Official Protocol Title:	RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO ASSESS CARDIOVASCULAR OUTCOMES FOLLOWING TREATMENT WITH ERTUGLIFLOZIN (MK-8835/PF-04971729) IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS AND ESTABLISHED VASCULAR DISEASE, THE VERTIS CV STUDY
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Statistical Analysis Plan for secondary analyses of heart failure and related outcomes in the VERTIS CV trial (Trial B1521021)
Version 4

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VERTIS CV is a multinational, placebo-controlled, double-blind, randomized, parallel-group Phase III trial to assess the impact of ertugliflozin therapy on cardiovascular (CV) outcomes in a population with type 2 diabetes mellitus (T2DM) and a history of atherosclerotic cardiovascular disease (ASCVD).

Here we describe the statistical considerations for additional exploratory analyses to further investigate the impact of ertugliflozin on heart failure (HF)-related outcomes to complement the primary assessment of HHF/CVD death in the primary statistical hierarchy and secondary outcomes of HHF. This document is a supplement to the HF hospitalization and related analyses in the protocol and the primary SAP, and is intended to prospectively specify a series of 'hypothesis-generating analyses'. Additional exploratory analyses may be conducted in the future based upon the results of the pre-specified analyses of HF related outcomes.

1. Background and Rationale

Time to composite of hospitalization for heart failure (HHF) and CV death defined as time from randomization to a confirmed event of hospitalization for HF or CV related death (i.e., an event meeting adjudication criteria) is a pre-specified VERTIS CV outcome included in the primary statistical analysis hierarchy. All reported hospital admissions for HF, including first and any recurrent events, will be CEC adjudicated. In addition HHF alone (time to first) is one of the secondary outcomes.

CEC-adjudicated events of hospitalization for HF are recognized as a standard component in HF development programs (either as an efficacy or a safety parameter, according to the specific program goals). Assessed in a controlled clinical study, the frequency of HF hospitalizations is expected to be driven by acute decompensations and correlate with general HF disease progression in a given cohort. However, although generally accepted by the clinical community, it is recognized that time to first event outcome has a number of limitations. For example, it does not incorporate analysis of recurrent events or does not consider results based on the presence or absence of HF at baseline including type of heart failure (HFrEF; HFpEF). Given the demonstrated benefit for the SGLT2 class on HHF and composite HHF/CV death diabetic population as well as recent publication demonstrating reduction in CV events in subjects with HFrEF without diabetes (DAPA HF reference) there is significant scientific interest in CV outcomes in subjects with different types of HF. Significant proportion of subjects in VERTIS CV had heart failure prior to study enrollment therefore additional prespecified analyses will be conducted to explore effects of ertugliflozin on reduction of HF related CV events/CV death.

Baseline characteristics:

Summary of baseline population characteristics will be presented in a tabular form by a) by presence or absence of prior HF at baseline and-randomized treatment assignment; and b) in subset of patients with prior history of HF by EF: rEF, pEF, and unknown EF and treatment assignment; and c)independent of prior HF status, stratified by EF: rEF; pEF; and Unknown EF and treatment assignment.
Format used will be similar to that in Example of potential display below (CARMELINA paper Table#1)

Overall study population (N = 8246; reference to primary publication)

a) Comparison of baseline characteristics, all ertu versus placebo based on baseline history of heart failure = Yes/No

b) Summary of baseline characteristics among those with prior HF by type of heart failure (same characteristics as above; table would have 3 column headings (HFrEF; HFpEF; HFunkEF + heart failure history = yes but with no baseline EF available)
c) overall study cohort by EF: rEF, pEF, and unknown EF.

