodilator)

The majority of enrolled patients should have an established history of heart failure (defined as present for ≥2 months and for which the patient is on treatment). Trial leadership will monitor this proportion and may cap enrollment of patients without an established history of heart failure (i.e., patients presenting with de novo heart failure).

3. Left ventricular ejection fraction (LVEF) measured within the past 12 months (including during the current hospitalization)
4. Elevated NT-proBNP or BNP during current hospitalization:
   a) For patients with LVEF ≤40%: NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL (NT-proBNP ≥2400 pg/mL or BNP ≥600 pg/mL if patient in atrial fibrillation or atrial flutter)
   b) For patients with LVEF >40%: NT-proBNP ≥1200 pg/mL or BNP ≥300 pg/mL (NT-proBNP ≥1800 pg/mL or BNP ≥450 pg/mL if patient in atrial fibrillation or atrial flutter)
5. Eligible patients will be randomized no earlier than 24 hours and up to 14 days after presentation while still hospitalized once they have been stabilized, as defined by:
   a) No increase (i.e., intensification) in the dose of intravenous diuretics during the 12 hours prior to randomization
   b) No use of intravenous vasodilators or inotropes during the 24 hours prior to randomization

   Patients across the spectrum of LVEF are eligible for participation in the trial. Trial leadership will monitor the proportion of patients with various LVEFs and may cap enrollment of certain subgroups to ensure a broad population.

In addition, patients with and without type 2 diabetes are eligible for participation in the trial. Trial leadership will monitor the proportion of patients with and without type 2 diabetes and may cap enrollment of one subgroup to ensure adequate representation of the other.

Exclusion Criteria

1. Symptomatic hypotension in the past 24 hours
2. Concurrent use of two or more intravenous inotropic agents during the index hospitalization
3. eGFR <25 ml/min/1.73 m^2 as measured by the CKD-EPI equation at screening or rapidly progressive renal disease
4. Current use of an SGLT2 inhibitor
5. Prior intolerance of SGLT2 inhibitors, including hypersensitivity to dapagliflozin, or to any excipient (inactive substance) in the study drug
6. Type 1 diabetes mellitus or history of diabetic ketoacidosis
7. (*Only applies to patients with T2DM who are on insulin and/or a sulfonylurea*) History of recurrent major hypoglycemia (i.e., resulting in severe impairment in consciousness or behavior, or requiring emergency external assistance)
8. Implantation of a cardiac resynchronization therapy (CRT) device or valve repair or replacement within 30 days prior to randomization or intent to do so during the trial
9. ST-segment elevation myocardial infarction or coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) within 30 days prior to randomization or intent to undergo coronary revascularization during the trial
10. Untreated sustained ventricular arrhythmias or Mobitz type II or third-degree heart block (i.e., without an ICD or pacemaker, respectively)
11. History of heart transplantation or current transplant listing; mechanical circulatory support use (either durable or temporary) during the index hospitalization
12. History of heart failure due to restrictive or infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy, uncorrected primary valvular disease, complex congenital heart disease, or heart failure felt to be due to a transient process (e.g., stress [takotsubo] cardiomyopathy, tachycardia-induced cardiomyopathy) expected to resolve within 2 months.
13. History of end-stage liver disease
14. Women of child-bearing potential (unless using highly effective contraception method) or currently breastfeeding
15. Current participation in a clinical trial with an unlicensed drug or device
16. Study staff or their family members
17. Any condition that, in the opinion of the investigator, would make trial participation not in the best interest of the subject, or would compromise compliance with the trial protocol (e.g., active severe infection, active malignancy)

7. Study Intervention

7.1 Investigational Product Information: Dapagliflozin 10 mg tablets and matching placebo tablets will be taken once daily orally in the morning at approximately the same time of day. Both dapagliflozin and placebo will be packaged and labeled in accordance with the US Code of Federal Regulations governing handling of investigational treatments and will be dispensed by the site personnel.

Study drug should be initiated as soon as possible during the index hospitalization once the patient qualifies for the trial.

