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Clinical Study Protocol

Drug Substance	dapagliflozin
Study Number	D1690C00081
Version	4.0
Date	20 November 2020

An International, Multicenter, Randomized, Double-blind, Placebo-controlled, Phase III Study Evaluating the Efficacy and Safety of Dapagliflozin in Respiratory Failure in Patients with COVID-19

Short Title: DARE-19 (Dapagliflozin in Respiratory failure in patients with COVID-19)

PROTOCOL APPROVAL

Study Title:	An International, Multicenter, Randomized, Double-blind, Placebo-controlled, Phase III Study Evaluating the Efficacy and Safety of Dapagliflozin in Respiratory Failure in Patients with COVID-19 Short Title: DARE-19 (Dapagliflozin in Respiratory failure in patients with COVID-19)
Protocol Number:	ESR-20-20653
Version:	4.0
Date of Issue:	20 November 2020
Sponsor Name and Address:	

Name	Job Title	Role

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practice, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.

VERSION HISTORY

Version 2.0, 10 April 2020
Revisions from Version 1.0 are as follows: • 'Acute kidney injury' is removed from the definition of new/worsened organ dysfunction in the primary outcome measure. This was in response to the FDA's recommendation in their MAY PROCEED letter to modify the kidney component of the primary outcome to focus on a more definitive and clinical meaningful kidney endpoint of renal replacement therapy, and move the laboratory endpoint of doubling serum creatinine into the secondary endpoints. • 'Time to acute kidney injury (defined as doubling of s-Creatinine compared to baseline)' is added as a secondary objective and outcome measure (see above for reason). • Removed the exclusion criterion 'Evidence of acute myocardial injury at Screening (defined as serum troponin levels above 5 times the local laboratory upper reference limit)'. A review of the most recent data suggests that this criterion may potentially exclude a large proportion of patients that would otherwise be eligible for the study, because of mildly elevated troponin levels, even though these patients may derive benefits from the intervention being studied. Removing this exclusion criterion will, therefore, make the study population and results more generalizable. **Administrative:** • Signature page added • Sponsor address amended on Title page • Background and rationale for conducting the study and for the study design are updated in Sections 1.1 and 1.2 • Clarification of the 2 definitions of respiratory decompensation made in footnote 'c' of the table of secondary objectives in Protocol synopsis and Section 2.2 • Definition of acute kidney injury added to the safety outcome measure in Protocol synopsis and Section 2.3 • Components of the primary endpoint removed as one of the exploratory outcome measures in the Protocol synopsis and in Section 2.4, because this analysis will be performed as part of the primary endpoint analysis • 'Acid-base monitoring may also include blood gas analysis, as applicable.' Added to footnote 'c' of Table 1 and to the definition of acid-base monitoring in Section 4.2 • Removed the need to record an AE as serious/not serious, as only SAEs and safety events (which are also SAEs) will be recorded (Section 6.4.3) • Pregnancy outcomes language in Section 6.8 revised to clarify that the pregnancy outcomes will be reported only for study subjects • Clarification that the analysis model will be fully detailed in the SAP, rather than in Section 8.5.1. Protocol synopsis also revised accordingly • References added to Section 11: Grasselli et al 2020, Petrie et al 2020, and Shi et al 2020
Version 3.0, 20 May 2020
Revisions from Version 2.0 are as follows: To clarify that patients with a history of DKA are excluded from the study, and to provide additional guidance on monitoring for DKA during the study: • 'A venous or arterial blood gas analysis for pH, blood levels of ketones (beta-hydroxybutyrate), and lactate should be investigated if DKA is suspected' added to Section 4.2 • Updated Section 1.3.2.1 to align with Section 4.2, and added criteria that should support a diagnosis of DKA during the study • Exclusion criteria 'History of DKA within last 6 months' changed to 'History of DKA'

- Glucose added to the standard of care metabolic panel in Section 4.2 and Table 1, footnote 'c'

Changes to inclusion criteria:

- 'Mild-moderate disease: SpO2≥94% with low-flow supplemental oxygen (3 liters or less)' changed to '…(5 liters or less)' . Three liters is too restrictive as many stable patients are requiring higher oxygen support
- 'Chest radiography or CT findings consistent with COVID-19'—a definition for the findings is replaced with 'in the opinion of the investigator', because the definition is too prescriptive
- New criterion added: Hospital admission no more than 4 days prior to screening. This is to ensure that included patients are relatively recent admissions, as the intent is to administer the treatment as quickly as possible after the presentation
- 'Confirmed SARS-CoV-2 infection by laboratory testing <72 hours prior to randomization…' changed to '…testing within 10 days prior to screening…', because 72 hours is too narrow a window given the clinical course of the disease

Other changes:

- An extended follow-up period of an additional 60 days of observational follow up (on top of the current active treatment duration of 30 days) has been added in response to a health authority request to consider following this patient population for longer than the 30-day treatment period. The intent of this extended observational follow-up period is to examine any potential longer-term effects of dapagliflozin 10 mg compared with placebo, after cessation of investigational product (added Sections 4.4and 8.5.7, and updated the Synopsis, Section1.2, Sections 1.4 and 5.1.4, Figure 1, and Table 1, including footnote 'g'). Section 3.9.3 text updated to clarify that discontinued patients should be followed up to Day 90.
- As soon as the pre-planned number of events has been reached, the database will be locked and unblinded for the analysis of 30-day treatment period data. After that, data collected on patients ongoing in the 60-day observational follow-up period will be unblinded (Section 8.1).
- The proportion of patients randomized without a confirmed SARS-CoV-2–positive test will be closely monitored, and may be capped if it becomes greater than anticipated (added to Synopsis, Section 8.2 and as a footnote to the relevant inclusion criterion in Section 3.1). This is to ensure that the dominant majority of patients in the study are confirmed SARS-CoV-2– positive, given that this is the intended patient population.
- IRT, instead of a call center, is providing the kit identification number (Sections 3.6 and 3.7).
- Recruitment period updated from 'approximately 3 months' to 'approximately 6 months', and the estimated date of last patient completed updated from '3Q 2020' to '4Q 2020' in the Synopsis and Section 9.3 to reflect the latest status.
- Number and location of sites increased to approximately 90 sites in North America, Latin America, and Europe (Synopsis and Sections 1.2 and 1.3.2).
- 'Refer to the Study Contact List for additional country fax numbers' added to contact details in Section 6.5.
- Reference to the DAPA ACT HF-TIMI 68 clinical trial added (Sections1.1and 11).

Clarifications:

- In Table 1 (study plan), footnote 'h' added to clarify that concomitant medication is recorded at Day 15 for previously discharged patients. Section 4.2 updated accordingly.
- Made clear that all safety assessments in Section 5.2 should be recorded daily approximately between 06:00 and 08:00 in the morning.
- Removed the reference to daily collection of concomitant medications in Section7.7 to align with Table 1.
- The system for generating the randomization scheme was revised from 'AZRand' to 'a validated system', as AZRand will not be used (Section 3.5).

Administrative:

- Study number corrected in the protocol header information.
- A number of words using British English have been changed to US English for consistency throughout.

Version 4.0, 20 November 2020

Revisions from Version 3.0 are as follows:

Changes to the primary objective and outcome measure/endpoint in the Synopsis and Sections 1.3.3, 2.1, 5.1.1, 5.1.2, and 5.2.3:

- The secondary objective of 'net clinical benefit' (now redefined as 'clinical recovery') and the associated hierarchical composite outcome measure (1) is added as a second primary objective to create dual primary endpoints. Since the original protocol was designed, the unpredictable nature of the evolving global pandemic and the change in standard of care for treatment of COVID-19 resulted in lower than expected event rates. As a consequence, faster and more complete recovery has now become an important treatment goal on par with prevention of complications and death in patients hospitalized with COVID-19, prompting the addition of recovery to the primary objectives.
- The term 'net clinical benefit' is replaced with the term 'clinical recovery' in one of the dual primary objectives because it is a better description of the outcome measure.
- In one of the dual primary outcome measures, time to new/worsened organ dysfunction is clarified as being during the index hospitalization.
- Bilevel positive airway pressure (BiPAP) is added to the list of mechanical ventilation types in the definition of respiratory decompensation since it is used for that purpose, and, therefore, considered an endpoint indicating worsened respiratory function. The veno-venous stipulation is removed from 'veno-venous ECMO' to allow veno-arterial ECMO.
- 3 components of the hierarchical outcome measure (1) are 'time to' an event; 'time to' has been removed because the ranking of endpoints within the hierarchical composite will be pre-specified in the SAP.
- In the definition of new/worsened organ dysfunction, the component 'Initiation of renal replacement therapy' is changed to 'Doubling of s-Creatinine or initiation of renal replacement therapy', which is an outcome that captures a broader spectrum of kidney dysfunction.

Changes to the secondary objectives and outcome measures in the Synopsis and Section 2.2:

- The 'net clinical benefit' (now redefined as 'clinical recovery') objective is added to the primary objective and removed as a secondary objective (see above). The hierarchical composite outcome measure (2) is removed and becomes a sensitivity analysis (to be described in the SAP).
- The 'reducing new or worsened organ dysfunction' objective is removed because the analysis of this endpoint will automatically be included as a component of one of the dual primary endpoints, as will be pre-specified in the SAP.
- The 'total number of days alive~~, out of hospital,~~ and~~/or~~ free from mechanical ventilation' objective and endpoint is simplified as indicated, without changing the nature of the endpoint.
- Similarly, the '/or' is removed in the 'total number of days alive, not in ICU, and~~/or~~ free from mechanical ventilation' objective and endpoint.
- 'Mechanical ventilation' replaced with 'respiratory decompensation requiring initiation of mechanical ventilation (includes invasive or non-invasive ventilation, CPAP, or BiPAP)' to be explicit and align with the definitions in the primary endpoints.
- The acute kidney injury endpoint has become a composite kidney endpoint to allow for the initiation of renal replacement therapy and all-cause death. Acute kidney injury is redefined as in the safety outcome measures (see below). Section 5.1.2 is updated accordingly.
- Endpoints referring to hospital discharge and respiratory decompensation are clarified as relating to the index hospitalization only.

Changes to the safety outcome measures in the Synopsis and Sections 2.3 and 5.1.2:

- Study time periods are added to each safety outcome measure to clarify the reporting periods.
- Definition of acute kidney injury is redefined as:

- An episode of doubling s-Creatinine compared to baseline during index hospitalization
- or SAE with preferred term of acute kidney injury following discharge and through Day 30

This is to identify all acute kidney injury events during the 30-day treatment period.

Changes to the exploratory outcome measures in the Synopsis and Section 2.4:

- Quantitative PCR for SARS-CoV-2 is removed as availability of quantitative PCR data is uncertain. Evaluation of quantitative PCR data, if available, will be pre-specified in the SAP.
- 'Out of hospital' is removed from 'Total number of days alive~~, out of hospital,~~ and not on renal replacement therapy' to simplify the endpoint. It does not change the nature of the endpoint. Clarified that the total number of days not on renal replacement therapy refers to the index hospitalization only.
- Phrase in brackets in 'Change in NT-proBNP, hs troponin, D-dimer, LDH, ALT, lymphocyte count, CRP between Day 1 and Day 15 (or discharge from hospital, whichever is earlier)'replaces '(or last available assessment)' to make the timepoint consistent with other exploratory outcome measures.

Changes to sites and number of patients planned in the Synopsis and in Sections 1.4 and 8.2:

- Number of patients to be randomized increased from 900 to approximately 1200 to provide adequate power for the dual primary endpoints.
- Sites will also be located in India.
- Recruitment period updated to 'approximately 8 months', and the estimated date of last patient completed updated to '1Q 2021' in the Synopsis and Section 9.3 because of the increase in the number of patients and lower than expected recruitment rate.

Changes to exclusion criteria in Section 3.2.

- Criteria 1 and 2 are updated to simplify the description of mechanical ventilation and include BiPAP.

Other changes

- Global Clinical Lead changed to Anna Maria Langkilde on protocol approval page.
- Section 1.1 is updated with the latest information about COVID-19 and to reflect the unpredictable and fast-evolving pandemic necessitating a change in the primary objective. When referring to the SARS-CoV-2 infection in the study, the term verified is removed since verification is not protocol mandated.
- Section 1.2 is updated with the latest information about COVID-19 that supports the changes to the primary endpoint.
- India is added to 'Patients with T2DM will be monitored in the hospital as part of standard of care, which in North America, Latin America, Europe, and India includes blood glucose monitoring.' in Section 1.3.2.
- 'T2DM' and 'T1DM' replaced with 'clinical studies in various clinical settings' in the statement about the safety profile of dapagliflozin in Section 1.3.2, since dapagliflozin has been studied also in patients with HF and CKD without diabetes, etc.
- Randomization will be stratified within each country to ensure balanced treatment allocation (Synopsis and Section 3.5).
- Attempts to contact a patient who cannot be reached should continue to be documented but not in the medical records (Section 3.9.3).
- Removed the constraint that 'Incorrect enrollment' as a reason for withdrawal is only valid for screen failures in Section 3.10.1. This is to more accurately reflect study procedures.
- Removed the statement 'If a patient withdraws from the study, he or she may request destruction of any samples taken, and the Investigator must document this in the site study records.' to more accurately reflect study procedures.
- Expected standard of care laboratory assessment broadened to allow for other means of acid-base monitoring (per local standard of care) than a basic metabolic panel (Table 1). Made clear that the associated footnote 'c' refers to daily assessment while hospitalized.
- Time points for assessments are replaced with cross-references to the study plan in Sections 4.2, 5.1.3, and 5.1.4 to avoid inconsistencies.