McGuire et al Linagliptin and Heart Failure in CARMELINA

Table 1. Baseline Characteristics of Participants in CARMELINA With or Without a History of Heart Failure

Characteristic	Participants With HF at Baseline		Participants Without HF at Baseline		Total CARMELINA Population
	Linagliptin	Placebo	Linagliptin	Placebo	
N (%)	952 (100)	921 (100)	2542 (100)	2564 (100)	6979 (100)
Age, y	66.5 (8.64)	65.8 (8.95)	65.9 (9.2)	65.6 (9.2)	65.9 (9.10)
Male, n (%)	561 (58.9)	581 (63.1)	1587 (62.4)	1661 (64.8)	4390 (62.9)
Race, n (%)					
White	845 (88.8)	813 (88.3)	1982 (78.0)	1956 (76.3)	5596 (80.2)
Asian	38 (4.0)	26 (2.8)	269 (10.6)	307 (12.0)	640 (9.2)
Black/African American	43 (4.5)	57 (6.2)	151 (5.9)	160 (6.2)	411 (5.9)
Other*	26 (2.7)	25 (2.7)	140 (5.5)	141 (5.5)	332 (4.8)
Region, n (%)					
Europe (including South Africa)	589 (61.9)	572 (62.1)	884 (34.8)	889 (34.7)	2934 (42.0)
Latin America	187 (19.6)	192 (20.8)	969 (38.1)	962 (37.5)	2310 (33.1)
North America	142 (14.9)	136 (14.8)	451 (17.7)	451 (17.6)	1180 (16.9)
Asia	34 (3.6)	21 (2.3)	238 (9.4)	262 (10.2)	555 (8.0)
Smoking status, n (%)					
Never smoker	553 (58.1)	539 (58.5)	1344 (52.9)	1317 (51.4)	3753 (53.8)
Ex-smoker	310 (32.6)	300 (32.6)	921 (36.2)	976 (38.1)	2507 (35.9)
Current smoker	88 (9.2)	81 (8.8)	274 (10.8)	269 (10.5)	712 (10.2)
Missing	1 (0.1)	1 (0.1)	3 (0.1)	2 (0.1)	7 (0.1)
History of heart failure, n (%)	952 (100)	921 (100)	0 (0)	0 (0)	1873 (26.8)
Ischemic heart disease, n (%)	745 (78.3)	760 (82.5)	1284 (50.5)	1292 (50.4)	4081 (58.5)
History of hypertension, n (%)	884 (92.9)	855 (92.8)	2287 (90.0)	2323 (90.6)	6349 (91.0)
Atrial fibrillation, n (%)	171 (18.0)	171 (18.6)	148 (5.8)	183 (7.1)	673 (9.6)
eGFR (MDRD), mL/min/1.73 m^2	55.8 (24.3)	55.1 (24.7)	54.2 (25.4)	54.3 (25.0)	54.6 (25.0)
eGFR (MDRD), n (%)					
≥60 mL/min/1.73 m^2	367 (38.6)	367 (39.8)	927 (36.5)	970 (37.8)	2631 (37.7)
≥45 to <60 mL/min/1.73 m^2	208 (21.8)	166 (18.0)	482 (19.0)	492 (19.2)	1348 (19.3)
≥30 to <45 mL/min/1.73 m^2	263 (27.6)	249 (27.0)	731 (28.8)	695 (27.1)	1938 (27.8)
<30 mL/min/1.73 m^2	114 (12.0)	139 (15.1)	402 (15.8)	407 (15.9)	1062 (15.2)
UACR, mg/g, median (25th–75th percentile)	139 (36–589)	158 (46–727)	173 (47–753)	163 (43–758)	162 (44–728)
UACR, n (%)†					
<30 mg/g	215 (22.6)	184 (20.0)	481 (18.9)	512 (20.0)	1392 (19.9)
30–300 mg/g	397 (41.7)	389 (42.2)	1066 (41.9)	1042 (40.6)	2894 (41.5)
>300 mg/g	340 (35.7)	348 (37.8)	993 (39.1)	1009 (39.4)	2690 (38.5)