7.2 Randomized Treatment Assignment: Each participating site will be provided a central supply of numbered bottles of dapagliflozin or matching placebo. Randomization to dapagliflozin vs. placebo will be done via the IRT in balanced blocks by site to ensure approximate balance between the two treatment arms. Patients will be dispensed the entire 2-month supply of study drug at randomization and will be assigned two bottles each containing 35 tablets. Treatment will be provided from the assigned bottle while the patients are in the hospital, and patients will take both bottles home upon discharge. It is possible to dispense an additional bottle of study drug to a patient during the trial in the case that a bottle is lost or damaged. Should this occur, the patient can return to the site to obtain the replacement bottle, or the bottle may be shipped to a patient's home when it is not feasible or advisable for a patient to travel to the clinic due to COVID-19 or other factors.

7.3 Blinding: A double-blind technique will be used. The active tablets and the matching placebo tablets will be identical in size, color, smell, and taste. No member of the study team will have access to the randomization scheme during conduct of the study. Unblinding may be carried out on an emergency basis by the site investigator by using the IRT when knowledge of the treatment allocation could materially influence the immediate medical management. The site investigator should contact the TIMI Hotline to inform the Sponsor of any patient unblinding.

7.4 Concomitant Medications: Treatment with any SGLT2 inhibitor other than the IP is not permitted for the duration of the study. All therapies for heart failure are at the discretion of the patient's treating physicians. Dapagliflozin does not increase the risk of hypoglycemia when used as monotherapy or in conjunction with drugs that do not increase the risk of hypoglycemia. However, certain diabetes therapies, such as insulin and insulin secretagogues (e.g., sulfonylureas) may cause hypoglycemia, the risk of which could potentially be accentuated by concomitant use of any other glucose-lowering medications, including SGLT2 inhibitors. Therefore, a lower dose of insulin or insulin secretagogues may be required to minimize the risk of hypoglycemia when used in combination with study drug. Reduction of insulin by 10-20% (total daily dose) and sulfonylurea by 25-50% and increased frequency of blood glucose monitoring should be considered in patients receiving insulin and/or a sulfonylurea and with a baseline HbA1c <7%, especially if there is any

history of significant hypoglycemic events. Of note, COVID-19 vaccines may be administered while patients are on study therapy.

7.5 Discontinuation of Study Drug: Patients may voluntarily discontinue study drug for any reason at any time. If adverse events occur that are believed to be due to study drug, or safety events occur that, in the opinion of the investigator, contraindicate further dosing of study drug, study drug may be temporarily interrupted or permanently discontinued. Whenever possible, restarting study drug should be encouraged, so long as the investigator judges that the potential benefit outweighs the risk. Situations that warrant permanent study drug discontinuation include severe non-compliance with the study protocol, diabetic ketoacidosis (DKA), and pregnancy. Refer to the Appendices for treatment guidelines for symptomatic hypotension, worsening renal function, and in patients with diabetes, what to do for hypoglycemia and the prevention and management of DKA. The investigator should contact the TIMI Hotline with any questions regarding study drug discontinuation and must update the IRT with any study drug discontinuation and record it in the eCRF. If a patient permanently discontinues study drug during the 2-month follow-up, an End of Treatment visit should be performed as soon as possible after the last dose of study drug is taken. Discontinuation of study drug does not mean discontinuation of follow-up. All study assessments should be continued even if study drug is discontinued.

7.6 Withdrawal of Consent: Patients are free to completely withdraw from the study at any time (which means permanent discontinuation of IP and all follow-up assessments) without prejudice to further treatment. Withdrawal of consent should only occur if the patient refuses any further assessments or contact whatsoever. Patients who do not want regular in-person follow-up after cessation of IP should be offered alternative methods of follow-up including periodic telephone follow-up, contact at study closure, or assessment of health status via treating physicians or medical records. Such patients would then not be viewed as withdrawals of consent. The investigator must explain to the patient all options for continued participation, and document which options were refused by the patient and the reason for refusal. Withdrawal of consent must be ascertained and documented in writing by the site investigator who must inform the TIMI Hotline and document the withdrawal of consent in the eCRF and medical records. Patients will be asked about the reason(s) for withdrawal of consent. For patients who withdraw from the study, direct ascertainment of health status at the end of the study or vital status via public records will be performed in compliance with local privacy laws/practices. Withdrawn patients will not be replaced.