- 'New/worsened organ dysfunction' removed from the list of time-to-event endpoints in Section 5.1.2 because the analysis of this endpoint will automatically be included as a component of one of the dual primary endpoints, and will be pre-specified in the SAP.
- Definitions of reportable SAEs, DAEs, and/or key safety events are added (Section 6.4.2).
- Text referring to reportable SAEs, DAEs, and key safety events are updated in Sections 5.2.3 and 6.4.
- ' ' is replaced by 'The Sponsor or delegate' in retaining the right to request additional information about unresolved events, in Section 6.4.4 to more accurately reflect the trial conduct.
- Fatal events due to disease progression must be reported as SAEs, added to Section 6.4.1.
- Causality assessment in relation to other medication is not assessed so is removed from Section 6.4.5.
- Overdose Section 6.7 is revised so that only an overdose associated with a SAE is to be reported.
- Executive Committee will make final decisions, not recommendations, with regard to early stopping or modifications to the study in Section 6.9.
- Orogastric tube as an option for administration of investigational product during mechanical ventilation added in the Synposis and in Section 7.2.
- Removed the accountability of the study personnel for returned investigational product since patients are not asked to return their unused investigational product (Section 7.6).
- This is no longer an event-driven study, so references to it being event-driven are removed from the Synopsis and Section 8.2. The study will remain blinded until the 30-day database lock (updated in Section 8.1).
- The methods for statistical analysis are revised in Section 8.5 to reflect the dual primary endpoint.

Clarifications:

- '~~Mild to moderate~~ COVID-19' removed from target population description in the Synopsis as 'mild to moderate' description is not aligned with the FDA definition of severity of the disease.
- Made clear that allocation of IP is blinded in Section 1.3.1.
- Made clear that patients must have SpO2 ≥ 94% <u>while receiving</u> low-flow supplemental oxygen (5 liters or less) to meet inclusion criterion number 7 in Section 3.1. Removed 'mild to moderate disease' as it is not aligned with the FDA definition of severity of the disease, and defining severity of disease is not necessary for this criterion.
- Removed reference to weekly monitoring of blinded safety data by the IDSMC in Section 3.7.1—the monitoring frequency is included in the IDSMC charter.
- Made clear in Section 3.7.1 that, in addition to the Sponsor, the Sponsor representatives are blinded in all data transfers provided to the IDSMC.
- A footnote is added to the NEWS 2 row in the study plan (Table 1) to clarify that NEWS 2 is only collected while the patient is hospitalized.
- A footnote is added to the SAEs row in the study plan (Table 1) to cross-reference the definition of a reportable event.
- Stipulated a ± 3-day window for the Day 15 and Day 30 follow-up calls after hospital discharge in Section 4.3.
- Stipulated a ± 7-day window for the Day 60 and Day 90 follow-up calls after hospital discharge in Section 4.4 and Table 1.
- Made clearer throughout Section 6.4 that only reportable events are recorded.
- Made clear that reportable events are recorded on a daily basis during index hospitalization and at Discharge, as well as during pre-specified post discharge phone follow up visits in Section 6.4.

Administrative:

- Additional definition of stage 3 to 4 CKD (ie, eGFR ≥ 25 mL/min/1.73m^2) is removed in Section 1.2, as it is not fully consistent with the inclusion criterion and is not a necessary detail for this section.
- The title of Section 5.1.1 is changed from 'Endpoint Event' to 'Primary Endpoint Events'.
- HbA1c is removed from Table 2 in Section 5.1.5. It had been included in the list of lab variables in error.
- Typographical error is corrected in the Levey et al 2009 citation in Section 5.1.5.

- The time period for collection of AEs corrected to 'through Day 90' (to include the additional 60-day observational period) in Section 6.4.1.
- The time period for follow up of unresolved AEs corrected to 'through Day 90' in Section 6.4.4.
- personnel or delegate' is corrected to 'The Sponsor or delegate' as responsible for generating the randomization scheme in Sections 3.5 and 3.6 to more accurately reflect trial conduct.
- 'Any discrepancy between dispensed and returned investigational product should be explained' is removed from Section 7.6 because the patient is not required to return investigational product.
- Section 3.7.1.1 renumbered as Section 3.7.1.
- is corrected to 'Sponsor or delegate' in being responsible for providing reports of any serious and unexpected adverse drug reactions from any other study conducted, to the PI in Section 10.3, to more accurately reflect trial conduct.

PROTOCOL SYNOPSIS

An International, Multicenter, Randomized, Double-blind, Placebo-controlled, Phase III Study Evaluating the Efficacy and Safety of Dapagliflozin in Respiratory Failure in Patients with COVID-19

International Co-ordinating Investigator

Study Site(s) and Number of Patients Planned

Approximately 1200 patients will be randomized to the study at approximately 90 sites in North America, Latin America, India, and Europe.

Study period		Phase of development
Estimated date of first patient enrolled	2Q 2020	Phase III
Estimated date of last patient completed	1Q 2021	

Study Design

This is an international, multicenter, parallel-group, randomized, double-blind, placebo-controlled, study in hospitalized adult patients with COVID-19. The study is evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily for 30 days in addition to background local standard of care therapy, in reducing complications or all-cause mortality, or improving clinical recovery. The study will recruit approximately 1200 patients with a fixed follow-up.

It is anticipated that the recruitment period will be approximately 8 months. When enrolled, patients can be screened twice if they do not fully meet the inclusion/exclusion criteria on the first screening. They must not be randomized more than once. Patients will be followed up for their 30-day treatment period, and will continue to take investigational product and be

followed up by telephone (at Day 15 and/or Day 30) if discharged from hospital. After the last dose of investigational product at Day 30, patients are followed up for an extended additional (observational) period of 60 days (total duration of follow up 90 days), with telephone visits on Day 60 and Day 90.

Objectives

All of the objectives are assessed during the 30-day treatment period.

Primary objective:	Outcome measure:
To determine whether dapagliflozin 10 mg is superior to placebo, in terms of reducing complications or all-cause mortality, or improving clinical recovery in patients hospitalized with COVID-19.	Dual primary endpoints of: **<u>Prevention of COVID-19 complications or death</u>** During the 30-day treatment period, time to first occurrence of new/worsened organ dysfunction during index hospitalization or death from any cause. New/worsened organ dysfunction is defined as at least one of the following: • Respiratory decompensation requiring initiation of mechanical ventilation (includes invasive or non-invasive ventilation, CPAP, or BiPAP), and/or initiation of ECMO • New or worsening congestive HF[a] • Requirement for vasopressor therapy and/or inotropic or mechanical circulatory support • Ventricular tachycardia or fibrillation lasting at least 30 seconds and/or associated with hemodynamic instability or pulseless electrical activity, or resuscitated cardiac arrest • Doubling of s-Creatinine or initiation of renal replacement therapy **<u>Improving clinical recovery</u>** Hierarchical composite outcome measure: 1 Death from any cause through Day 30 2 New/worsened organ dysfunction (as defined above) 3 Clinical status at Day 30 for patients still hospitalized and without any worsening organ dysfunction (using points 3 to 5 of a 7-point ordinal scale[b]) 4 Hospital discharge before Day 30 and alive at Day 30

[a] Congestive HF is defined as at least one of the following 1) initiation of new intravenous therapy for heart failure 2) reinstitution of previous intravenous therapy for heart failure 3) increase in current intravenous therapy for heart failure. This is based on modification on previous definition of in-hospital worsening heart failure (McMurray et al 2007)

[b] 7-point Patient Clinical Status scale:

1 Not hospitalized, no limitations on activities

2 Not hospitalized, limitation on activities
3 Hospitalized, not requiring supplemental oxygen
4 Hospitalized, requiring supplemental oxygen
5 Hospitalized, on high flow oxygen devices
6 Hospitalized, on invasive mechanical ventilation or ECMO
7 Death

BiPAP Bilevel positive airway pressure; COVID-19 Coronavirus disease 2019; CPAP Continuous positive airway pressure; ECMO extracorporeal membrane oxygenation; HF Heart failure.

Secondary objectives:	Outcome measures:
To compare the effect of dapagliflozin 10 mg versus placebo on time to hospital discharge	Time to hospital discharge[a]
To compare the effect of dapagliflozin 10 mg versus placebo on total number of days alive and free from respiratory decompensation requiring mechanical ventilation	Total number of days alive and free from respiratory decompensation[a] requiring initiation of mechanical ventilation (includes invasive or non-invasive ventilation, CPAP, or BiPAP) from randomization through Day 30
To compare the effect of dapagliflozin 10 mg versus placebo on total number of days alive, not in ICU, and free from respiratory decompensation requiring mechanical ventilation	Total number of days alive, not in the ICU, and free from respiratory decompensation[a] requiring initiation of mechanical ventilation (includes invasive or non-invasive ventilation, CPAP, or BiPAP) from randomization through Day 30
To compare the effect of dapagliflozin 10 mg versus placebo on a composite kidney endpoint	Time to composite of acute kidney injury[b] or initiation of renal replacement therapy[c], or death from any cause through Day 30
To compare the effect of dapagliflozin 10 mg versus placebo in reducing the incidence of all-cause mortality	Time to death from any cause through Day 30

[a] Refers to index hospitalization only
[b] Acute kidney injury defined as:
- An episode of doubling s-Creatinine compared to baseline during index hospitalization
- or SAE with preferred term of Acute kidney injury following discharge and through Day 30

[c] Renal replacement therapy defined as:
- Initiation of renal replacement therapy during index hospitalization
- or SAE with a preferred term for renal replacement therapy (ie, Haemodialysis, Haemofiltration, Continuous haemodiafiltration, Dialysis, Peritoneal dialysis, Dialysis device insertion, Renal replacement therapy, or Artificial kidney device user) following discharge and through Day 30

BiPAP Bilevel positive airway pressure; COVID-19 Coronavirus disease 2019; CPAP Continuous positive airway pressure; ECMO Extracorporeal membrane oxygenation; ICU Intensive care unit; SAE Serious adverse event.

Safety objective:	Outcome measure:
To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients hospitalized with COVID-19	• Serious adverse events from randomization to Day 30[a] • Acute kidney injury defined as: ° An episode of doubling of s-Creatinine compared to baseline during index hospitalization ° or SAE with preferred term of acute kidney injury following discharge and through Day 30 • Incidence of diabetic ketoacidosis from randomization through Day 30

[a] SAEs will be collected through Day 90 but comparison of treatment groups will be assessed based on the data obtained through Day 30. For the definition of reportable SAEs, see Section 6.4.2.

COVID-19 Coronavirus 2019; SAE Serious adverse event.

Exploratory objective:	Outcome measures:
To compare the effect of dapagliflozin 10 mg to placebo on the components of the primary endpoint, biomarkers, and patient's clinical status	• Change in NT-proBNP, hs troponin, D-dimer, LDH, ALT, lymphocyte count, CRP between Day 1 and Day 15 (or discharge from hospital, whichever is earlier) • Qualitative PCR for SARS-CoV-2 in oropharyngeal/nasopharyngeal swab at baseline (while hospitalized); and Day 15 (if still hospitalized) or discharge from hospital • Change in NEWS 2 from Day 1 to Day 15 (or discharge from hospital, whichever is earlier). • Patient's clinical status (on a 7-point ordinal scale) at Day 15 (or discharge from hospital, whichever is earlier) • Total number of days alive and not on renal replacement therapy[a] • Proportion of patients with acute coronary syndrome[b]

[a] Refers to index hospitalization only

[b] Acute coronary syndrome defined as: during index hospitalization, abnormal troponin level above 99th percentile of the local laboratory reference range or, if abnormal at baseline, further rise in troponin levels accompanied by at least 1 of the following: 1) ischemic symptoms 2) ischemic ST-segment changes on ECG (Thygesen et al 2018)

NEWS 2 is a standardized assessment of acute-illness severity and can prompt critical care intervention. It is used as an adjunct to clinical judgment.

ALT Alanine aminotransferase; COVID-19 Coronavirus disease 2019; CRP C-reactive protein;
ECG Electrocardiogram; hs troponin High-sensitivity cardiac troponin; LDH lactate dehydrogenase; NEWS 2 National Early Warning Score 2; NT-proBNP N-terminal-pro B-type natriuretic peptide; PCR Polymerase chain reaction; SARS-CoV-2 Severe acute respiratory syndrome-coronavirus-2.

Target Patient Population

The target population includes male and female adult patients (≥18 years) currently hospitalized with SARS-CoV-2 infection and COVID-19, and with a medical history of at least one of the following: hypertension, type 2 diabetes mellitus, atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease stage 3/4. Patients with type 1

diabetes mellitus are excluded.

To ensure balance within countries, stratification will be employed. Given the unpredictable and rapidly-shifting incidence of COVID-19 across different countries, balanced representation across countries cannot be ensured.