2. Analysis of time to first event of HF hospitalizations (HHF) and of HHF/CV Death composite

The VERTIS protocol and primary SAP already include (Tables and KM will be available):

a) Secondary hypothesis superiority testing - time to the first composite of HHF/CV death as pre-specified efficacy outcome, which will be analyzed both in the intention-to-treat (CV ITT; primary analysis strategy) and the on treatment analysis (CV FAS with +14 and +30 days censoring window) utilizing Cox Proportional Hazard (CPH) statistical method.
b) Secondary outcome of time to first Hospitalization for HF utilizing CPH model (CVITT and on treatment CV FAS + 14 days)
c) **NEW**: **KM-individual treatment groups (5 mg, 15 mg) for HHF will be generated** (KM - individual treatment groups for the composite already exists)

Additional proposed analysis will include (Tables and KM curves):

I. Time to event analyses using Cox proportional hazards models will be performed for these assessments, using the Fine and Gray method to account for competing risk of non-CV mortality in analyses of the HHF/CV Death composite outcome (CV ITT) and HHF (CV ITT). Exposure times of all patients will be censored at the date they were last known to be free of all components of the individual and composite outcomes analyzed.

II. A supportive analysis for the composite HHF/CV Death and HHF will be performed (CPH, CV ITT) in the subsets of patients with history of HF at baseline (1900/8238; 23.1%), and in those without prior HF. The time to first confirmed event will be modeled univariably with treatment, and also in multivariable analyses including region and baseline type of ASCVD status as ASCVD risk factors. Baseline CVD status /risk factors will include 5 different model terms:
    - CAD,
    - cerebrovascular disease,
    - PVD,
    - prior MI,
    - prior stroke

In addition, univariablee analyses CPH (CV ITT) with factor for HF at baseline will be conducted for:

- MACE;
- HHF/CV Death;
- CV death;
- HHF
- All-cause death

3. Total events (composite of HF hospitalization or CV death)

The classical analysis of time to first event has the disadvantage of excluding all events that occur subsequent to the first. In order to gain maximal information from the study, it is important to consider events that occur after a first non-fatal event has occurred.

I. Analyses will be performed to explore the effect of ertugliflozin on total events including the first and subsequent events for HHF and HHF/CV Death outcomes. Anderson-Gill method will be used as the primary analysis method (CV ITT) to analyze multiple occurrences of these outcomes (1 event, 2 events, ≥3 events), with treatment as an explanatory factor, region as a stratification factor, and history of HF and CVD status at baseline as other factors. CVD status will include CAD, cerebrovascular disease, PVD, prior MI, and prior stroke. A point estimate and two sided 95% confidence interval for the hazard ratio and the resulting p value will be reported. Descriptive statistics will also be reported for recurrent events, displaying the number of patients with 1, 2, and ≥3 events) by treatment group.

Alternative methods for analyses of first + recurrent events, including Wei-Lin-Weisfeld (WLW) method, negative binomial regression and frailty models will not be used in initial analysis but will be provided as sensitivity analyses if requested by the peer review process.

4. Subgroup analyses (table /forest plots).

Analyses of time to first event of HHF and of HHF/CV death (CV ITT), pooled doses, stratified by the following baseline characteristics will be included, using formal test of heterogeneity of the treatment effect among these subgroups:

- Median split for age
- Sex
- Race
- Ethnicity
- Region
- Median split BMI
- Median split for diabetes duration
- Baseline – <8.5, ≥ 8.5% HbA1c
- Baseline UACR (<30; 30-300; and > 300)
- Baseline ACEI/ARB
- Baseline MRA use
- Baseline beta blocker use
- Baseline loop diuretic use
- Baseline insulin use
- Baseline metformin use
- Prior HF
- Ejection Fraction (<40%; 40-50%; >50%; unknown EF)
- Prior MI (Yes/No)
- CAD (Yes/No)
- Atrial fibrillation
- Hypertension
- Baseline eGFR (<45, 45<60, 60 <90, and ≥90) and dichotomously by eGFR <60: Y/N

5. **Additional analyses of time to first primary and key secondary outcomes (CV ITT population) by EF (< 45%; ≥45%; unknown):**

    a) among those with HF at baseline; and

    b) in the overall population regardless of HF history at baseline:

Forest plots will be available for primary and key efficacy outcomes based on presence or absence of prior HF at baseline.