7.7 Lost to Follow-Up: To prevent patients from being lost to follow-up, their contact details, including next of kin contacts should be collected initially and updated regularly by the site staff or representative. The site investigator should educate the patient on the importance of contact with the study site throughout the study. Repeated attempts will be made to locate and obtain pertinent medical information for patients who are potentially lost to follow-up. A patient will be classified as lost to follow-up at the end of the study only if s/he has failed to return for the required study visits and his/her vital status remains unknown despite multiple attempts to contact him/her via telephone, fax, e-mail, certified letter or

through patient locator agencies. The informed consent forms will include language to grant the option to employ outside companies to assist in obtaining updated contact information or ascertainment of vital status of lost patients using publicly available sources.

8. Study Outcomes

Efficacy outcomes

Primary outcome: Time to first occurrence of CV death or worsening heart failure defined as:

1. Worsening HF during the index admission requiring at least one of the following:
   a) initiation or re-initiation of inotropic therapy for ≥24 hours
   b) mechanical circulatory support
   c) invasive ventilatory support for heart failure
   d) heart transplantation
2. Readmission for worsening heart failure (i.e., rehospitalization for heart failure)
3. Worsening heart failure leading to an urgent visit with administration of intravenous diuretic therapy (e.g., outpatient setting, emergency department) without associated hospital admission

Secondary outcomes

1. Time to first occurrence of composite of CV death, rehospitalization for heart failure, or urgent heart failure visit
2. Time to first occurrence of composite of CV death or rehospitalization for heart failure
3. Time to first occurrence of rehospitalization for heart failure or urgent heart failure visit
4. Time to each individual component of the primary composite outcome
5. Hierarchical composite endpoint composed of: (1) time to CV death, (2) number of worsening HF events, (3) time to first worsening HF event, or (4) change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ)-12 total symptom score (TSS) at 2 months, analyzed using a win ratio approach with hierarchy based on the order of the components listed
6. Time to death

Exploratory outcomes

1. Total number of rehospitalizations for heart failure (first and recurrent) or CV death
2. Total number of days alive and out of the hospital
3. Readmission within 30 days of hospital discharge
4. Readmission within 60 days of hospital discharge
5. Time to composite of CV death or CV rehospitalization
6. Hierarchical composite endpoint composed of: (1) time to CV death during the index hospitalization, (2) time to worsening heart failure (using a hierarchical order of heart transplantation, mechanical circulatory support, invasive ventilatory support for heart

failure, or initiation or re-initiation of inotropic therapy for ≥24 hours) during the index hospitalization, or (3) longer time to discharge from index hospitalization, analyzed using a win ratio approach with hierarchy based on the order of the components listed

7. Health-related quality of life as measured by the KCCQ-12, including:
    a. Change from baseline in KCCQ-12 TSS at 2 months
    b. ≥5-point increase from baseline in KCCQ-12 TSS at 2 months
    c. ≥10-point increase from baseline in KCCQ-12 TSS at 2 months
    d. ≥15-point increase from baseline in KCCQ-12 TSS at 2 months
    e. Change from baseline in KCCQ-12 clinical summary score (CSS) at 2 months
    f. ≥5-point increase from baseline in KCCQ-12 CSS at 2 months
    g. ≥10-point increase from baseline in KCCQ-12 CSS at 2 months
    h. ≥15-point increase from baseline in KCCQ-12 CSS at 2 months
8. Composite congestion score
9. Time to first occurrence of composite of myocardial infarction, ischemic stroke, or CV death
10. New or recurrent atrial fibrillation

<u>Safety outcomes</u>

1. Symptomatic hypotension leading to hospitalization or study drug discontinuation
2. Worsening renal function resulting in at least a doubling of serum creatinine (sCr), hospitalization, study drug discontinuation, dialysis, or renal death

9. Visit Schedule and Assessments

Procedures	Screening (Day -14 to Day 0)*	Visit 1 In-hospital Randomization (Day 0)*	Visit 2 (Week 1)	Visit 3 (Month 1)	Visit 4 End of Study Visit (Month 2)	End of Treatment Visit**
Informed consent	X					
Review of inclusion/exclusion	X					
Medical history	X					
Vital signs (including weight)	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Pregnancy testing (WOCBP)***	X					
Randomization		X				
Dispense treatment		X				
Drug accountability			X	X	X	X
Assess for efficacy & safety events			X	X	X	X
HF signs and symptoms	X	X	X	X	X	X
BNP or NT-proBNP (local)	X					
Creatinine and potassium (local)	X	X	X	X	X	X
KCCQ questionnaire		X			X	

* Screening and randomization visits can be performed concurrently if the patient is fully eligible at the time of screening. If this occurs, it is not necessary to duplicate screening and randomization assessments (e.g., vital signs, creatinine and potassium, HF signs and symptoms), though these combined screening and randomization assessments should be performed on the day of randomization.