The proportion of patients randomized without a confirmed SARS-CoV-2–positive test will be closely monitored, and may be capped if it becomes greater than anticipated.

Duration of Treatment

Eligible patients will be randomized to start treatment with either dapagliflozin 10 mg or placebo daily (double-blind) as soon as possible.

Investigational product will be administered for 30 days, with follow-up assessments every 24 hours until either hospital discharge, Day 30, or death. Patients discharged from hospital will continue with their treatment for the remainder of the 30 days and be followed up by telephone on Day 15 and/or Day 30. After the last dose of investigational product at Day 30, patients are followed up for an extended additional (observational) period of 60 days (total duration of follow up 90 days), with telephone visits on Day 60 and Day 90.

Investigational Product, Dosage and Mode of Administration

Patients will be randomized 1:1 to either dapagliflozin 10 mg or placebo once daily per oral use. Every attempt should be made to maintain patients on dapagliflozin 10 mg or matching placebo during the course of the study. The investigational product should be taken as soon as possible after randomization and then once daily in the morning, at approximately the same time every day, during the 30-day treatment period.

For patients requiring a mechanical ventilator, the tablet will be crushed and flushed with water down the patient’s nasogastric (or orogastric) tube. The tube will then be rinsed with water to ensure all the tablet has been consumed.

Statistical Methods

The primary objectives are to determine the superiority of dapagliflozin versus placebo in reducing the incidence of complications or all-cause mortality (prevention of worsening COVID-19) or improving clinical recovery in patients hospitalized with COVID-19. The treatment effect on prevention of worsening COVID-19 or clinical recovery will be tested as dual primary endpoints.

The treatment effect on prevention will be assessed as the time to first event of the composite endpoint of complications or all-cause mortality, analyzed using a Cox proportional hazards

model. The treatment effect on recovery will be evaluated by a hierarchical composite endpoint, using a win ratio analysis method.

It is estimated that a sample size of approximately 1200 patients will provide adequate power to detect the treatment effect on prevention or recovery, when the dual endpoints are tested with alpha split between these outcomes.

All patients randomized will be included in the full analysis set according to their randomized investigational product assignment, irrespective of the treatment actually received. The full analysis set will be considered the primary analysis set for the primary, secondary, and exploratory efficacy variables.

All patients who received at least 1 dose of randomized treatment will be included in the safety population. Patients will be analyzed according to the treatment actually received. The safety analysis set will be considered the primary analysis set for all safety variables.

Interim analysis for safety only will be performed by an independent data and safety monitoring committee after the first 100 patients have completed the 30-day treatment period; no interim efficacy analyses are planned.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BiPAP	Bilevel positive airway pressure
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CKD	Chronic kidney disease
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CRP	C-reactive protein
CSP	Clinical Study Protocol
CT	Computed tomography
DCI	Data collection instruments
DKA	Diabetic ketoacidosis
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HF	Heart failure
HR	Hazard ratio
hs troponin	High-sensitivity troponin
ICF	Informed consent form
ICH	International Council on Harmonisation

Abbreviation or special term	Explanation
ICU	Intensive care unit
IDSMC	Independent data and safety monitoring committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
LSLV	Last subject last visit
MedDRA	Medical Dictionary for Regulatory Activities
NEWS 2	National Early Warning Score 2
NIH	National Institute of Health
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal-pro B-type natriuretic peptide
O2 SAT	Oxygen saturation
PI	Principal investigator
PLTs	Platelets
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SDV	Source data verification
SGLT2	Sodium-glucose co-transporter 2
SGLT2i	Sodium-glucose co-transporter 2 inhibitors
SpO2	Blood oxygen saturation
SD	Standard deviation
T2DM	Type 2 diabetes mellitus
US	United States
WBC	White blood cell
WHO	World Health Organization
WP	Win proportion
WR	Win ratio

1 INTRODUCTION

1.1 Background and Rationale for Conducting this Study

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, in December 2019 as the cause of an outbreak of COVID-19, a type of viral pneumonia. The following COVID-19 pandemic has since then affected millions of people worldwide. Early epidemiologic data indicated that ~12% of SARS-CoV-2-positive patients develop symptoms requiring hospitalization, and of these, nearly 24% may need intensive care (CDC 2020, Guan et al 2020). In the US, approximately 14% of COVID-19 infected patients have required hospitalization and about 14% of the hospitalized patients (2% of the total) have been admitted to ICUs (NIH COVID-19 Treatment Guidelines). Hospital admission occurs at a median time of Day 7 from the onset of symptoms, and many recover with supportive care (Huang et al 2020). In others, progressive deterioration is seen. Although respiratory failure is a key manifestation in most patients with COVID-19, it is increasingly being recognized that COVID-19 is a systemic disease in which cardiovascular and kidney complications are common, and may be key drivers of poor outcomes, including death (Arentz et al 202, Guzik et al 2020, Li et al 2020, Madjid et al 2020, Ronco et al 2020). As an example, nearly 80% of patients hospitalized with COVID-19 have evidence of cardiac involvement (Puntmann et al 2020). In addition, average NT-proBNP among critically ill patients in one of the initial reports from the US was ~4700 pg/mL (higher than what is typically seen in trials of patients with HF and reduced ejection fraction). It is possible (and likely), based on these findings, that HF may be a significant component of the disease process. Furthermore, nearly 30% of patients had evidence of acute myocardial injury (Shi et al 2020). The risk of disease progression, need for intensive care, and death was dramatically higher in COVID-19 patients that develop cardiac injury versus those that do not (risk of death is 51% versus 14%). Collectively, these findings suggest that cardiovascular complications are prominent in patients hospitalized with COVID-19 and appear to be key drivers of poor outcomes and death. It thus follows that prevention of these complications may lead to lower risk of disease progression and death.

Risk factors for adverse outcomes associated with COVID-19 include older age and presence of cardiometabolic comorbidities such as T2DM, ASCVD, hypertension, HF and CKD (Arentz et al 202, Grasselli et al 2020, Guan et al 2020, NIH COVID-19 Treatment Guidelines). Individuals that have a combination of such underlying health conditions, and with evidence of acute cardiac involvement and/or kidney injury, have a high risk of death due to COVID-19 (Guo et al 2020, Pranata et al 2020, Ronco et al 2020, Shi et al 2020, Vrsalovic and Vrsalovic Presecki 2020). The underlying mechanisms for this greater risk are not yet fully understood, but compromised baseline organ function and metabolism combined with greater susceptibility to endothelial injury, inflammatory insults and tissue hypoxia are likely

to play a role (Ayres 2020, Guzik et al 2020, Kang et al 2020, Madjid et al 2020).

Currently, remdesivir is the only drug approved for treatment of hospitalized patients with COVID-19 by the FDA. Dexamethasone has been authorized for emergency use in hospitalized COVID-19 patients, and remdesivir and dexamethasone are recommended therapies in the NIH guidelines (NIH COVID-19 Treatment Guidelines). Remdesivir is an anti-viral therapy (with limited supply) recommended to be used for 5 days or until hospital discharge in hospitalized patients with COVID-19 who require supplement oxygen but who do not require mechanical or high-flow device ventilation. Dexamethasone, an anti-inflammatory drug, is also recommended for treatment up to 10 days or until discharge in hospitalized COVID-19 patients. The evidence is stronger for a positive effect of this treatment when the patients are mechanically ventilated.

Over the past several months, the unpredictable nature of the evolving global pandemic and the change in available medications for treatment of COVID-19 resulted in lower rates of complications and death than what was observed during the pandemic's initial phase. As a consequence, faster and more complete recovery has now become an important treatment goal on par with prevention of complications and death in patients hospitalized with COVID-19.

Dapagliflozin inhibits SGLT2, the major transporter responsible for renal sodium and glucose reabsorption in the proximal convoluted tubule of the kidney. In addition to the primary action, SGLT2 inhibitors including dapagliflozin have been shown to provide substantial cardiorenal protection in patient populations similar to those at risk for COVID-19 complications, namely, patients with T2DM, ASCVD, HF, and CKD. SGLT2 inhibitors were shown to reduce the risk of cardiovascular and kidney events in patients with T2DM in 4 large outcome trials investigating empagliflozin, canagliflozin and dapagliflozin (Neal et al 2017, Perkovic et al 2019, Wiviott et al 2019, Zinman et al 2015). In the DAPA-HF trial, dapagliflozin reduced the risk of death and worsening of HF by 26% in patients with HFrEF, with identical effects in patients with and without T2DM (McMurray et al 2019, Petrie et al 2020). These benefits were observed within days and were significant by 28 days of treatment (Sabatine et al 2019). SGLT2 inhibitors also consistently reduce the risk of kidney disease progression and acute kidney injury (Neal et al 2017, Perkovic et al 2019, Wiviott et al 2019, Zinman et al 2015). Recently released results from the DAPA-CKD trial demonstrate a statistically significant and clinically meaningful benefit of dapagliflozin on the risk of worsening of renal function or death in adult patients with CKD; with and without T2DM (Heerspink et al 2020).

The mechanisms that could explain the protective effects of SGLT2 inhibitors overlap substantially with those involved in COVID-19. Firstly, the decrease in glucose and insulin levels, shift of energy metabolism to increased lipid oxidation with reduced reliance on

glucose, and inhibition of glycolysis may be especially important in COVID-19, as SARS-CoV-2 may depend on the glycolytic pathway for its replication, stimulating lipogenesis that appears to be one of the key drivers of cellular damage (Codo et al 2020, Daniele et al 2016). Secondly, SGLT2 inhibitors improve endothelial function within 48 hours of treatment, probably because of reduced oxidative stress, and have significant anti-inflammatory effects with reduction of C-reactive protein and interleukin-6 (Bonnet and Scheen 2018, Solini et al 2017). In addition, experimental studies have shown reduced activation of the NLRP3 inflammasome, and protection against septic acute kidney injury on SGLT2 inhibitor treatment (Kim et al 2020, Maayah et al 2020). SGLT2 inhibitors also increase erythropoiesis resulting in increased haematocrit, which together with improved endothelial function may improve oxygen delivery to tissues (Ghanim et al 2020, Lambers Heerspink et al 2013, Solini et al 2017). Moreover, SGLT2 inhibitors reduce the extracellular volume in patients with fluid overload, such as those with CKD and HF (Griffin et al 2020, Ohara et al 2020), and appear to rapidly reduce pulmonary artery pressure in patients with HF, leading to hemodynamic decongestion (Mullens et al 2020). Taken together, SGLT2 inhibitors may favorably impact multiple processes, including but not limited to energy metabolism, endothelial function, oxidative stress, inflammation, and autophagy, that are dysregulated during a major acute illness such as COVID-19 (Aragón-Herrera et al 2019, Esterline et al 2018, Ferrannini 2017, Kim et al 2020, Packer 2020, Tanaka et al 2018). Such metabolic restoration may help to prevent multi-organ damage in the setting of COVID-19, and could provide critical and complementary efficacy to other therapeutic approaches across various stages of the disease course, including remdesivir and dexamethasone, in patients hospitalized with COVID-19 but not yet critically ill (Ayres 2020).

Therefore, we hypothesize that dapagliflozin, a potent, highly-selective, and orally-active inhibitor of human renal SGLT2, has the potential to afford end-organ protection against SARS-CoV-2-mediated injury (ie, lowering the risk of cardiovascular and kidney complications and multi-organ failure), thereby, reducing the risk of morbid complications and improving clinical recovery. Our dual primary objectives are, therefore, aligned to capture both critical components of treatment benefit (prevention of complications and improving clinical recovery). Finding a therapeutic effect for either or both dual primary endpoints would, therefore, be considered a significant and clinically meaningful benefit for patients hospitalized with COVID-19. If found to be effective, SGLT2i are already approved (for different indications) and available in most countries, and have a well-established safety profile, having been studied in tens of thousands of patients, and having been prescribed to millions around the world since their introduction in 2011.

In this study, patients hospitalized with SARS-CoV-2 infection that are at high risk for complications will be treated with dapagliflozin or matching placebo for 30 days to investigate the effects on risk of complications and all-cause death, or improvement in clinical recovery in

adult patients hospitalized with COVID-19 compared to placebo.

1.2 Rationale for Study Design, Doses and Control Groups

This is a randomized, multicenter, double-blind, placebo-controlled, parallel-group, Phase III study in countries with high prevalence of COVID-19 (countries in North America, Latin America, and Europe, plus India). Randomization and double-blinding study treatment will minimize potential bias.

Patients with serious COVID-19 complications, including death, frequently have cardiometabolic disease (hypertension, T2DM, ASCVD, HF, and/or kidney disease at baseline) (Arentz et al 202, Grasselli et al 2020, Guan et al 2020, NIH COVID-19 Treatment Guidelines). Individuals that have a combination of such underlying health conditions, and with evidence of acute cardiac involvement and/or kidney injury, have a high risk of death due to COVID-19 (Guo et al 2020, Pranata et al 2020, Ronco et al 2020, Shi et al 2020 Vrsalovic and Vrsalovic Presecki 2020). These findings suggest that cardiovascular and kidney complications are prominent in patients hospitalized with COVID-19 and appear to be key drivers of poor outcomes and death. It thus follows that prevention of these complications may lead to either lower risk of disease progression or improved clinical recovery. In summary, the patients at highest risk of COVID-19 complications appear to be those with cardiometabolic disease at baseline and the rate of cardiorenal complications in the setting of COVID-19 is high—especially in patients with pre-existing cardiovascular and kidney disease.

