

Supplemental Table 1: Baseline Characteristics Based on First Adjudication Committee

Confirmed HHF

	Adjudicated HHF N=588	No adjudicated HHF N=3142
Age, years	67.0±11.2	66.8±11.0
Female sex	126 (21.4)	767 (24.4)
Race		
White	382 (65.0)	2247 (71.5)
Black/African American	59 (10.0)	198 (6.3)
Asian	122 (20.7)	550 (17.5)
Other including mixed races	10 (1.7)	104 (3.3)
Missing	15 (2.6)	43 (1.4)
Region		
North America	97 (16.5)	328 (10.4)
Latin America	168 (28.6)	1118 (35.6)
Europe	201 (34.2)	1152 (36.7)
Asia	105 (17.9)	388 (12.3)
Other	17 (2.9)	156 (5.0)
NYHA class		
II	372 (63.3)	2428 (77.3)
III	210 (35.7)	700 (22.3)
IV	6 (1.0)	14 (0.4)
Body mass index, kg/m ²	28.2±5.7	27.8±5.3
Heart rate, beats/min	73.6±11.8	70.8±11.7
Systolic blood pressure, mmHg	118.8±15.4	122.6±15.6
Diastolic blood pressure, mmHg	73.2±10.7	74.0±10.8
NT-proBNP, pg/mL, median, (IQR)	3090.5 (1709.0 – 5853.0)	1762.0 (1039.0 – 3095.0)

Cause of heart failure		
Ischemic	302 (51.4)	1627 (51.8)
Medical history		
DM at baseline	341 (58.0)	1515 (48.2)
Atrial fibrillation	249 (42.3)	1120 (35.6)
Hypertension	455 (77.4)	2243 (71.4)
History of HHF in the last 12 months	251 (42.7)	900 (28.6)
eGFR		
mL/min/1.73 m ²	58.3±22.2	62.7±21.4
<60 mL/min/1.73 m ²	324 (55.1)	1475 (46.9)
Device therapy		
ICD or CRT-D	227 (38.6)	944 (30.0)
CRT	88 (15.0)	354 (11.3)
Heart failure medication		
ACE inhibitor	241 (41.0)	1462 (46.5)
ARB	151 (25.7)	757 (24.1)
ARNi	116 (19.7)	611 (19.4)
Diuretic other than MRA	554 (94.2)	2694 (85.7)
MRA	400 (68.0)	2261 (72.0)
Beta blocker	549 (93.4)	2984 (95.0)

Data are n (%) or mean +/-SD, unless otherwise stated.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal-prohormone brain natriuretic peptide.

Supplemental Table 2: Baseline Characteristics Based on First Adjudication Committee

Confirmed HHF

	First HHF – SCTI N=520	First HHF – non-SCTI N=68
Age, years	67.1±11.2	66.3±11.5
Female sex	109 (21.0)	17 (25.0)
Race		
White	332 (63.8)	50 (73.5)
Black/African American	52 (10.0)	7 (10.3)
Asian	113 (21.7)	9 (13.2)
Other including mixed races	8 (1.5)	2 (2.9)
Missing	15 (2.9)	0
Region		
North America	89 (17.1)	8 (11.8)
Latin America	142 (27.3)	26 (38.2)
Europe	176 (33.8)	25 (36.8)
Asia	97 (18.7)	8 (11.8)
Other	16 (3.1)	1 (1.5)
NYHA class		
II	330 (63.5)	42 (61.8)
III	185 (35.6)	25 (36.8)
IV	5 (1.0)	1 (1.5)
Body mass index, kg/m ²	28.2±5.8	27.8±5.1
Heart rate, beats/min	73.7±11.9	73.1±11.0
Systolic blood pressure, mmHg	118.3±15.1	122.6±17.3
Diastolic blood pressure, mmHg	73.0±10.6	74.7±11.1
NT-proBNP, pg/mL, median, (IQR)	3264.0 (1806.5–5878.5)	2330.0 (1470.5–4575.0)
Cause of heart failure		