** If a patient permanently discontinues study drug during the 2-month follow-up, an End of Treatment (EoT) visit should be performed as soon as possible after the last dose of study drug. Patients should continue all remaining regularly scheduled visits but do not need any additional laboratory testing following the EoT visit.

*** Negative pregnancy test required for WOCBP (Women of Childbearing Potential)

9.1 Visit Windows

All follow-up visits can be scheduled within the following time windows:

- Visit 2: 7 days after randomization (±3 business days)
- Visit 3: 30 days after randomization (±3 business days)
- Visit 4 (End of Study Visit): 60 days after randomization (+5 business days). Visit 4 should not be performed prior to 60 days after randomization.

If scheduled visits cannot be conducted at clinical sites (e.g. due to the COVID-19 pandemic), telehealth visits by study site personnel are permitted in countries where this is logistically feasible and considered acceptable. Arrangements should be made for safety labs (creatinine and potassium) to be obtained as close to the visit date as possible.

Additional details about study procedures and visits can be found in the Manual of Operations.

10. Site Training and Monitoring

10.1 Training of Study Site Personnel: Before enrolling patients into the study, the requirements of the Clinical Study Protocol and related documents will be reviewed with the investigational staff who will be trained in any study-specific procedures. The site principal investigators will ensure that appropriate training relevant to the study is given to all staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The site principal investigator will also maintain a record of all individuals involved in the study.

10.2 Monitoring of Study Sites: Site monitoring will be performed based on the Monitoring Plan. Site visits will occur on a regularly scheduled basis and, as needed, based on site performance and perceived training needs. The purpose of such visits will be to ensure that the study is being conducted in accordance with the protocol, particularly through helping study site staff resolve any local problems and providing extra training focused on specific needs. Particular attention will be given to the effectiveness of strategies to recruit appropriate participants, the completeness of follow-up, the maintenance of participant adherence to study treatment, and the reporting of study outcomes and collection of relevant supporting documentation. A report of each visit will be prepared by the study monitor. If on-site monitoring visits are not possible (e.g. due to the COVID-19 pandemic), remote monitoring visits are permitted in countries where this is logistically feasible and considered acceptable.

11. Data Analysis Plan

Please note further details can be found in the Statistical Analysis Plan.

11.1 Analysis Sets

a) The Full Analysis Set will consist of all randomized patients with the exception of those who were not qualified for randomization and did not receive study drug but were inadvertently randomized into the study. Following the intention-to-treat principle, patients will be analyzed according to the treatment group to which they were assigned at randomization. Efficacy outcomes will be analyzed based on the Full Analysis Set.

b) The Safety Set will consist of all randomized patients who received at least one dose of study drug. Patients will be included in the analysis according to the treatment actually received. The Safety Set will be used for the analyses of safety outcomes.

c) The On-Treatment Analysis Set will consist of all randomized patients who received at least one dose of study drug. However, only those observations collected during treatment with study drug or within 3 days of the last dose of study drug will be part of this analysis set.

11.2 Analyses

The primary efficacy analysis will be performed in the Full Analysis Set. The primary efficacy assessment will involve an intention-to-treat (ITT) comparison of the effect of allocation to dapagliflozin versus placebo on the primary efficacy outcome through the 2-month follow-up period. Cumulative clinical event rates will be calculated according to the Kaplan–Meier method. Differences in clinical outcomes between the two treatment groups will be assessed using the log-rank test. Hazard ratios and 95% confidence intervals will be calculated with a Cox proportional-hazards model stratified by randomization stratification factors.

11.3 Subgroup Analyses

The following subgroups will be analyzed for the primary efficacy outcome:

a) Presence of type 2 diabetes
b) Established vs. newly diagnosed (i.e., *de novo*) heart failure
c) Age
d) Sex
e) Systolic blood pressure
f) LVEF at baseline
g) Estimated GFR at randomization
h) NT-proBNP concentration at randomization
i) BNP concentration at randomization

j) Use of concomitant heart failure therapies both prior to admission and at randomization (beta-blockers vs not; angiotensin receptor-neprilysin inhibitors [ARNI] vs not; inhibitors of the renin-angiotensin system [including ARNI] vs not; mineralocorticoid receptor antagonists [MRA] vs not; loop diuretics vs not)

Further details regarding the analysis sets, analytic periods, and analytic methods can be found in the Statistical Analysis Plan (SAP).