Additional exploratory analyses:

I) Time to first primary and key secondary outcomes stratified by EF (CV ITT population)

Analyses of the primary and key efficacy outcomes will be presented based on type of HF in patients with HF at baseline, and in the entire population regardless of HF presence at baseline (EF cut off <45):

a) 6 groups:
- rEF and HF+
- rEF and HF-
- pEF and HF+
- pEF and HF-
- unk EF and HF+
- unk EF and HF-

b) Entire study population analyses based on EF alone regardless of HF status:
- rEF
- pEF
- unkEF

Data will be produced for:
- MACE;
- CV/HHF composite;
- CV death;
- HHF;
- All-cause death;
- HHF or CV death (all first + recurrent)
- HHF or all-cause death (all first + recurrent)

II) Descriptive summary of readmissions and death among subjects who experienced at least one HHF (CV ITT), Example table 14.2.20 below:

- Descriptive summary of readmissions and deaths among subjects w/ at least one HHF event in study
- Same as previous but broken down by prior HF at baseline
- Same as previous but broken down by EF (45) at baseline
- Same as previous but broken down by HF/EF category at baseline

6. **Absolute difference NNT table for the following outcomes:**
    - MACE
    - CV Death
    - All cause mortality
    - HHF
    - HHF or CV Death

7. **High level summary of key safety findings:**

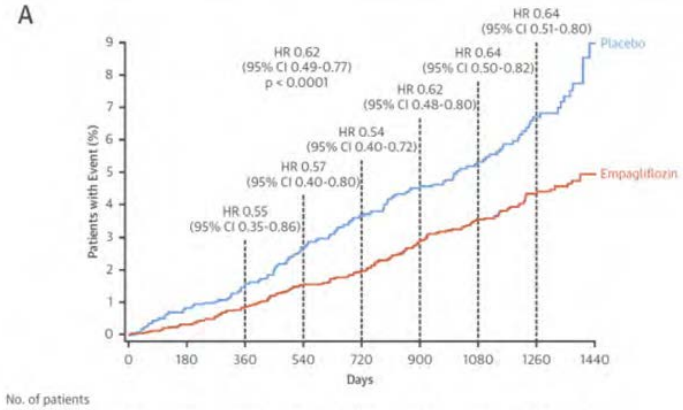
CV SOC table / High Level Group Term or PT (MeDRA dictionary SOC only) (AFib , CHF AEs etc - expecting less AEs in active arm.

APPENDIX 1:

8. Additional future analyses for consideration beyond the initial publication at ESC (perhaps for AHA 2020 or ACC 2021):

I. Benchmark analysis similar to what was presented in prior publications.

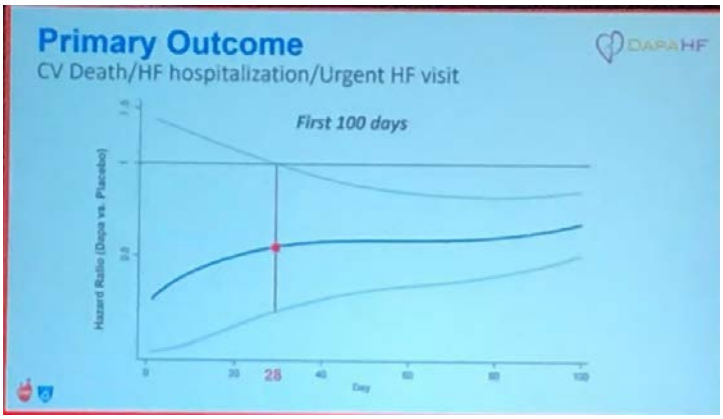
FIGURE 1 Cardiovascular Death Over Time and by Cardiovascular Disease at Baseline, and a Sensitivity Analysis Excluding Presumed Cardiovascular Death