SGLT2 inhibitors may favorably impact multiple processes, including but not limited to energy metabolism, endothelial function, oxidative stress, inflammation, and autophagy, that are dysregulated during a major acute illness such as COVID-19 (Aragón-Herrera et al 2019, Esterline et al 2018, Ferrannini 2017, Kim et al 2020, Packer 2020, Tanaka et al 2018). Such metabolic restoration may help to prevent multi-organ damage or improve clinical recovery in the setting of COVID-19, and could provide critical and complementary efficacy to other therapeutic approaches across various stages of the disease course.

The study population will include hospitalized patients with respiratory manifestations of COVID-19 of any duration, but without the need for mechanical ventilation. The eligible patients should have a medical history including risk factors for developing serious complications of COVID-19. These risk factors include patients with a history of hypertension, T2DM, ASCVD, HF and/or CKD stage 3 to 4. Patients with reduced renal function usually present a clinical profile of increased intra glomerular pressure, hypertension, proteinuria and fluid/sodium overload. Existing data demonstrate that SGLT2 inhibition can improve all these abnormalities (Kosiborod et al 2017, McMurray et al 2019, Neal et al 2017, Perkovic et al 2019, Wiviott et al 2019, Zinman et al 2015). Thus, patients with HF and reduced renal function could be expected to benefit from treatment with dapagliflozin.

Patients will be treated for 30 days, with either dapagliflozin 10 mg daily or placebo, each to be given in addition to the usual standard of care in the participating hospital. In the natural course of the disease, serious complications of COVID-19 can occur up to 10 to 15 days after the start of symptoms, so the treatment period of 30 days should be sufficient to assess efficacy. Per the protocol, treatment with dapagliflozin or matching placebo will continue even if mechanical ventilation becomes necessary. In that case, the tablets will be crushed and given to the patient via the gastric tube. The 10-mg dose of dapagliflozin has a well-characterized efficacy and safety profile in the T2DM clinical development program and is the recommended dose in the majority of countries worldwide. All patients will be treated according to local guidelines on standard of care treatment for patients with COVID-19.

The study assessments include only those that are absolutely critical for ensuring the safety of the patients, to measure efficacy outcomes, and collect biomarker data, so as not to place too high a burden on the study personnel and to minimize additional risk of exposure to SARS-CoV-2.

The dual primary efficacy endpoints of the study are time to first event of either complications or death from any cause, and improved clinical recovery through 30 days of follow-up. An extended follow-up period of 60 days (after the 30-day treatment period) is included, in order to examine longer-term trajectory of recovery from COVID-19 among trial participants.

The safety data will be monitored by an Independent Data and Safety Monitoring Committee and an interim safety analysis of the first 100 patients will be performed.

1.3 Benefit/risk and Ethical Assessment

Dapagliflozin has global marketing approval in more than 90 countries. More detailed information about the known and expected benefits and risks and reasonably expected AEs of dapagliflozin may be found in the Investigator’s Brochure. The following is a summary of benefit-risk considerations relevant to the COVID-19 target population.

1.3.1 Potential Benefits to Subjects

All patients in the study are expected to be treated optimally according to background local standard of care therapy, including treatments to control co-morbidities. Dapagliflozin or matching placebo will be administered in addition to these treatments.

These patients are hospitalized and will receive close medical attention, irrespective of blinded treatment allocation.

1.3.2 Potential Risks to Subjects

The safety profile of dapagliflozin is already well established from prior clinical studies in

various clinical settings. These studies have demonstrated that dapagliflozin is generally safe and well tolerated.

Dapagliflozin, as an inhibitor of SGLT2, increases urinary glucose excretions, which is commonly believed to increase the risk of urinary tract infections. Urinary tract infections have been reported in dapagliflozin-treated patients in a slightly higher proportion than in placebo-treated patients in some global Phase III studies, although the rates of urinary tract infections (and serious urinary tract infections) observed in large clinical trials of dapagliflozin and other SGLT2i have been similar to placebo (Wiviott et al 2019, McMurray et al 2019). Increased urinary glucose excretion may also lead to an increased risk of developing genital infections. Genital infections are considered common side effects (in ≥1/100 to <1/10 patients).

Dapagliflozin reduces BP and may reduce blood volume from its diuretic effect, which could be a concern in patients with COVID-19, but could also be an important mechanism of a potential treatment effect. A pooled analysis of patients with T2DM and HF in the dapagliflozin development program, showed no increase of volume depletion events, but an increase in renal events, mainly creatinine increases, in patients treated with dapagliflozin (n=171) compared with patients treated with placebo (n=149). About half of the patients were on loop diuretics (Kosiborod et al 2017). In the dapagliflozin T2DM program, the rate of events related to volume depletion and impaired renal function has been similar between dapagliflozin and placebo.

Dapagliflozin has not been shown to induce hypoglycemia in non-diabetic patients. In clinical pharmacology studies, healthy subjects have been treated with single oral doses of up to 500 mg and multiple oral doses of 100 mg up to 14 days without any hypoglycemic events. However, in patients with T2DM and on insulin or sulfonylurea medication, there is an increased risk of hypoglycemia. Patients with T2DM will be monitored in the hospital as part of standard of care, which in North America, Latin America, Europe, and India includes blood glucose monitoring.

There have been reports of ketoacidosis, including DKA, in patients with T2DM taking dapagliflozin and other SGLT2 inhibitors. Diabetic ketoacidosis is considered a rare (in ≥1/10000 to <1/1000 patients) adverse drug reaction for dapagliflozin in patients with T2DM.

Patients treated with dapagliflozin who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise, and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, interruption of dapagliflozin treatment should be considered, and the patient should be evaluated promptly.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (eg, type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction, reduced caloric intake, or increased insulin requirements caused by infections, illness or surgery and alcohol abuse. Dapagliflozin should be used with caution in patients in these circumstances.

1.3.2.1 Protection Against Risks

Appropriate measures are in place to monitor and minimize potential risks to participating patients, including the use of an IDSMC that will continuously evaluate safety data. Patients with type 1 diabetes mellitus and patients with a history of DKA are excluded from this study. Careful, frequent monitoring of acid-base balance of diabetes patients with T2DM during hospitalization is important and represents a standard of care in most institutions. Should there be an abnormal increase in anion gap and/or reduced bicarbonate levels, measurement of blood levels of ketones, lactate, and analysis of pH must be performed if DKA is suspected. Also, if careful monitoring of acid-base balance according to Table 1 can't be performed, dosing of study medication should be temporarily interrupted until monitoring can be resumed. At discharge, patients with diabetes should be instructed about symptoms associated with DKA and to seek immediate health care contact if such symptoms occur.

A diagnosis of DKA should only be made in a clinical setting consistent with DKA (based on patient history, symptoms, and physical exam) and in the absence of more likely alternative diagnoses and causes of acidosis (such as lactic acidosis). The following biochemical data should support diagnosis:

- Ketonemia ≥3.0 mmol/L and/or significant ketonuria (more than 2+ on standard urine sticks) in the absence of elevated lactate (lactate should be <2 mmol/L to be considered a potential DKA)

and

- At least one of the following criteria suggesting high anion gap metabolic acidosis:
  (a) Arterial or Venous pH ≤7.3
  (b) Serum bicarbonate ≤18 mEq/L
  (c) Anion gap [Na – (Cl + HCO3)] >10

1.3.3 Conclusion

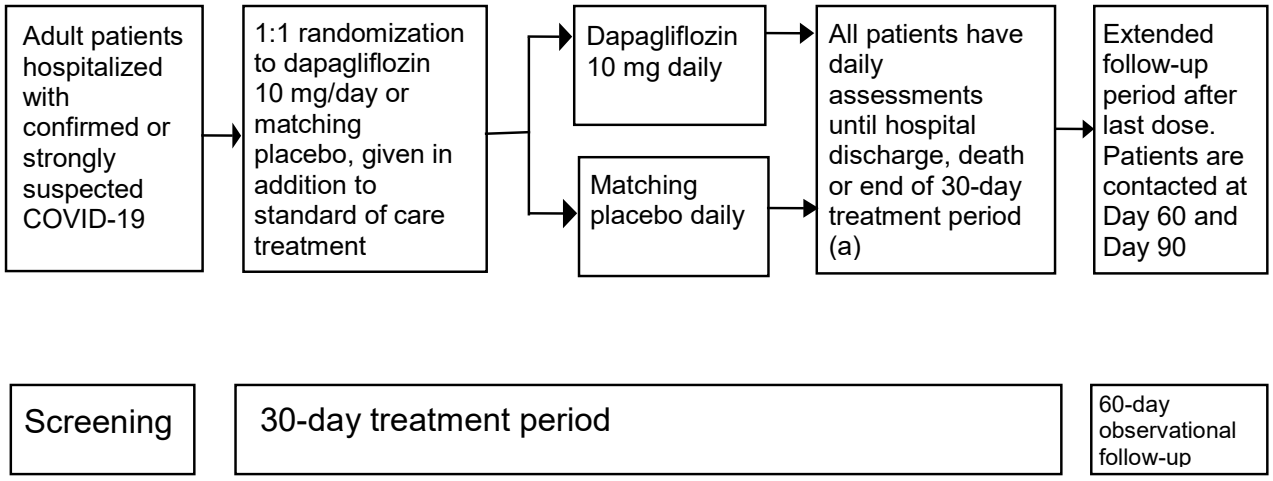
Considering the nonclinical and clinical experience with dapagliflozin and the precautions included in the study protocol, participation in this study should present a minimal and thus acceptable risk to eligible patients. This clinical study will test the hypothesis that dapagliflozin is superior to placebo in reducing the risk of complications or death, or

improving clinical recovery in patients hospitalized with COVID-19. The results could offer substantial benefit to patients with COVID-19, a global patient population with very high risk and an urgent unmet need for effective treatments.

1.4 Study Design

This is an international, multicenter, parallel-group, randomized, double-blind, placebo-controlled, Phase III study in approximately 1200 hospitalized adult COVID-19 patients. The study is evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily for 30 days in addition to background local standard of care therapy, including treatments to control co-morbidities. The screening period should be as short as possible (no more than 2 days), and patients should start investigational product the same day as randomization. Following last dose of investigational product at Day 30 patients are followed up for an extended additional (observational) period of 60 days.

Figure 1 Study flow chart



(a) Discharged patients will be asked to attend telephone visits at Day 15 and Day 30

2 STUDY OBJECTIVES

All objectives are assessed during the 30-day treatment period.

2.1 Primary Objective

Primary objectives:	Outcome measure:
To determine whether dapagliflozin 10 mg is superior to placebo, in terms of reducing complications or all-cause mortality, or improving clinical recovery in patients hospitalized with COVID-19.	Dual primary endpoints of: **<u>Prevention of COVID-19 complications or death</u>** During the 30-day treatment period, time to first occurrence of new/worsened organ dysfunction during index hospitalization or death from any cause. New/worsened organ dysfunction is defined as at least one of the following: • Respiratory decompensation requiring initiation of mechanical ventilation (includes invasive or non-invasive ventilation, CPAP, or BiPAP), and/or initiation of ECMO • New or worsening congestive HF[a] • Requirement for vasopressor therapy and/or inotropic or mechanical circulatory support • Ventricular tachycardia or fibrillation lasting at least 30 seconds and/or associated with hemodynamic instability or pulseless electrical activity, or resuscitated cardiac arrest • Doubling of s-Creatinine or initiation of renal replacement therapy **<u>Improving clinical recovery</u>** Hierarchical composite outcome measure: 1 Death from any cause through Day 30 2 New/worsened organ dysfunction (as defined above) 3 Clinical status at Day 30 for patients still hospitalized and without any worsening organ dysfunction (using points 3 to 5 of a 7-point ordinal scale[b]) 4 Hospital discharge before Day 30 and alive at Day 30

[a] Congestive HF is defined as at least one of the following 1) initiation of new intravenous therapy for heart failure 2) reinstitution of previous intravenous therapy for heart failure 3) increase in current intravenous therapy for heart failure. This is based on modification on previous definition of in-hospital worsening heart failure (McMurray et al 2007)

[b] 7-point Patient Clinical Status scale:

1 Not hospitalized, no limitations on activities

2 Not hospitalized, limitation on activities

3 Hospitalized, not requiring supplemental oxygen

4 Hospitalized, requiring supplemental oxygen
5 Hospitalized, on high flow oxygen devices
6 Hospitalized, on invasive mechanical ventilation or ECMO
7 Death

BiPAP Bilevel positive airway pressure; COVID-19 Coronavirus disease 2019; CPAP Continuous positive airway pressure; ECMO extracorporeal membrane oxygenation; HF Heart failure.