11.4 Sample Size Considerations

With a 2-sided alpha of 0.05, a 16% event rate in the control arm (estimated based on 3 recent trials of AHF patients),[13-15] and a 0.5% dropout rate (i.e., non-cardiovascular death, withdrawal of consent, lost to follow-up), 2400 AHF patients should provide at least 320 events and therefore at least 80% power to detect a 27% relative risk reduction (RRR) in the primary endpoint. In the DAPA-HF study of dapagliflozin in patients with stable, chronic HFrEF, there was a 26% RRR in the primary composite endpoint of cardiovascular death or worsening heart failure;[8] in the subgroup of patients who had been hospitalized for heart failure within the past year, there was a 36% RRR.[10]

Trial leadership will monitor the aggregate event rate during the course of the trial and may consider capping one or more subgroups or expanding the enrollment to ensure accrual of an adequate number of primary endpoint events.

12. Data and Safety Monitoring and Review

12.1 Data Collection

An electronic case record form (eCRF) will be used for data collection and query handling. The site investigator will ensure that data are recorded in the eCRF as specified in the study protocol and in accordance with the instructions provided. The investigator ensures the accuracy, completeness, and timeliness of the data recorded. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site. Data will be validated as defined in the Data Management Plan.

12.2 Safety Monitoring

Dapagliflozin 10 mg daily has been shown to be safe in multiple large cardiovascular outcomes trials and is an approved dose in the United States, Canada, and Europe. This study has received an exemption from the need for an Investigational New Drug (IND). Investigators are required to report: (1) Serious Adverse Events Related to Study Drug, (2) Unanticipated Problems, (3) Adverse Events Leading to Study Drug Discontinuation, (4) Adverse Events of Special Interest, and (5) Non-Heart Failure Hospitalizations.

1. Reporting of Serious Adverse Events Related to Study Drug

A serious adverse event (SAE) related to study drug must meet the following criteria:

a) Be serious, meaning that in the view of either the local investigator or the TIMI Study Group physician, the adverse event results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

b) Be related to study drug, meaning that there is a reasonable possibility that the drug caused the adverse event. “Reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. In making this assessment, there should be consideration, based on the available information, of the probability of an alternative cause, the timing of the event with respect to study treatment, the response to withdrawal of the study treatment, and (where appropriate) the response to subsequent re-challenge.

Reports of all such events are to be discussed immediately with a physician on the TIMI Hotline. It will be reviewed for seriousness and relatedness, and any additional information required will be sought (e.g., medical history, treatment before and after randomization). Events that qualify as an SAE related to study drug and occur after the first dose of study drug has been administered (through the end of the study period), should be reported in the eCRF on the appropriate pages and reviewed with the TIMI Hotline physician. SAEs related to study drug must be reported within 24 hours of knowledge of their occurrence. They should be clinically followed until the event has resolved or stabilized. All confirmed SAEs related to study drug will be reported to relevant regulatory authorities, ethics committees, Institutional Review Boards, and investigators in an expedited manner in accordance with regulatory requirements.

2. Reporting of Unanticipated Problems (UPs):

To qualify as a UP, an event must meet all of the following criteria:

a) Be unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
b) Be related or possibly related to participation in the research. “Possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

c) Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

3. Reporting of Adverse Events Leading to Study Drug Discontinuation: All adverse events (AEs) leading to investigational product discontinuation should be reported via the eCRF within 3 working days of knowledge of their occurrence.

4. Reporting of Adverse Events of Special Interest: The following adverse events of special interest (AEOSI) will be reported via the eCRF within 3 working days of knowledge of their occurrence:
   a) Symptomatic hypotension
   b) Worsening renal function resulting in at least a doubling of serum creatinine, hospitalization, study drug discontinuation, dialysis, or renal death
   c) Major hypoglycemia (i.e., resulting in severe impairment in consciousness or behavior, or requiring emergency external assistance)
   d) Diabetic ketoacidosis
   e) COVID-19 diagnosis or treatment

5. Non-Heart Failure Hospitalizations: All non-heart failure hospitalizations should be recorded in the eCRF regardless of whether they qualify as a reportable adverse event.