Ischemic	270 (51.9)	32 (47.1)
Medical history		
DM at baseline	302 (58.1)	39 (57.4)
Atrial fibrillation	225 (43.3)	24 (35.3)
Hypertension	402 (77.3)	53 (77.9)
History of HHF in the last 12 months	226 (43.5)	25 (36.8)
eGFR		
mL/min/1.73 m ²	58.3±21.9	58.7±24.4
<60 mL/min/1.73 m ²	290 (55.8)	34 (50.0)
Device therapy		
ICD or CRT-D	204 (39.2)	23 (33.8)
CRT	81 (15.6)	7 (10.3)
Heart failure medication		
ACE inhibitor	211 (40.6)	30 (44.1)
ARB	132 (25.4)	19 (27.9)
ARNi	109 (21.0)	7 (10.3)
Diuretic other than MRA	489 (94.0)	65 (95.6)
MRA	349 (67.1)	51 (75.0)
Beta blocker	482 (92.7)	67 (98.5)
Duration of HHF stay*, median (IQR)	9 (6–16)	8 (5–12)

Data are n (%) or mean +/-SD, unless otherwise stated.

* Duration of HHF stay calculation is based on all HHF events and not restricted to first event.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI,

angiotensin receptor neprilysin inhibitor; CRT-D, cardiac resynchronization therapy

defibrillator; diabetes mellitus; eGFR, estimated glomerular filtration rate; HHF,

hospitalization for heart failure; ICD, implantable cardioverter defibrillator; MRA,

mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-

terminal-prohormone brain natriuretic peptide; and SCTI, Standardized Data Collection for Cardiovascular Trials Initiative.

Supplemental Table 3: Efficacy Outcomes Based on SCTI criteria and no-SCTI criteria

Endpoint	Placebo N=1867		Empagliflozin N=1863		HR (95% CI)	p-value
	N (%)	Inc. rate per 100pt years (95% CI)	N (%)	Inc. rate per 100pt years (95% CI)		
Time to first HHF or CV death, incl. non-SCTI	462 (24.7)	21.00 (19.13, 22.96)	361 (19.4)	15.77 (14.19, 17.44)	0.75 (0.65, 0.86)	<0.0001
Time to first HHF or CV death, excl. non-SCTI	427 (22.9)	19.08 (17.32, 20.94)	351 (18.8)	15.22 (13.67, 16.85)	0.79 (0.69, 0.91)	0.0013
First and recurrent HHF, incl. non-SCTI	553	-	388	-	0.70 (0.58, 0.85)	0.0003
First and recurrent HHF, excl. non-SCTI	487	-	361	-	0.74 (0.61, 0.91)	0.0039

CV, cardiovascular; HHF, hospitalization for heart failure; pt, patient; SCTI, Standardized Data Collection for Cardiovascular Trials Initiative.

Supplemental Table 4: Event Accumulation Based on Investigator vs. CEC assessment

Month of accrual^a	Adjudicated primary endpoint events N	Investigator-reported primary endpoint events N	Additional events N (%)
1	1	1	0 (0)
2	1	1	0 (0)
3	1	2	1 (100)
4	5	8	3 (60)
5	12	16	4 (33)
6	22	29	7 (32)
7	33	40	7 (21)
8	51	60	9 (18)
9	65	77	12 (18)
10	80	100	20 (25)
11	101	124	23 (23)
12	123	147	24 (20)
13	137	166	29 (21)
14	162	195	33 (20)
15	182	218	36 (20)
16	209	242	33 (16)
17	249	286	37 (15)
18	284	332	48 (17)
19	316	364	48 (15)
20	354	412	58 (16)
21	396	467	71 (18)
22	436	513	77 (18)
23	476	555	79 (17)
24	528	613	85 (16)
25	269	665	96 (17)
26	614	719	105 (17)