2.2 Secondary Objectives

Secondary objectives:	Outcome measures:
To compare the effect of dapagliflozin 10 mg versus placebo on time to hospital discharge	Time to hospital discharge[a]
To compare the effect of dapagliflozin 10 mg versus placebo on total number of days alive and free from respiratory decompensation requiring mechanical ventilation	Total number of days alive and free from respiratory decompensation[a] requiring initiation of mechanical ventilation (includes invasive or non-invasive ventilation, CPAP, or BiPAP) from randomization through Day 30
To compare the effect of dapagliflozin 10 mg versus placebo on total number of days alive, not in ICU, and free from respiratory decompensation requiring mechanical ventilation	Total number of days alive, not in the ICU, and free from respiratory decompensation[a] requiring initiation of mechanical ventilation (includes invasive or non-invasive ventilation, CPAP, or BiPAP) from randomization through Day 30
To compare the effect of dapagliflozin 10 mg versus placebo on a composite kidney endpoint	Time to composite of acute kidney injury[b] or initiation of renal replacement therapy[c], or death from any cause through Day 30
To compare the effect of dapagliflozin 10 mg versus placebo in reducing the incidence of all-cause mortality	Time to death from any cause through Day 30

[a] Refers to index hospitalization only
[b] Acute kidney injury defined as:
- An episode of doubling s-Creatinine compared to baseline during index hospitalization
- or SAE with preferred term of Acute kidney injury following discharge and through Day 30

[c] Renal replacement therapy defined as:
- Initiation of renal replacement therapy during index hospitalization
- or SAE with a preferred term for renal replacement therapy (ie, Haemodialysis, Haemofiltration, Continuous haemodiafiltration, Dialysis, Peritoneal dialysis, Dialysis device insertion, Renal replacement therapy, or Artificial kidney device user) following discharge and through Day 30

BiPAP Bilevel positive airway pressure; CPAP Continuous positive airway pressure; ICU Intensive care unit; SAE Serious adverse event.

2.3 Safety Objectives

Safety objective:	Outcome measure:
To evaluate the safety and tolerability of dapagliflozin compared to placebo in patients hospitalized with COVID-19.	• Serious adverse events from randomization to Day 30[a] • Acute kidney injury defined as: ° An episode of doubling s-Creatinine compared to baseline during index hospitalization ° or SAE with preferred term of acute kidney injury following discharge and through Day 30 • Incidence of diabetic ketoacidosis from randomization through Day 30

[a] SAEs will be collected through Day 90 but comparison of treatment groups will be assessed based on the data obtained through Day 30. For the definition of reportable SAEs, see Section 6.4.2.

COVID-19 Coronavirus 2019; SAE Serious adverse event.

2.4 Exploratory Objectives

Exploratory objective:	Outcome measures:
To compare the effect of dapagliflozin 10 mg to placebo on the components of the primary endpoint, biomarkers, and patient's clinical status.	• Change in NT-proBNP, hs troponin, D-dimer, LDH, ALT, lymphocyte count, CRP between Day 1 and Day 15 (or discharge from hospital, whichever is earlier) • Qualitative PCR for SARS-CoV-2 in oropharyngeal/nasopharyngeal swab at baseline (while hospitalized); and Day 15 (if still hospitalized) or discharge from hospital • Change in NEWS 2 from Day 1 to Day 15 (or discharge from hospital, whichever is earlier). • Patient's clinical status (on a 7-point ordinal scale) at Day 15 (or discharge from hospital, whichever is earlier) • Total number of days alive and not on renal replacement therapy[a] • Proportion of patients with acute coronary syndrome[b]

[a] Refers to index hospitalization only

[b] Acute coronary syndrome defined as: during index hospitalization, abnormal troponin level above 99th percentile of the local laboratory reference range or, if abnormal at baseline, further rise in troponin levels accompanied by at least 1 of the following: 1) ischemic symptoms 2) ischemic ST-segment changes on ECG (Thygesen et al 2018)

NEWS 2 is a standardized assessment of acute-illness severity and can prompt critical care intervention. It is used as an adjunct to clinical judgment.

ALT Alanine aminotransferase; COVID-19 Coronavirus disease 2019; CRP C-reactive protein; ECG Electrocardiogram; hs troponin High-sensitivity cardiac troponin; LDH lactate dehydrogenase; NEWS 2 National Early Warning Score 2; NT-proBNP N-terminal-pro B-type natriuretic peptide; PCR Polymerase chain reaction SARS-CoV-2 Severe acute respiratory syndrome-coronavirus-2.

3 SUBJECT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

In this study, patients will be recruited from sites with adult patients hospitalized with confirmed or strongly suspected COVID-19. Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomized to investigational product. Under no circumstances can there be exceptions to this rule. Patients can be re-screened once, but must be considered screen failures if they still do not meet the entry requirements (Section 3.3).

In this study, "enrolled" patients are those who sign the ICF. "Randomized" patients are those who undergo randomization and receive a randomization number.

3.1 Inclusion Criteria

For inclusion in the study patients should fulfill the following criteria based on local regulations:

1 Provision of informed consent prior to any study specific procedures. The ICF process is described in Section 10.4
2 Male or female patients aged ≥18 years on the day consent given
3 Currently hospitalized
4 Hospital admission no more than 4 days prior to screening
5 Confirmed SARS-CoV-2 infection by laboratory testing within 10 days prior to screening, or strongly suspected SARS-CoV-2 infection on presentation*
6 Chest radiography or CT findings that, in the opinion of the investigator, are consistent with COVID-19
7 SpO2 ≥ 94% while receiving low-flow supplemental oxygen (5 liters or less)
8 Medical history of at least one of the following:
   (a) hypertension
   (b) T2DM
   (c) atherosclerotic cardiovascular disease
   (d) heart failure (with either reduced or preserved LVEF)
   (e) CKD stage 3 to 4 (eGFR between 25 to 60 mL/min/1.73 m^2)

*Note that the proportion of patients randomized without a confirmed SARS-CoV-2–positive test will be closely monitored, and may be capped if it becomes greater than anticipated.

3.2 Exclusion Criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1 Respiratory decompensation requiring mechanical ventilation (includes invasive or non-invasive ventilation, CPAP, or BiPAP)

2 Expected need for mechanical ventilation (includes invasive or non-invasive ventilation, CPAP, or BiPAP) within the next 24 hours

3 Anticipated transfer to another hospital facility, which is not another study site, within 72 hours

4 Expected survival of less than 24 hours at the time of presentation, in the judgement of the Investigator

5 eGFR <25 mL/min/1.73 m^2 or receiving renal replacement therapy/dialysis

6 Evidence of oliguria (urine output <500 mL in 24 hours or <0.5 mL/kg/hour) or serum creatinine ≥1.5x baseline pre-hospitalization value, if available at the time of screening

7 Systolic BP <95 mmHg and/or requirement for vasopressor treatment and/or inotropic or mechanical circulatory support at Screening

8 History of type 1 diabetes mellitus

9 Currently receiving or has received in the last 14 days, experimental immune modulators and/or monoclonal antibody therapies for COVID-19**

10 History of diabetic ketoacidosis

11 Current treatment with any SGLT2i (eg, dapagliflozin, canagliflozin, empagliflozin, ertugliflozin) or having received treatment with any SGLT2i within 4 weeks prior to screening

12 History of hypersensitivity to dapagliflozin

13 Any other condition that in the judgment of the investigator would jeopardize the patient's participation in the study or that may interfere with the interpretation of study data or if the patient is considered unlikely to comply with study procedures, restrictions and requirements

14 Women of childbearing potential: Current or planned pregnancy or currently lactating.

(a) Women of childbearing potential are defined as any female who has experienced menarche and who is NOT permanently sterile or post-menopausal

(b) Post-menopausal is defined as 12 consecutive months with no menses without an alternative medical cause

(c) Women of childbearing potential, who are sexually active, must agree to use a medically-accepted method of birth control for the duration of the study. Acceptable birth control methods include:

- Surgical sterilization (such as a hysterectomy or bilateral tubal ligation)
- Progesterone hormonal contraceptives (birth control pills or implants)
- Barrier methods (such as a condom or diaphragm) used with a spermicide
- An intrauterine device

15 Involvement in the planning and/or conduct of the study (applies to both Investigator staff and/or staff at the study site)

16 Previous enrolment in the present study. (Note: the study design allows 2 attempts to meet the randomization criteria after enrolment.)

17 Current participation in another interventional clinical trial (with an investigational drug) that is not an observational registry

**Note that use of rescue therapies including immune modulators, monoclonal antibody therapies, antiviral therapies, and other agents that are approved or being used through open-label compassionate/expanded use programs or in accordance with the local standard of care is permitted during the study.

Procedures for withdrawal of incorrectly enrolled patients are in Section 3.4.

3.3 Subject Enrolment and Randomization

Investigator(s) or designee should keep a record (the patient's screening log) of patients who entered pre-study screening.

The Investigator(s) or designee will:

1 Obtain informed consent from the potential patient or their guardian/legal representative before any study specific procedures are performed

2 Assign potential subject a unique enrolment number

3 Determine patient eligibility (see Sections 3.1 and 3.2). More than 1 attempt to meet the randomization criteria is allowed

4 Assign eligible patient a unique randomization code

5 If a patient withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused

Randomization codes will be assigned strictly sequentially as patients become eligible for randomization (see Section 3.5).

3.4 Procedures for Handling Incorrectly Enrolled or Randomized Subjects

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive investigational product. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment (note that more than 1 attempt to meet the randomization criteria is allowed).

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the Sponsor immediately, and a discussion should occur between the Sponsor and the Investigator regarding whether to continue or discontinue the patient from treatment. The Sponsor must ensure all decisions are appropriately documented.

3.5 Methods for Assigning Treatment Groups

All patients will be randomly assigned to investigational product centrally using an Interactive Response Technology system. Randomization to investigational product will be performed in balanced blocks to ensure approximate balance between the treatment groups (1:1). The Sponsor or delegate is responsible for generating the randomization scheme for this study using a validated system. Before the study starts, the instructions for accessing and using the Interactive Response Technology system will be provided to each site.

Investigational product (dapagliflozin or placebo) should be administered the same day the investigational product kit number is assigned and as soon after randomization as possible.

To ensure balanced randomization, stratification will be employed by country.

3.6 Methods for Ensuring Blinding

The blinding of treatment is ensured by using a double-blind technique of matching placebo. The IRT will provide the Investigator with the kit identification number to be allocated to the patient when investigational product is dispensed.

No member of the extended Sponsor study team, personnel at study sites, study team, or the Sponsor's delegate handling study data will have access to the randomization scheme during the study. The Sponsor or delegate generating the randomization scheme and the Supply Chain Study Management may be able to access the randomization scheme as appropriate. Neither the patient nor any of the Investigator's staff/designee who are involved in the treatment or clinical evaluation and monitoring of the patients will be aware of the treatment received. In the event that the treatment allocation for a patient becomes known to

the Investigator or other study staff involved in the management of study subjects, the Investigator must notify the Sponsor immediately.

3.7 Methods for Unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists at the study site from the IRT. Instructions for code breaking/unblinding are provided to each study site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The date and reason that the blind was broken must be recorded in the source documentation and eCRF as applicable. The Investigator is to document and report the action to the Sponsor or Sponsor representative, without revealing the treatment given to the patient.

The Sponsor or Sponsor representative retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to the investigational product and that potentially require expedited reporting to regulatory authorities.

3.7.1 Unblinding for Independent Data and Safety Monitoring Committee

An IDSMC will be established to monitor blinded safety data to ensure the safety of patients enrolled in this study, and to ensure the integrity of the study. An interim analysis of safety only (not efficacy) will occur when approximately 100 patients complete the 30-day treatment period. The IDSMC will be provided with partially unblinded data (data that are summarized by treatment group using masked treatment group labels). The IDSMC may choose to unblind the data for additional review as specified in the IDSMC charter. The Sponsor and Sponsor representatives will remain blinded to all data transfers provided to the IDSMC. Details about the IDSMC will be included in the IDSMC Charter (see Section 6.9.2).

3.8 Restrictions (Not Applicable)

There are no restrictions affecting the patient's daily life activities associated with participation in the study during the course of the study.

3.9 Discontinuation of Investigational Product

If the patient temporarily or permanently discontinues from investigational product, it is important that the scheduled study visits, data collection and procedures continue according to the study protocol until study closure (see the Study plan in Table 1).

Patients may be discontinued from investigational product in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event or other safety reasons that, in the opinion of the investigator, contraindicates further dosing with investigational product.
- Severe non-compliance with the study protocol
- DKA, consider temporarily interrupting investigational product if DKA is suspected. If DKA is confirmed, investigational product should be discontinued permanently
- Positive pregnancy test (discontinue investigational product and notify the Sponsor)

3.9.1 Evaluation of Volume Status and Investigational Dose Reduction/interruption

Dapagliflozin is a SGLT2i which by its mechanism of action reduces the reabsorption of glucose and sodium in the proximal tubules in the kidney. SGLT2 inhibition has a mild diuretic effect and an initial hemodynamic change with an initial increase in creatinine may occur.

Unexpected acute declines in eGFR

If an unexpected, acute decline in kidney function is observed, the patient should be evaluated. Volume depletion, hypotension, intercurrent medical problems and concomitant drugs may cause increases in blood creatinine. Urinary tract infection and urinary obstruction should be considered (the latter especially in men). Several drugs may cause a decline in kidney function, especially NSAIDs and certain antibiotics such as trimethoprim. If any drug is suspected of causing or contributing to worsening kidney function, their use should be re-considered.