6. Pregnancy: If any pregnancy occurs during the course of the study, investigators or other site personnel should contact the TIMI Hotline immediately but no later than 24 hours after knowledge of its occurrence. Investigational product should be discontinued immediately. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up (even if after trial completion) and documented on the paper Pregnancy Outcome Report form and sent to the TIMI Safety Desk.

12.3 Data Monitoring Committee (DMC)

An independent DMC will be appointed by the TIMI Study Group. The DMC will be responsible for safeguarding the interests of the patients in the study by assessing the efficacy and safety of the intervention during the trial, and for reviewing the overall conduct of the clinical trial. They will review overall safety in the trial and specifically the incidence of symptomatic hypotension and worsening renal function. The DMC statistician will be able to have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. The DMC Charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data.

12.4 Clinical Events Committee (CEC)

Suspected outcome events in the study including the components of the primary efficacy endpoint will be centrally adjudicated by an independent clinical events committee. Suspected outcome events in the study will be identified either by the site investigator or by electronic review of reported AEs. For all events identified for adjudication, the investigator will complete the appropriate modules of the eCRF and provide source documentation (e.g., discharge summaries, death certificates, autopsy reports, etc).

13. Ethics and Dissemination

13.1 Ethical Conduct of the Study

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the most recent version of the Declaration of Helsinki.

An Ethics Committee (EC) or Institutional Review Board (IRB) will approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to patients.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure).

13.2 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the TIMI Study Group and the IRB prior to implementation.

13.3 Informed Consent Procedures

a) Eligible patients may only be included in the study after providing written informed consent
b) Informed consent must be obtained before conducting any study-specific procedures (i.e., all procedures described in the protocol)

13.4 Publications

The Principal Investigators, in collaboration with the other Steering Committee members, will be responsible for drafting the main report from the trial for publication and for secondary and supplementary analyses.

14. References

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15. Appendices

1. Study Organization and Oversight

This study was initiated by independent scientists at the TIMI Study Group at Brigham and Women's Hospital and Harvard Medical School, in collaboration with AstraZeneca. The TIMI Study Group will act as the sponsor for the trial.

TIMI Principal Investigators

The Principal Investigators have overall responsibility for:

a) Design and conduct of the study in collaboration with the Steering Committee;
b) Preparation of the protocol and subsequent revisions;
c) Development of the eCRF;
d) Development of the statistical analysis plan;
e) Interpretation of the final data and reporting of the study.

Steering Committee

The Steering Committee is responsible for:

a) Reviewing and commenting on the final protocol and statistical analysis plans;
b) Reviewing progress of the study and, if necessary, advising on protocol revisions;
c) Reviewing study publications and substudy proposals;
d) Reviewing external new studies that may be of relevance.

Data Monitoring Committee

The indepedendent Data Monitoring Committee is responsible for:

a) Reviewing unblinded data as per the DMC charter;
b) Advising the Principal Investigators if, in its view, the data provide evidence that may warrant modification of the trial protocol or early termination for either efficacy or safety.

Clinical Events Committee

The Clinical Events Committee is responsible for:

a) Independently reviewing, interpreting, and adjudicating potential endpoints that are experienced by the patients. (NB: The precise responsibilities and procedures applicable to the CEC will be detailed in the CEC Charter.)

2. Guidelines for Management of Symptomatic Hypotension

Patients with symptomatic hypotension should have their regular medications reviewed, with consideration given to reducing the dose of, or stopping, concomitant non-essential medications, including diuretics and certain medications that lower blood pressure (e.g., calcium channel blockers, alpha adrenoceptor antagonists). By contrast, efforts should be made to continue all essential evidence-based, disease-modifying treatments (i.e., angiotensin converting enzyme inhibitors [ACEI], angiotensin receptor blockers [ARB], angiotensin receptor-neprilysin inhibitors [ARNI], mineralocorticoid receptor antagonists [MRA], and beta-blockers). The need for conventional diuretics (or the dose of diuretic used) should be re-evaluated in the context of the patient's signs and symptoms; discontinuation of diuretics should be undertaken cautiously.

3. Guidelines for Management of Worsening Renal Function

If an acute decline in kidney function is observed, the patient should be evaluated. Volume depletion, hypotension, intercurrent medical issues, and concomitant medications may cause a decline in kidney function. Urinary tract infection and urinary obstruction should also be considered (the latter especially in men). Several medications may cause a decline in kidney function, especially non-steroidal anti-inflammatory drugs (NSAIDs) and certain antibiotics, such as trimethoprim. If any drug is suspected of causing or contributing to worsening kidney function, its use should be reconsidered.