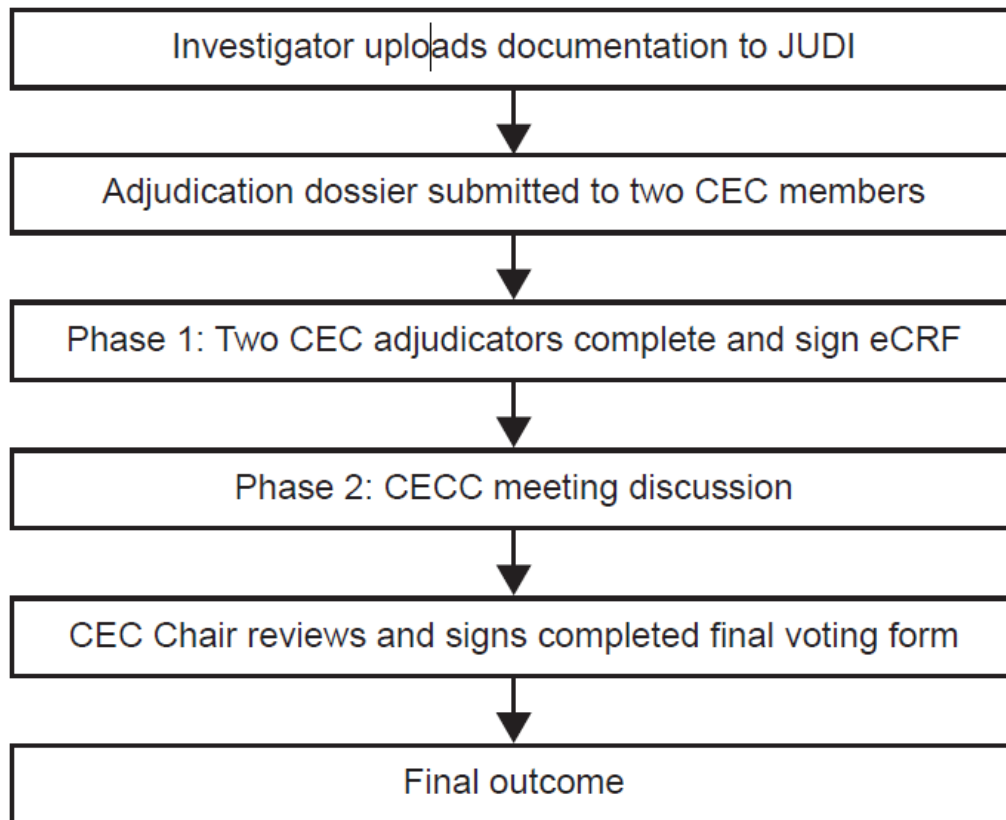
27	657	766	109 (17)
28	690	804	114 (17)
29	718	840	122 (17)
30	760	876	116 (15)
31	795	919	124 (16)
32 ^b	815	945	130 (16)
33	821	949	128 (16)
34	822	950	128 (16)
35	823	951	128 (16)