Volume depletion/hypotension

Patients with clinically relevant symptoms/signs of suspected volume depletion and/or hypotension, should have their regular medication reviewed, and consideration given to reducing the dose of, or stopping concomitant non-essential medications, as assessed on an individual basis, including diuretics and drugs that lower BP (except essential treatments). The need for conventional diuretics (or the dose of diuretic used) should be re-evaluated in light of the patient's symptoms and signs. In patients with HF, discontinuation of diuretic should only be undertaken cautiously. Hypotension may also occur with other BP lowering drugs and once again the need for (and dose of) non-essential agents of this type (eg, calcium channel blockers, alpha adrenoceptor antagonists and nitrates) should also be re-considered.

3.9.2 Investigational Product Restart

Restart of randomized investigational product is always encouraged. If stopped, whenever

possible, randomized investigational product should be restarted.

Every attempt should be made to maintain patients on dapagliflozin 10 mg or matching placebo during the course of the study. If the dose has been interrupted, the dose should be re-introduced as soon as, in the opinion of the investigator, the patient's condition is stable.

3.9.3 Procedures for Discontinuation of Investigational Product

At any time, patients are free to discontinue investigational product or withdraw from the study (ie, investigational product and assessments—see Section 3.10), without prejudice to further treatment. A patient that decides to discontinue investigational product will always be asked about the reason(s). If investigational product is in a patient's possession, they should dispose of the study drug according to local regulations.

Discontinuation from investigational product is not the same as complete withdrawal from the study. If a patient is completely withdrawn from study, see the procedures in Section 3.10.2.

It is essential to collect data for all patients throughout the study. For that reason, a patient who discontinues investigational product should optimally continue to follow up study assessments up to and including Day 90. Alternatively, if the patient does not agree to this approach, modified follow-up should be arranged (eg, less frequent assessments, one contact at Day 30, or other means). Patients who agree to some kind of modified follow-up are still participating in the study. The modified visits and procedures that are done will be recorded in the eCRF.

If a patient for some reason cannot be reached during the study, every attempt should be made to retrieve as much information regarding this patient as possible. The site should continuously try to reach the patient, the patient's family, or pre-identified contact person and search for information regarding the patient's status in applicable sources to protect the validity of data. These attempts should be documented.

3.10 Criteria for Withdrawal

3.10.1 Screen Failures

Once enrolled in the study, patients can be re-screened one more time, if they do not fully meet the inclusion/exclusion criteria during the first attempt at screening. Ultimately, screening failures are patients who do not fulfill the eligibility criteria for the study, and, therefore, must not be randomized. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrollment' (ie, patient does not meet the required inclusion/exclusion criteria).

3.10.2 Withdrawal of the Informed Consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment. Withdrawal of consent should only occur if the patient has received appropriate information about, and does not agree to, any kind of further assessments or contact, including modified follow-up options. Discontinuation of investigational product in itself is not considered withdrawal of consent.

A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

If a patient withdraws from participation in the study, then his/her enrollment and/or randomization code cannot be reused. Withdrawn patients will not be replaced.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up patients as medically indicated.

To ensure validity of study data, it is very important to collect as much data as possible throughout the study (including after hospital discharge) and especially vital status (dead or alive) (also for patients who have withdrawn their informed consent). Therefore, if informed consent has been withdrawn completely or the patient is non-contactable following hospital discharge, the investigator will attempt to collect information on all patients' vital status from publicly available sources at study closure, in compliance with local privacy laws/practices.

3.11 Discontinuation of the Study

The study may be stopped if, in the judgment of the Sponsor, patients are placed at undue risk because of clinically relevant findings. The judgment may be based on recommendations from the IDSMC, see IDSMC Charter for details. The study can also be stopped based on results of the interim analysis (see Section 8.5.4).

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4 STUDY PLAN AND TIMING OF PROCEDURES

The schedule of assessments is shown in Table 1 and explained further in Sections 4.1 and 4.2.

Table 1 Study Plan Detailing the Procedures

Day number (week 1) **Day number (week 2)** **Day number (week 3)** **Day number (week 4)**	**Day 0 (Screening and enrollment)**	**1** **8** **16** **23**	**2** **9** **17** **24**	**3** **10** **18** **25**	**4** **11** **19** **26**	**5** **12** **20** **27**	**6** **13** **21** **28**	**7** **14** **22** **29**	**15** **30**	**Discharge from hospital**	**Follow-up at Day 60 and Day 90**
Informed consent	X										
Demographics	X										
Weight and height	X										
Medical history	X										
Concomitant medication	X								X[a]	X	X
Vital signs (temperature, BP, pulse, O2 SAT)	X	X	X	X	X	X	X	X	X	X	
Site laboratory assessment[b]	X[c]	Day 1[b]		Day 3[b]					Day 15[b]	X[b]	
Expected standard of care laboratory assessment[d] (eg, basic metabolic panel and/or other means of acid-base monitoring per local standard of care)		X	X	X	X	X	X	X	X		
Oropharyngeal or nasopharyngeal swab	X								Day 15[e]	X[e]	
Local pregnancy test (female patients of child bearing potential only)	X										
Inclusion/exclusion criteria	X										
Randomization to study treatment		Day 1									

Table 1 Study Plan Detailing the Procedures

Day number (week 1) **Day number (week 2)** **Day number (week 3)** **Day number (week 4)**	**Day 0 (Screening and enrollment)**	**1** **8** **16** **23**	**2** **9** **17** **24**	**3** **10** **18** **25**	**4** **11** **19** **26**	**5** **12** **20** **27**	**6** **13** **21** **28**	**7** **14** **22** **29**	**15** **30**	**Discharge from hospital**	**Follow-up at Day 60 and Day 90**
New/worse organ dysfunction assessed (as defined in primary outcome)		X	X	X	X	X	X	X	X	X	
NEWS 2[f]		Day 1							X	X	
Patient's clinical status (7-point ordinal scale)[g]		Day 1							X	X	X
Telephone follow up for discharged patients[g]									X		
Treatment dispensed		X	X	X	X	X	X	X	X	X[h]	
Serious adverse events and key safety events[i]		X	X	X	X	X	X	X	X	X	X
AEs leading to discontinuation of IP[j]		X	X	X	X	X	X	X	X	X	
Telephone follow-up for all patients during extended follow-up period[k]											X

[a] Recorded at Day 15 only for previously discharged patients. For all other patients, this is recorded at Day 30.

[b] On Day 1, Day 3, Day 15, and Discharge only, laboratory assessment includes: renal panel (creatinine, BUN or urea, electrolytes, bicarbonate), NT-proBNP, hs troponin, D-dimer, CBC (RBC, WBC with differential, PLTs), LDH, ALT, AST, CRP and total bilirubin. All laboratory assessments will be done by site laboratories.

[c] Screening laboratory assessment includes: glucose, renal panel (creatinine, BUN or urea, electrolytes, bicarbonate), NT-proBNP, hs troponin, D-dimer, CBC (RBC, WBC with differential, PLTs), LDH, ALT, AST, CRP, and total bilirubin. All laboratory assessments will be done by site laboratories.

[d] Patients with diabetes should be evaluated daily while hospitalized with respect to acid-base balance to detect early change in bicarbonate levels and/or anion gap; acid-base monitoring may also include blood gas analysis, as applicable. If that happens, investigation of blood levels of ketones and lactate should be done. Glucose levels should be monitored per routine practice in these patients.

[e] Oropharyngeal or nasopharyngeal swab will be obtained during screening and Day 15 (if patient still hospitalized) or Discharge from hospital.

[f] All patients are assessed at Day 1 (pre-randomization), Day 15 if hospitalized, Day 30 if hospitalized, and/or Discharge from hospital.

[g] All patients are assessed at Day 1 (pre-randomization), Day 15, and Day 30 and/or Discharge from hospital. Hospitalized patients have all scheduled assessments. Discharged patients are followed up by telephone for SAEs, Patient's clinical status, vital status, investigational product adherence, and subsequent hospitalization, if any. The window for the follow up phone call on Day 15 or Day 30 is ± 3 days.

[h] The remaining investigational product is provided to the patient so that he/she can continue taking their investigational product until Day 30.

[i] Events fulfilling the reportable SAE criteria and/or key safety events (see Section 6.4.2 for the definition of a reportable SAE or key safety event) will be collected from time of informed consent through Day 30. In addition, following the 30-day treatment period, all SAEs will continue to be collected through Day 90 (which includes the extended observational follow-up period of an additional 60 days).

[j] If patient is still receiving IP.

[k] All patients are followed up by telephone, if not still hospitalized, for concomitant medication, SAEs, Patient's clinical status, vital status, and subsequent hospitalization, if any. The window for the follow-up phone call is ± 7 days.

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BP Blood pressure; BUN Blood urea nitrogen; CBC Complete blood count; CRP C-reactive protein; DAEs AEs leading to investigational product discontinuation; hs troponin High-sensitivity cardiac troponin; IP Investigational product; LDH lactate dehydrogenase; NEWS 2 National Early Warning Score 2; NT-proBNP N-terminal-pro B-type natriuretic peptide; O2 SAT Oxygen saturation level; PLTs Platelets, RBC Red blood cells; SAE Serious adverse event; WBC White blood cells.

4.1 Screening and Enrollment Period (Day 0)

Following hospital admission, participants will undergo screening and the following assessments and procedures will be completed.

- Patient provides informed consent before any study procedures
- Patient is enrolled and assigned an E-code
- Demography (including smoking status), medical history, concomitant medication will be recorded
- Vital signs (temperature, BP, pulse, O2 SAT, and body weight) and height will be recorded
- Laboratory samples will be collected and sent to site laboratory (hemoglobin, glucose, renal panel (creatinine, BUN, electrolytes, bicarbonate), NT-proBNP, hs troponin, D-dimer, CBC (RBC, WBC with differential, PLTs), LDH, ALT, AST, CRP, and total bilirubin)
- An oropharyngeal or nasopharyngeal swab will be collected and sent to the local site laboratory
- Local pregnancy test (female patients of child bearing potential only)
- The Investigator reviews the **inclusion and exclusion criteria**. Patients who do not meet these criteria must not be randomized in the study

Patients can be re-screened one more time if they do not fully meet the eligibility criteria during their first screen. Patients who do not meet the inclusion/exclusion criteria must not be randomized in the study. Screening should take no more than 2 days.

Procedures conducted as part of the patient's routine clinical management and obtained before signing of the ICF may be used for screening or baseline purposes (eg, chest radiography or CT scan), provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the inclusion/exclusion criteria.

Procedures will be performed according to the Study Plan (Table 1).

4.2 Treatment Period (Day 1 to Day 30)

Eligible patients will be randomized to start treatment with either dapagliflozin 10 mg or placebo daily (double-blind) as soon as possible.

Investigational product will be administered for 30 days, with follow-up assessments every 24 hours until either hospital discharge, Day 30, or death.

The following assessments will be completed.

- Concomitant medications at time points defined in the study plan in Table 1
- Vital signs (temperature, BP, pulse, O2 SAT) at time points defined in the study plan in Table 1
- Site laboratory assessments:
  (a) Renal panel (creatinine, BUN, electrolytes, bicarbonate), NT-proBNP, hs troponin, D-dimer, CBC (RBC, WBC with differential, PLTs), LDH, ALT and AST, CRP and total bilirubin at time points defined in the study plan in Table 1.
  (b) Expected standard of care basic metabolic panel (sodium, potassium, bicarbonate, anion gap, BUN, creatinine, glucose), and/or other acid-base monitoring per local standard for care to detect early change in bicarbonate levels and anion gap in diabetes patients (may also include blood gas analysis, as applicable). A venous or arterial blood gas analysis for pH, as well as blood levels of ketones (beta-hydroxybutyrate), and lactate should be investigated if DKA is suspected. This is performed at time points defined in the study plan in Table 1
- An oropharyngeal or nasopharyngeal swab at time points defined in the study plan in Table 1
- If the patient has experienced any potential endpoints: death, SAEs, developed new/worsened organ dysfunction (defined in Section 5.1) since the previous day (at time points defined in the study plan in Table 1)
- A NEWS 2 assessment will be completed at time points defined in the study plan in Table 1
- Patient Clinical Status will be assessed using a 7-point scale (defined in Section 5.1) at time points defined in the study plan in Table 1

4.3 Follow-up Period after Hospital Discharge

Patients discharged from hospital will continue with daily treatment for the remainder of the 30 days, and are followed up by telephone at Day 15 and/or Day 30 (± 3 days).

The following assessments will be completed:

- Concomitant medications will be recorded
- Follow up of ongoing reportable SAEs. Details of any new reportable SAEs will be recorded.
- Vital status
- Investigational product adherence

- Details of any re-hospitalization for the patient
- Patient Clinical Status will be assessed using a 7-point scale (defined in Section 5.1)

4.4 Extended Follow-up Period after Day 30

Following last dose of investigational product at Day 30, patients are followed up by telephone at Day 60 and Day 90 (± 7 days).