4. Guidelines for Management of Hypoglycemia

Patients with diabetes who develop severe hypoglycemia should be evaluated immediately. If appropriate, they should be treated with active administration of oral carbohydrates, intravenous dextrose infusion, intramuscular glucagon, and/or other resuscitative actions according to local guidelines. Once patients with severe hypoglycemia have been stabilized, their medications should be carefully reviewed, with consideration given to reducing the dose of the agents responsible for the hypoglycemia, such as insulin or insulin secretagogues (e.g., sulfonylureas). Less stringent HbA1c goals (e.g., 7.5 to 8%) may be appropriate for patients who have had major hypoglycemic episodes.

5. Guidelines for Prevention and Management of Diabetic Ketoacidosis (DKA)

Although rare, diabetic ketoacidosis (DKA), often euglycemic, can be seen in patients with T2DM taking an SGLT2 inhibitor. It is therefore prudent to temporarily interrupt study drug if a patient with T2DM develops a major illness beyond their heart failure (e.g., an acute infectious process) that may predispose them to serious dehydration or prolonged fasting (i.e., routine "sick-day" precautions). Similarly, in anticipation of any major surgery, study drug should be held for 3 days prior to the procedure and resumed once a patient with T2DM is tolerating a normal diet.

Patients with T2DM who present with signs and symptoms consistent with severe metabolic acidosis (e.g., altered mental status, nausea/vomiting, tachypnea, dehydration) should be assessed for ketaoacidosis regardless of presenting blood glucose levels. Patients with diabetic ketoacidosis should be evaluated and treated immediately according to local guidelines, which may involve admission to an intensive care unit for administration of intravenous insulin, intravenous fluids, and carbohydrates. In patients with confirmed diabetic ketoacidosis, study drug should be permanently discontinued.

6. Women of Childbearing Potential

Women of Childbearing Potential may participate in the trial. A negative pregnancy test is required prior to randomization. The patient must use a highly effective form of contraception to avoid pregnancy during the trial and for four (4) weeks after the last dose of study drug. Highly effective forms of contraception include any of the following: combined hormonal or progestogen-only hormal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal, injectable or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner or sexual abstinence.

16. Changes to the Protocol

16.1 Protocol Amendment 1 – December 24, 2020

- Inclusion Criteria
    - The protocol now permits BNP testing in patients who have been treated with an angiotensin receptor neprilysin inhibitor [ARNI] in the 4 weeks prior to randomization to meet inclusion criterion #4
    - Clarification that the higher natriuretic peptide thresholds apply to patients with both atrial fibrillation and atrial flutter
- Exclusion Criteria
    - Clarification that exclusion criterion #2 refers to ***concurrent*** use of two or more inotropic agents during the index hospitalization
    - For clarity, additional emphasis that exclusion criterion #7 only applies to patients with T2DM who are on insulin and/or a sulfonylurea
    - Heart failure felt to be due to a transient process (e.g., stress [takotsubo] cardiomyopathy, tachycardia-induced cardiomyopathy) is added to the list of specific type of conditions that are excluded
    - Clarification that study staff rather than any employee of the hospital system are excluded from participation in the study
- Visit Schedule and Assessments
    - Clarification that the Heart Failure Signs and Symptoms assessment should be performed at each study visit
    - Update to visit windows to include business days only
- Safety Monitoring
    - "COVID-19 diagnosis or treatment" is added as an AE of special interest
    - Clarification that all non-heart failure hospitalizations should be recorded in the eCRF regardless of whether they qualify as a reportable adverse event
- Appendices
    - Clarification that the recommendation to temporarily interrupt study drug if a patient develops a major illness beyond their heart failure that may predispose them to serious dehydration or prolonged fasting (i.e., routine "sick-day" precautions) only applies to patients with T2DM