^a Relative to trial start

^b Start of trial close-out

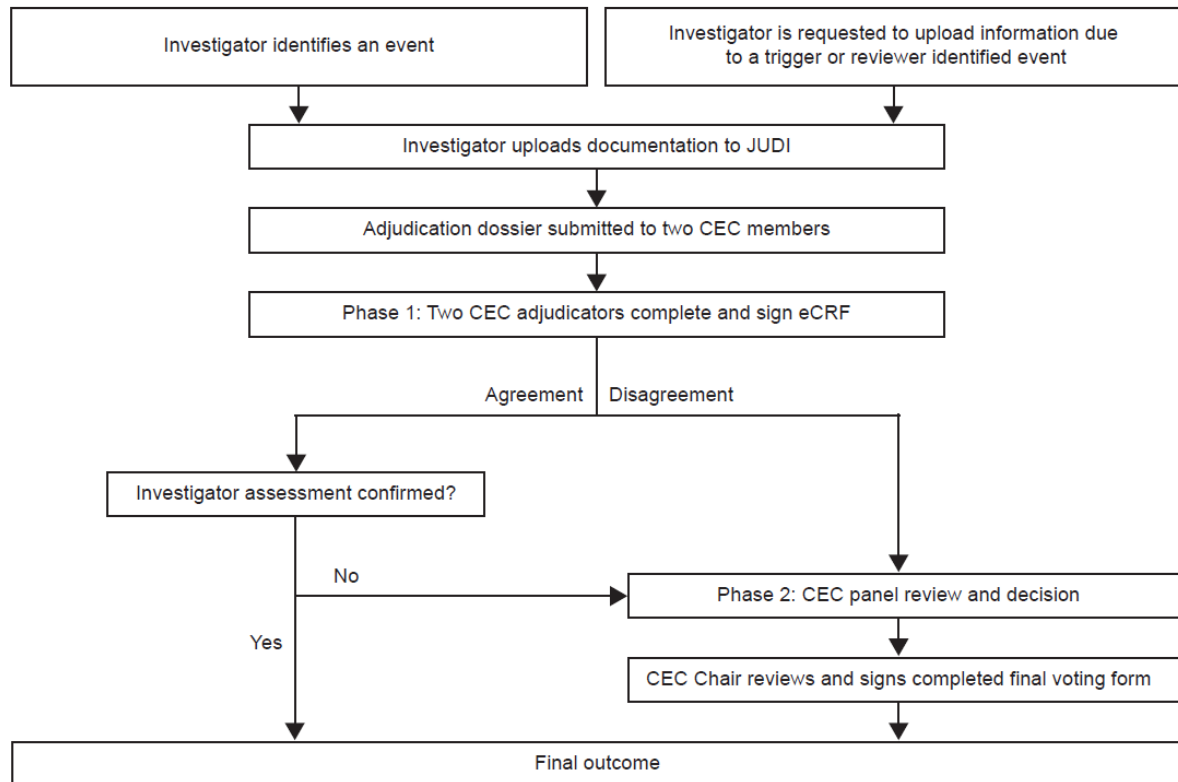
CEC, clinical events committee.

Supplemental Figure 1: Data Process Flow Chart for Fatal Events



CEC, clinical events committee; CECC, clinical events committee cardiology; eCRF, electronic clinical report form; JUDI, the electronic adjudication platform used (AG Mednet).

Supplemental Figure 2: Data Process Flow Chart for Heart Failure Hospitalization



CEC, clinical events committee; CECC, clinical events committee cardiology; eCRF, electronic clinical report form; JUDI, the electronic adjudication platform used (AG Mednet).

Supplemental Methods

ADJUDICATED OUTCOME EVENT DEFINITIONS: HOSPITALIZATION FOR HEART FAILURE AND CAUSE OF DEATH

All cardiovascular endpoint definitions were modifications based on draft recommendations for CDISC August 20, 2014 (Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials for CDISC, Hicks KA et al August 2014) and were included in the Clinical Endpoint Committee (CEC) Charter. The CEC Charter specified that in the case of limited or missing data, the committee was to adjudicate events based on their clinical expertise and the totality of the evidence.

Hospitalization for heart failure

A Heart Failure Hospitalization should include the following criteria:

- 1) The adjudicated primary diagnosis is admission to hospital for heart failure.
- 2) The patient's length-of-stay in hospital extends for at least 12 hours (or a change in calendar date if the hospital admission and discharge times are unavailable). Emergency room visit for ≥ 12 hours with intravenous therapy would be considered equivalent as admission to hospital.
- 3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:
 - a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal dyspnea)
 - b. Decreased exercise tolerance
 - c. Fatigue
 - d. Other symptoms of worsened end-organ perfusion such as dizziness, mental confusion or volume overload such as weight gain or lower extremity swelling.
- 4) The patient has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:
 - a. Physical examination findings considered to be due to heart failure, including new or worsened:
 - i. Peripheral edema
 - ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
 - iii. Pulmonary rales/crackles/crepitations
 - iv. Increased jugular venous pressure and/or hepatojugular reflux
 - v. S3 gallop
 - vi. Clinically significant or rapid weight gain thought to be related to fluid retention
 - b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
 - c. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT proBNP) concentrations consistent with decompensation of heart failure. In patients with

chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

- d. Radiological evidence of pulmonary congestion
- e. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: $E/e' > 15$ or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI))
OR
- f. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m²

5) The patient receives initiation or intensification of treatment specifically for HF, including at least ONE of the following:

- a. Augmentation in oral diuretic therapy. NOTE: If the intensification is solely oral diuretics, the duration of hospitalization must be at least 24 hours.
- b. Intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator)
- c. Mechanical or surgical intervention, including:
 - i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
 - ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis).

An endpoint heart failure hospitalization requires admission to the hospital for heart failure, worsening of symptoms of heart failure, a duration of hospitalization of at least 12 hours, the intensification of heart failure therapy, and a committee consensus that the hospitalization was primarily due to worsening heart failure. Changes in physical signs or laboratory tests, whenever available and documented, will be considered to be supportive.

Cause of death

Cause of death was adjudicated, as either Cardiovascular death or Non-Cardiovascular death. Cause of death was further categorized when possible.

Cardiovascular death includes the following categories:

1. Death due to Acute Myocardial Infarction: refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days after a MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. We note that there may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs ≤ 30 days of the myocardial infarction, it will be considered a death due to myocardial infarction. Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis.

Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.

Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e. chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. Sudden Cardiac Death refers to a death that occurs unexpectedly, not following an acute

MI, and includes the following deaths:

- a. Death witnessed and occurring without new or worsening symptoms
- b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
- c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
- d. Death after unsuccessful resuscitation from cardiac arrest (e.g., implantable cardioverter defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest)
- e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
- f. Unwitnessed death in a subject seen alive and clinically stable ≤ 72 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is noted to be alive ≤ 72 hours of being found dead, sudden cardiac death (criterion 2f) should be recorded. For patients who were not observed alive within 72 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

3. Death due to Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

New or worsening signs and/or symptoms of congestive heart failure (CHF) may include any of the following:

- New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
- Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration
- Confinement to bed predominantly due to heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as the consequence of a primary event
- Cardiogenic shock, manifest as clinical signs and symptoms of hypoperfusion felt to be secondary to cardiac dysfunction, and not occurring in the context of an acute myocardial infarction or as the consequence of a primary arrhythmic event
- Patients who are hospitalized and are being actively treated for heart failure and who have a sudden death as the terminal event will be classified as having a heart failure related death.

4. Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

5. Death due to Cardiovascular Procedures refers to death caused by the immediate complications of a cardiac procedure.

6. Death due to Cardiovascular Hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

Non-cardiovascular death is defined as any death with a specific cause that is not thought to be cardiovascular in nature.

The following is a suggested list of non-CV causes of death:

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g., Systemic Inflammatory Response Syndrome (SIRS) / Immune (including autoimmune) (may include anaphylaxis from environmental (e.g., food allergies)
- Hemorrhage that is neither cardiovascular bleeding or a stroke
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose
- Prescription drug reaction or overdose (may include anaphylaxis)
- Neurological (non-cardiovascular)
- Malignancy
- Other non-CV causes

Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause.

Occasionally, it may not be possible to determine exact causality when 2 lethal conditions contribute to death equally. In this circumstance all events not due solely to non-CV causes should be adjudicated as CV-related.

All events for which there is “lack of information” (e.g., the only available information is “patient died”) or when there is insufficient supporting information or detail to assign the cause of death should be adjudicated as undetermined cause of death.