The following assessments will be completed:

- Concomitant medications will be recorded
- Follow up of ongoing reportable SAEs. Details of any new reportable SAEs will be recorded.
- Vital status
- Details of any re-hospitalization for the patient
- Patient Clinical Status will be assessed using a 7-point scale (defined in Section 5.1)

5 STUDY ASSESSMENTS

The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided. If the eCRFs are not fully operational in time for patients being screened and enrolled, paper-based patient documentation will be used initially and data will be transferred into electronic systems when available.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Research Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy Assessments

5.1.1 Primary Endpoint Events

Endpoint events of death from any cause or developed new/worsened organ dysfunction through 30 days of follow up, defined as at least one of the items listed below, are identified from information received through review of medical records and laboratory data (see Table 1 for timings).

- Respiratory decompensation requiring initiation of mechanical ventilation[a] (includes invasive or non-invasive ventilation, CPAP, or BiPAP), and/or initiation of ECMO
- New or worsening congestive HF during current hospitalization
- Requirement for vasopressor therapy and/or inotropic or mechanical circulatory support
- Ventricular tachycardia or fibrillation lasting at least 30 seconds and/or associated with hemodynamic instability or pulseless electrical activity, or resuscitated cardiac arrest
- Doubling of s-Creatinine or initiation of renal replacement therapy[a]

[a] Duration of mechanical ventilation and renal replacement therapy events will be collected.

The hierarchical composite endpoint includes all the outcomes defined above. In addition, it includes the outcome of hospital discharge as well as any clinical status change in patients who are still hospitalized at Day 30 and did not experience any of the events described above. Clinical status change will be used as collected in Section 5.1.4 (points 3 to 5).

5.1.2 Time to Event Endpoints

A number of efficacy endpoints, listed below, relate to the timing of an event. Patients are reviewed daily for the occurrence of each of these events. The date and time (24 hr) (time if known) of the event will be recorded.

- Death from any cause
- Hospital discharge
- Composite kidney endpoint, defined as composite of acute kidney injury or initiation of renal replacement therapy, or death from any cause through Day 30 (See Section 2.2 for the definitions of acute kidney injury and renal replacement therapy)

5.1.3 National Early Warning Score 2

The NEWS 2 can be used on all hospitalized patients to allow for the early detection of clinical deterioration and potential need for higher level of care. It determines the degree of illness of a patient and prompts critical care intervention. Patients with low NEWS 2 can continue receiving their usual care and observation. Patients with high NEWS 2 should be watched more attentively and considered for transfer to a higher care unit such as an ICU.

A NEWS 2 assessment is recorded as specified in the Study Plan (Table 1).

5.1.4 Patient Clinical Status

A 7-point scale is recorded as specified in the Study Plan (Table 1) to assess the clinical status of the patient:

1 Not hospitalized, no limitations on activities

2 Not hospitalized, limitation on activities

3 Hospitalized, not requiring supplemental oxygen

4 Hospitalized, requiring supplemental oxygen

5 Hospitalized, on high flow oxygen devices

6 Hospitalized, on invasive mechanical ventilation or ECMO

7 Death

5.1.5 Laboratory Assessments

Blood samples for determination of clinical chemistry and hematology, will be taken at the times indicated in the study plan (Table 1), if not already available as standard of care.

The clinical chemistry and hematology will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Table 2 Laboratory Variables

Hematology/hemostasis (whole blood)	Clinical chemistry (serum or plasma)
B-Hemoglobin (Hb)	S/P-Creatinine[a]
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)—Lymphocyte count[a]	S/P-Aspartate transaminase (AST)
B-Platelet count	S/P-Alanine transaminase (ALT)[a]
B-Hematocrit	S/P-Blood urea nitrogen (BUN) or urea
	S/P-Bicarbonate
	S/P-Electrolytes
	S/P-Sodium
	S/P-Potassium
	S/P Glucose
	S/P CRP[a]
	S/P LDH[a]
	S/P NT-proBNP[a]
	S/P hs troponin[a]
	P D-dimer[a]
	Arterial/venous Blood gas
	Arterial/venous Anion gap

[a] Outcome measure and recorded in the eCRF
CRP C-reactive protein; eCRF Electronic case report form; hs troponin High-sensitivity cardiac troponin, LDH lactate dehydrogenase; NT-proBNP N-terminal-pro B-type natriuretic peptide; P Plasma; S Serum.

For calculation of eGFR using the CKD-EPI equation (Levey et al 2009):

$$GFR=141x\ \min(S_{cr}/\kappa, 1)^{\alpha}\ x\ \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

Where:

S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1

The equation does not require weight because the results are reported normalized to 1.73 m² body surface area, which is an accepted average adult surface area.

The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

5.2 Safety Assessments

All safety assessments in this section should be recorded daily approximately between 06:00 and 08:00 in the morning.

5.2.1 Physical Examination (not applicable)

There will be no physical examination performed in order to minimize the risk of exposure to the study personnel.

5.2.2 Vital Signs

Vital signs (temperature, BP, pulse, O2 SAT) will be recorded daily according to the study plan (Table 1).

5.2.3 Adverse Events

Occurrences of reportable SAEs, AEs leading to investigational product discontinuation (DAEs), and safety events of acute kidney injury (defined as an episode of doubling s-Creatinine compared to baseline during index hospitalization, or an SAE with the preferred

term of acute kidney injury following discharge and through Day 30) and DKA (as presented in Section 1.3.2.1), will be recorded by the study sites. Routine AEs will not be collected. See Section 6 for additional details of safety reporting.

6 SAFETY REPORTING AND MEDICAL MANAGEMENT

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of Adverse Events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

Adverse events for malignant tumors reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a non-serious AE. For example, if the tumor is included as medical history and progression

occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the Investigator(s) and communicated to the Sponsor.

For further guidance on the definition of an SAE, see Appendix A Additional Safety Information.

6.3 Definition of Suspected Unexpected Serious Adverse Event

A suspected adverse reaction related to an investigational product that is both unexpected and serious.

6.4 Recording of Adverse Events

Occurrences of reportable SAEs, DAEs and safety events of acute kidney injury and DKA, will be recorded on a daily basis during index hospitalization and at Discharge, as well as during pre-specified post-discharge phone follow up visits.

6.4.1 Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease.

Worsening of the patient's condition that is directly attributable to the COVID-19 disease and which occurs during the original (index) hospitalization, is not considered an SAE and must not be reported as such unless it is a fatal event (a fatal event should always be reported as a an SAE).

If the SAE occurs after the discharge from the primary (index) admission (during the follow-up period or re-admission), all events that fit the SAE criteria must be reported as such, regardless if they are directly attributable to the COVID-19 or not.

6.4.2 Definition of Reportable Events

Reportable SAEs are all events leading to death and non-fatal SAEs that are **not** due to worsening of the patient's condition directly attributable to COVID-19 during the index hospitalization. All SAEs occurring after discharge from the index hospitalization are

reportable SAEs.

All DAEs (for patients receiving investigational product) and key safety events will be reported regardless of whether they fulfill the SAE criteria, are directly attributable to the COVID-19 disease, or whether they occur during index hospitalization or after discharge.

6.4.3 Time Period for Collection of Adverse Events

Events fulfilling the reportable SAE criteria, DAEs (for patients receiving investigational product), and/or key safety events will be collected from time of informed consent through Day 30. In addition, following the 30-day treatment period, all SAEs will continue to be collected through Day 90 (which includes the extended observational follow-up period of an additional 60 days).

6.4.4 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at Day 90 in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. The Sponsor or delegate retains the right to request additional information for any patient with ongoing reportable AE(s)/SAE(s) at the end of the study, if judged necessary.

6.4.5 Variables

The following variables will be collected for each reportable event (see Section 6.4.2 for the definition of reportable event) assessed in the study;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity or intensity:

1 mild (awareness of sign or symptom, but easily tolerated)
2 moderate (disturbing but still tolerable)
3 severe (intolerable)

- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Outcome.

In addition, the following variables will be collected for reportable SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to

- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Description of SAE.

It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.4.6 Causality Collection

The Investigator will assess causal relationship between investigational product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A Additional Safety Information to the Clinical Study Protocol.

6.4.7 Adverse Events Based on Signs and Symptoms

All reportable SAEs, key safety events, and DAEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous day/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting reportable AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

See Section 6.4.1 for the reporting of COVID-19-related signs and symptoms.

6.4.8 Adverse Events Based on Examinations and Tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should only be reported as AEs if they fulfill the criteria for reportable SAEs, DAEs, or key safety events (see Section 6.4.2).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported if it fulfills the criteria for a reportable SAE, DAE, and/or key safety event, and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported if they fulfill the criteria for a reportable SAE, DAE, and/or key safety event.

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE unless it fulfills the definition of a reportable SAE, DAE, and/or key safety event.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported if it fulfills the criteria of a reportable SAE, DAE, and/or key safety event.

6.5 Reporting of Serious Adverse Events to the IRB/IEC and/or the Regulatory Authority

Section 5.6 of the Investigator's Brochure serves as the Reference Safety Information for this study.

All reportable SAEs have to be reported, whether or not considered causally related to the investigational product. The Sponsor representative is responsible for informing the IRB/IEC and/or the Regulatory Authority of the SAE as per local requirements.

If any reportable SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate Sponsor representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all the necessary information is provided to the database **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other reportable SAEs.

For fatal or life-threatening reportable SAEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Sponsor representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for dapagliflozin.

Sponsor and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected AEs that occur in accordance with the reporting obligations of 21 CFR 312.32. It is the responsibility of the Sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines.

reporting information:
via email:
via Fax (US Fax number: ; UK and EU Fax Number:). Refer to the Study Contact List for additional country fax numbers.

6.6 Reporting of Serious Adverse Events to Company

Investigators or other site personnel inform Sponsor representatives of the reportable SAE. The Sponsor is responsible for informing of the SAE. All reportable SAEs have to be reported to whether or not considered causally related to the investigational product.

Reportable SAEs related to the investigational product must be provided to on an ongoing basis as individual case reports.

Reportable SAEs unrelated to the investigational product must be provided to as individual case reports on an ongoing basis.

At the end of the study a final unblinded summary line listing of all reportable SAEs notified to the regulatory authority and/or during the study, must be provided to to enable reconciliation of safety information held for its product(s).

Send SAE reports (individual case reports and line listings) and accompanying cover page to

SAEs that do not require expedited reporting to the Regulatory Authority/IRB/IEC still need to be reported to as individual case reports on an ongoing basis.

Suspected Unexpected Serious Adverse Reactions must be reported to at the same time these events are notified to the Regulatory Authority.

may request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

6.7 Overdose

Dapagliflozin has been well tolerated at doses of up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and patients with T2DM. For further information, refer to the Investigator's Brochure. If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.5.

6.8 Pregnancy

Pregnancies and outcomes of pregnancy in patients that are participating in this study should be reported to Sponsor and .

6.8.1 Maternal Exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

If pregnancy occurs in a study subject during the course of the study, then the Investigator or other site personnel informs the Sponsor within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor data entry site within 1 or 5 calendar days for SAEs (see Section 6.5) and within 30 days for all other pregnancies in study subjects.

6.9 Study Governance and Oversight

6.9.1 Executive Committee

Together with the Sponsor, the Executive Committee will be responsible for the final overall study design, including the development of the study protocol and eCRF, supervision of the

study conduct and progress, development of any protocol amendments needed during the study, liaison with the IDSMC as needed, development of the SAP, interpretation of the final data and reporting (presentations at international congresses and publications in peer reviewed journals) of the study. The Executive Committee will make final decisions with regard to early stopping or modifications of the study based on the information received from the IDSMC.

The Executive Committee will be comprised of the overall study PI (Chair), designated international academic leaders, and non-voting members of and will operate under an Executive Committee Charter.

6.9.2 Independent Data and Safety Monitoring Committee

The IDSMC is the independent data and safety monitoring group for the study, operating under an IDSMC charter. It is an external expert group which, on a regular basis, reviews accumulating study data, evaluates the treatments for excess adverse effects, determines whether the basic study assumptions remain valid, judges whether the overall integrity and conduct of the study remain acceptable, and makes recommendations to the Executive Committee. The IDSMC will carry out an interim analysis of safety on the first 100 patients who complete the 30-day treatment period in the study.

6.9.3 Scientific Advisory Committee (not applicable)

There will be no Scientific Advisory Committee for the study.

7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of Investigational Product(s)

Table 3 Investigational Product

Investigational product	Dosage form and strength	Manufacturer
Dapagliflozin 10 mg	Green, plain, diamond shaped, film coated tablets 10 mg	
Matching placebo for dapagliflozin 10 mg	Green, plain, diamond shaped, film coated tablets placebo	

Dapagliflozin and its matching placebo tablets will be packed in bottles. The tablets may contain lactose, which may cause discomfort in lactose-intolerant individuals.

7.2 Dose and Treatment Regimens

At randomization (Day 1), eligible patients will be randomly assigned to 1 of 2 treatments:

- Dapagliflozin 10 mg, given once daily per oral use

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

The investigational product should be taken as soon as possible after randomization and then once daily in the morning, at approximately the same time every day, during the treatment period of 30 days. If the patient, for any reason is not administered the investigational product in the morning, any other time point during the day may be applied, provided the investigational product is routinely administered in approximately 24-hour intervals. For patients requiring a mechanical ventilator, the tablet will be crushed and flushed with water down the patient's nasogastric (or orogastric) tube. The tube will then be rinsed with water to ensure all the tablet has been consumed.