16.2 Protocol Amendment 2 – June 24, 2021

- Inclusion Criteria
    - For inclusion #5, expansion of the window for enrollment to between 24 hours and 14 days after presentation while still hospitalized
    - For inclusion #5, modification of the definition of clinical stability to indicate that there should be no increase (i.e., intensification) in the dose of intravenous diuretics during the 12 hours (rather than 24 hours) prior to randomization
- Exclusion Criteria
    - Expansion of the renal function eligibility criterion (exclusion #3), namely that patients are only excluded if they have an eGFR <25 ml/min/1.73 m^2 (rather than <30 ml/min/1.73 m^2) as measured by the CKD-EPI equation at screening or have rapidly progressive renal disease
    - Clarification that exclusion #11 only refers to mechanical circulatory support use (either durable or temporary) during the index hospitalization
- Visit Schedule and Assessments
    - Updated Visit Windows for Visit 2 and Visit 3 to be ±3 business days
    - Clarification that the Visit Window for Visit 4 is 60 days after randomization +5 business days

16.3 Protocol Amendment 3 – November 05, 2021

- Inclusion Criteria
    - Modification of inclusion #3 to allow patients to be enrolled with any left ventricular ejection (LVEF)
    - Expansion of the natriuretic peptide eligibility criteria (inclusion #4) for patients with LVEF >40%, namely that these patients must have NT-proBNP ≥1200 pg/mL or BNP ≥300 pg/mL during the current hospitalization (NT-proBNP ≥1800 pg/mL or BNP ≥450 pg/mL if patient in atrial fibrillation or atrial flutter)
- Exclusion Criteria
    - Clarification that exclusion #2 refers to concurrent use of two or more intravenous inotropic agents during the index hospitalization
    - Updated the renal function eligibility criterion (exclusion #3) to be the same in the US and Canada, reflecting current dapagliflozin labeling. Patients are excluded if they have an eGFR <25 ml/min/1.73 m^2 in both the US and Canada.
    - Modification of exclusion #4 to only exclude patients currently on an SGLT2 inhibitor (i.e., use within the last 30 days is no longer an exclusion)

- Modification of exclusion #8 to only exclude patients with implantation of a cardiac resynchronization therapy (CRT) device or valve repair or replacement within 30 days prior to randomization or intent to do so during the trial
- Modification of exclusion #9 to only exclude patients with ST-segment elevation myocardial infarction or coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) within 30 days prior to randomization or intent to undergo coronary revascularization during the trial
- Modification to exclusion #13 to only exclude patients with a history of *end-stage* liver disease

16.4 Protocol Amendment 4 – March 25, 2022

- Study Design
  - Clarification that patients will be enrolled in both North America and Europe across a planned 150-250 sites
- Study Intervention
  - Clarification that a replacement bottle of study drug can be dispensed during the trial if needed
  - Clarification that COVID-19 vaccines may be administered while patients are on study therapy
- Study Outcomes
  - Updated several secondary and exploratory outcomes to align with the language used in the Statistical Analysis Plan (SAP)
- Visit Schedule and Assessments
  - Clarification that when screening and randomization visits are performed on the same day, it is not necessary to duplicate screening and randomization assessments (e.g., vital signs, labs, HF signs and symptoms), but these should be performed on the day of randomization
  - Clarification that a negative pregnancy test is required for WOCBP
  - Clarification that telehealth visits may be performed if a visit cannot be conducted at the clinical site
- Site Training and Monitoring
  - Clarification that remote monitoring visits are permitted if on-site monitoring visits cannot be conducted
- Data Analysis Plan

- Modification of the on-treatment analysis set to include only those observations collected during treatment with study drug or within 3 days of the last dose of study drug (to align with the SAP)
- Updated the list of subgroups to align with the language used in the SAP

- Ethics and Dissemination
  - Clarification that consent cannot be obtained from a legally authorized representative (LAR)

16.5 Protocol V5.1 Czech Republic only – December 08, 2022

- Study Population
  - Exclusion 5 updated to specifically include hypersensitivity to dapagliflozin or to any excipient (inactive substance) in the study drug
  - Exclusion 14 edited to clarify that women of childbearing potential must use highly effective form of contraception in order to participate in trial
- Study Intervention
  - Section 7.3 “Blinding” clarified language around contacting the TIMI Hotline in case of any emergency unblinding of a subject
- Appendices
  - Appendix 6 "Women of Childbearing Potential" added to describe highly effective forms of contraception.

16.6 Protocol V6.0 EUROPE – June 22, 2024
Harmonized protocol for Europe, including requirements for Czech Republic that were previously included in Czech-specific protocol V5.1

- Study Timeline
  - Section 2 estimated date of last subject completed updated