7.3 Labeling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language.

7.4 Storage

All investigational product should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage conditions.

7.5 Compliance

The administration of all investigational products should be recorded in the appropriate sections of the eCRF.

7.6 Accountability

The investigational product provided for this study will be used only as directed in the study protocol. The study personnel will account for all investigational products dispensed to the patients.

Any investigational product deliberately or accidentally destroyed must be recorded.

For studies where investigational product is destroyed at site: study site personnel, will account for all investigational product received at the site, unused investigational product, and for appropriate destruction. Certificates of delivery, destruction, and return should be signed.

7.7 Concomitant and Other Treatments

All patients will be treated according to local guidelines on standard of care treatment for patients with COVID-19 and existing co-morbidities (including treatment for hypertension,

ischemic heart disease, atrial fibrillation, diabetes, hyperlipidemia), and recorded in the CRF. There are no restricted medications and compassionate use of experimental medications is permitted. However, concomitant treatment with open label SGLT2i (eg, dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, tofogliflozin and luseogliflozin and fixed-dose combinations containing these drugs), is prohibited.

Background medications should be part of clinical practice and will not be provided by the Sponsor.

7.7.1 Other Concomitant Treatment

Medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

7.8 Post-study Access to Study Treatment

Patients will receive their last dose of investigational product on Day 30. Post-study treatment will not be provided by the Sponsor. Patients should receive standard of care therapy after Day 30, at the discretion of the Investigator.

8 STATISTICAL ANALYSES

8.1 Statistical Considerations

All personnel involved with the analysis of the study will remain blinded until the 30-day database lock and protocol violations have been identified and documented.

A comprehensive SAP will be developed and reviewed by the Sponsor prior to first patient randomized. Any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

The analysis will be performed by the Sponsor or its representative, and the results of the key study outcome will be independently validated by an biometrics team.

All analyses described in Sections 8.5.1 to 8.5.6 will be carried out on data collected up to and including Day 30. As soon as the pre-planned number of patients have completed their 30-day treatment period, the database will be locked and unblinding performed for these analyses. After that, data collected on patients ongoing in the 60-day observational follow-up period will be unblinded.

8.2 Sample Size Estimate

The primary objectives of the study are to determine the superiority of dapagliflozin versus

placebo in reducing the incidence of complications or all-cause mortality (prevention of worsening COVID-19) or improving clinical recovery. It is estimated that a sample size of approximately 1200 patients will provide adequate power to detect the treatment effect on prevention or recovery, when the dual endpoints are tested with alpha split between these endpoints.

Since the original protocol was designed, the unpredictable nature of the evolving global pandemic and the change in standard of care for treatment of COVID-19 resulted in lower than expected event rates. As a consequence, faster and more complete recovery has now become an important treatment goal on par with prevention of complications and death in patients hospitalized with COVID-19, prompting the addition of 'recovery' to the primary objectives.

The initial version of the protocol (CSP version 1.0, 10 April 2020) specified an event-driven approach with 380 events needed to detect HR of 0.75 with 80% power. In a fixed follow-up study that would have required 42% of initially randomized 900 patients to experience an event. The provision for a potential increase of sample size was included in the initial design and intended as a way of balancing the possible decrease in event rates, while the recruitment rate of 900 patients was anticipated to occur over a period of approximately 3 months. It is now estimated that around 10 to 20% of patients will develop COVID-19 related complications during the index hospitalization or will experience death during the 30-day treatment period, while 80 to 90% of patients will recover without experiencing worsening. Therefore, the sample size of approximately 1200 patients will provide approximately 100 to 250 events for the first dual primary endpoint (prevention).

With dual primary endpoints of prevention of COVID-19 complications or death and improvement in clinical recovery, an effect on any one will be sufficient evidence of the effectiveness of study medication. This is per the FDA guidance on Multiple Endpoints in Clinical Trials (FDA 2017). To control the type I error for dual primary endpoints, the allocated alpha of 5% will be split between them. Table 4 below shows the true hazard ratio required for 80% power for a hypothetical scenario of an even split of alpha (2.5% two-sided for each primary endpoint) depending on the number of events observed. Since no prior studies are available for SGLT2 inhibitors in the COVID-19 setting, possible scenarios of event rates and treatment effects are considered to infer the sample size (Table 4).

Table 4 2.5% Alpha (80% Power, Time-to-event Analysis)

Number of Events	Hazard Ratio (Dapagliflozin versus Placebo) required for 80% power	Minimal Detectable Hazard Ratio
100	0.54	0.64

Table 4 2.5% Alpha (80% Power, Time-to-event Analysis)

Number of Events	Hazard Ratio (Dapagliflozin versus Placebo) required for 80% power	Minimal Detectable Hazard Ratio
150	0.6	0.69
200	0.65	0.73
250	0.68	0.75

For the second dual primary endpoint (recovery) the sample size of 1200 patients will detect a win ratio (WR) of 1.23 with at least 80% power for hypothetical alpha of 2.5% (The power is calculated based on asymptotic normality property of the win proportion [WP] where WR = WP/[1-WP] and the estimated standard deviation (SD) for the WP is assumed to be SD = 1/sqrt[3] = 0.57735 [Kawaguchi et al 2011], as it is a conservative estimate.) This is based on an overall 1:1 allocation between dapagliflozin and placebo.

Study-wise (overall) type I error multiplicity control strategy and the final allocation of alpha will be specified in the SAP, which will be finalized before database lock.

8.3 Definitions of Analysis Sets

8.3.1 Full Analysis Set

All patients who have been randomized to study treatment will be included in the FAS irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized investigational product assignment, irrespective of the treatment actually received. The FAS will be considered the primary analysis set for the primary, secondary, and exploratory efficacy variables.

8.3.2 Safety Analysis Set

All patients who received at least 1 dose of randomized treatment will be included in the safety population. Patients will be analyzed according to the treatment actually received. The Safety analysis set will be considered the primary analysis set for all safety variables.

8.4 Outcome Measures for Analyses

8.4.1 Primary Outcome Measures

The primary outcome measures are detailed in Section 2.1.

8.4.2 Secondary Outcome Measure

The secondary outcome measures are detailed in Section 2.2.

8.4.3 Safety Outcome Measure

The safety outcome measures are detailed in Section 2.3.

8.4.4 Exploratory Outcome Measure

The exploratory outcome measures are detailed in Section 2.4.

8.5 Methods for Statistical Analyses

For the primary endpoints the following 2 hypotheses will be tested with alpha allocated to each hypothesis to maintain an overall 5% 2-sided significance level:

Prevention

H0:HR [dapagliflozin:placebo] = 1

versus

H1:HR [dapagliflozin:placebo] ≠ 1

Recovery

H0:WR [dapagliflozin:placebo] = 1

versus

H1:WR [dapagliflozin:placebo] ≠ 1

A strong type 1 error control rate will be applied in testing the primary and secondary efficacy endpoints. Details of the multiplicity plan, including allocation of alpha between the dual primary hypotheses, will be provided in the SAP.

8.5.1 Analysis of the Primary Variable(s)

The first primary variable is the time to first event included in the primary composite endpoint.

In this analysis treatments (dapagliflozin versus placebo) will be compared using a Cox proportional hazards model. The p-value, HR, and 95% confidence interval will be reported. The full details of the analysis model will be specified in the SAP.

The contribution of each component of the primary composite endpoint to the overall treatment effect will be examined. Methods similar to those described for the primary analysis will be used to separately analyze the time from randomization to the first occurrence of each component of the primary composite endpoint. HR and 95% confidence intervals will be

reported. Kaplan-Meier estimates of the cumulative incidence to the first occurrence of any event in the primary endpoint will be calculated and plotted.

The second primary variable is a hierarchical composite endpoint. In this analysis treatments (dapagliflozin versus placebo) will be compared using WR analysis methods. The p-value, WR, and 95% confidence interval will be reported. Contribution of each component will be reported as well.

The primary analyses will be based on the intent-to treat principle using the FAS. The full details of the analyses methods will be specified in the SAP.

8.5.2 Analysis of the Secondary Variable(s)

The secondary variables will be analyzed as specified in the SAP.

8.5.3 Subgroup Analysis

Subgroup variables will include demography, baseline disease characteristics, and others. Subgroup analysis will be performed for both dual primary endpoints to examine treatment effects within relevant subgroups separately. The p-values for the subgroup analyses will not be adjusted for multiple comparisons as the tests are exploratory and will be interpreted descriptively.

Treatment differences with 95% confidence intervals will be reported for each subgroup. HRs, WRs, and confidence intervals for overall analysis and subgroups will be presented with forest plots as well. Further details of the subgroup analysis, including the efficacy endpoints and the list of subgroup variables, will be provided in the SAP.

8.5.4 Interim Analysis

Interim analysis for safety only will be performed by the IDSMC after the first 100 patients have completed the 30-day treatment period; no interim efficacy analyses are planned.

8.5.5 Sensitivity Analysis

Details of the sensitivity analysis will be provided in the SAP.

8.5.6 Exploratory Analysis

The exploratory variables will be analyzed as specified in the SAP.

8.5.7 Analysis of the Observational Data

These analyses will be detailed in the SAP.

9 STUDY AND DATA MANAGEMENT

9.1 Training of Study Site Personnel

Before the first patient is entered into the study, a Sponsor representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and train them in any study specific procedures and system(s) utilized. Training will conducted via Skype or another telecommunications application.

The PI in each country will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the Study

During the study, a Sponsor representative will have regular contacts with the study sites to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- As a part of the data collection process, the eCRF platform will have the ability for SDV to be performed remotely, obviating the need for onsite SDV.

The Sponsor representative will be available at any time if the Investigator(s) or other staff at the site needs information and advice about the study conduct.

9.2.1 Source Data

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Refer to the Research Agreement for location of source data.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or

institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

9.2.2 Research Agreement(s)

The PIs in each county should comply with all the terms, conditions, and obligations of the Research Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Research Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of patients, the terms of the Research Agreement shall prevail.

Agreements between the Sponsor and the PIs should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of Study Documents

The Sponsor follows the principles outlined in the Research Agreement.

9.3 Study Timetable and End of Study

The end of the study is defined as ‘the last visit of the last subject undergoing the study’—also known as LSLV.

The study is expected to start in second quarter 2020, with LSLV in the first quarter 2021.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. Sponsor may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin.

9.4 Data Management

Data management will be performed by , according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to WHO Drug Dictionary. Classification coding will be performed by .

Data Collection Instruments

Data collection instruments will be used in this study (eg, eCRFs). These instruments are used to transmit the information collected during the performance of this study to the Sponsor or

Sponsor's designee and regulatory authorities. The Investigator must review the DCIs for completeness and accuracy and must approve all data, including any changes made. Furthermore, the Investigator retains full responsibility for the appropriateness and accuracy of all data collected in the DCIs. As a part of the data collection process, the eCRF platform will have the innate ability for remote SDV to be performed, obviating the need for onsite SDV. If the eCRF is not immediately available for logistical reasons, source documentation will be used and then the data transferred into the eCRF.

The eCRF platform is 21 CFR Part 11 compliant, and complies with all applicable regulations, including the General Data Protection Regulation.

Data validation

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event Reconciliation

Serious AE reconciliation will be done between the study database and the safety database.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

10.2 Subject Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and Regulatory Review

An IRB or IEC should approve the final study protocol, including the final version of the ICF

and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The Investigator should submit the written approval to the Sponsor before enrollment of any patient into the study.

Sponsor should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IEC annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The Sponsor will handle the distribution of any of these documents to the national regulatory authorities.

Sponsor will provide Regulatory Authorities, IRB/IECs and PIs with safety updates/reports according to local requirements.

For the United States, each PI is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. The Sponsor or delegate will provide this information to the PI so that he/she can meet these reporting requirements.

10.4 Informed Consent

The PI(s) at each site will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by IRB/IEC.

10.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the PIs and the Sponsor. Any substantial changes to the study protocol will be documented in a study protocol amendment and, where required, in a new version of the study protocol (Revised Clinical Study Protocol). The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

Sponsor will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to IRB/EC see Section 10.3.

If a protocol amendment requires a change to a site's ICF, the Sponsor and the site's IRB/EC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/EC.

10.6 Audits and Inspections

Authorized representatives of Sponsor, a regulatory authority, or an IRB/IEC may perform audits or inspections at the site, including SDV. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will notify the Sponsor immediately if contacted by a regulatory agency about an inspection at the site.

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Appendix A Additional Safety Information

A 1 Further Guidance on the Definition of a Serious Adverse Event

A 1.1 Life Threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

A 1.2 Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

A 1.3 Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A 1.4 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there

is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? Sponsor would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of ‘related’ is made if following a review of the relevant data, there is evidence for a ‘reasonable possibility’ of a causal relationship for the individual case. The expression ‘reasonable possibility’ of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as ‘not related’.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

A 1.5 Medication Error

For the purposes of this study, a medication error is an unintended failure or mistake in the treatment process for an study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human- or process-related failure while the drug is in control of the study site staff or participant.