No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cox regression analyses in patients treated with ≥1 dose of study drug

II. Time to onset of effect similar as presented for DAPA HF, AHA meeting 2019.



III. Heart failure risk stratification analysis - paper similar to Berg et al.

Circulation

ORIGINAL RESEARCH ARTICLE

Heart Failure Risk Stratification and Efficacy of Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes Mellitus

Berg et al

Table 2. TRS-HF_{DM} in the Derivation Cohort

Risk Indicator	Adjusted HR (95% CI)	*P* Value	Points
Prior heart failure	4.22 (3.18–5.59)	<0.001	2
Atrial fibrillation	2.26 (1.62–3.14)	<0.001	1
Coronary artery disease	2.06 (1.45–2.93)	<0.001	1
eGFR <60 mL·min^{-1}·1.73 m^{-2}	1.85 (1.40–2.46)	<0.001	1
Urine albumin-to-creatinine ratio			
>300 mg/g	4.50 (3.18–6.36)	<0.001	2
30–300 mg/g	2.08 (1.50–2.87)	<0.001	1

eGFR <60 mL·min^{-1}·1.73 m^{-2} represents chronic kidney disease. Urine albumin-to-creatinine ratio 30–300 mg/g represents moderately increased albuminuria, whereas >300 mg/g represents severely increased albuminuria. eGFR indicates estimated glomerular filtration rate; HR, hazard ratio; TIMI, Thrombolysis in Myocardial Infarction; and TRS-HF_{DM}, TIMI Risk Score for Heart Failure in Diabetes.

Berg et al Heart Failure Risk Stratification in Diabetes

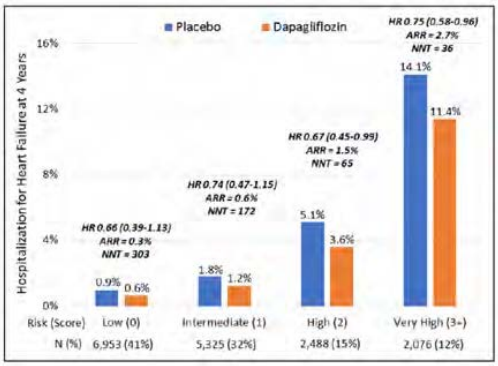


Figure 2. **Treatment effect of dapagliflozin by baseline risk of hospitalization for heart failure.** Although relative risk reductions were similar across risk score categories, absolute reductions in Kaplan-Meier estimates of hospitalization for heart failure risk at 4 years were greater in those at higher baseline risk (χ^2=3.24; 1-sided *P* for trend=0.04). ARR indicates absolute risk reduction; HR, hazard ratio; and NNT, number needed to treat.

IV. Future biomarker analyses in 2021 – biomarkers TBD

APPENDIX 2: Below section includes only key reference points with regards to primary SAP and data collection (background material):

Statistical considerations: Existing key analyses primary SAP:

Stage 2 Analyses

Endpoint	Analysis Set	Statistical Method	Ascertainment Window (Days)	Description
MACE	CV FAS	CPH	365	Primary NI analysis
	CV ITT		No limit	On-study analysis
	CV FAS		14	On-treatment analysis
			30	On-treatment analysis
		Min Risk	365	Sensitivity analysis
CV death/HHF	CV ITT	CPH	No limit	Secondary superiority analysis
	CV FAS		14	On-treatment analysis
			30	On-treatment analysis
CV death	CV ITT	CPH	No limit	Secondary superiority analysis
	CV FAS		14	On-treatment analysis
			30	On-treatment analysis
Renal composite	CV ITT	CPH	No limit	Secondary superiority analysis
	CV FAS		14	On-treatment analysis
			30	On-treatment analysis
MACE plus	CV ITT	CPH	No limit	Secondary analysis
	CV FAS		14	On-treatment analysis
FNF MI	CV ITT	CPH	No limit	Secondary analysis
	CV FAS		14	On-treatment analysis
FNF stroke	CV ITT	CPH	No limit	Secondary analysis
	CV FAS		14	On-treatment analysis
Hospitalization for HF	CV ITT	CPH	No limit	Secondary analysis
	CV FAS		14	On-treatment analysis
All-cause mortality	CV ITT	CPH	No limit	Secondary analysis
	CV FAS		14	On-treatment analysis
Total MACE	CV ITT	Andersen-Gill	No limit	Exploratory analysis
Total CV death/HHF	CV ITT	Andersen-Gill	No limit	Exploratory analysis

MACE=Major Adverse Cardiovascular Event; FNF=Fatal or Non-Fatal; MI=Myocardial Infarction; UA=unstable angina; HF=Heart Failure; NI = Non-Inferiority

Subgroup analysis primary SAP:

For Stage 2, analyses of MACE and the secondary CV endpoints included in the formal testing sequence will be performed in subgroups based on region, gender, age (<65 and ≥65 years), race, ethnicity, category of chronic kidney disease (CKD; based on baseline eGFR: <60, 60 to <90, and ≥90 mL/min/1.73 m^2), history of heart failure, baseline HbA1c (<8.5 and ≥8.5%), baseline BMI (<30 and ≥30 kg/m^2), and use of the following concomitant medications at baseline: statins, ezetimibe, ASA/anti-platelets, diuretics, beta blockers, calcium channel blockers, mineralocorticoid receptor antagonists, renin-

angiotensin-aldosterone system (RAAS) blockers, insulin, DPP-IV inhibitors, metformin, sulfonylureas, and GLP-1 agonists. Selected subgroups (to be specified in the list of tables) will also be analyzed for the renal composite endpoint. These subgroup analyses will be considered exploratory and will not be adjusted for multiple comparisons. The same model used for the primary analysis will be run within each subgroup. The data will also be summarized descriptively by treatment group within each subgroup.

In order to provide model-based point and interval estimates of the hazard ratios for MACE and the endpoints in the formal testing sequence for each dose of ertugliflozin (5 mg and 15 mg), an analysis of Study B1521021 will be conducted using the individual dose groups.

For Stage 2, a summary of the sub-group of subjects experiencing at least one adjudicated and confirmed hospitalization for heart failure will be produced in order to evaluate these subjects for all-cause and CV mortality (including the adjudicated causes of death) and

Key data collection reference points:

Collection of Background CV conditions at baseline:

Associated Vascular Diagnosis (AVD) CRF page: Collected on all subjects with instructions to mark conditions if they met protocol Inclusion #4 criteria:

Coronary Artery Disease	• Select the appropriate response ❖ Absent ❖ Present
Cerebrovascular Disorder	• Select the appropriate response ❖ Absent ❖ Present
Peripheral Arterial Disease	• Select the appropriate response ❖ Absent ❖ Present

Inclusion #4

4. Subjects must have evidence or a history of atherosclerosis involving the coronary, cerebral or peripheral vascular systems as follows **(must have at least one of the following a-d):**

   a. Coronary artery disease as indicated by a history of presumed spontaneous myocardial infarction (hospitalized with final diagnosis of myocardial infarction, excluding peri-procedural or definite secondary myocardial infarction [eg, due to profound anemia or hypertensive emergency, troponin increase in sepsis] in which the most recent event occurred at least 3 months (90 days) prior to the Screening visit (V1); **OR**

   b. Coronary artery disease as indicated by a history of coronary revascularization through either a Percutaneous Coronary Intervention (PCI) at least 3 months (90 days) prior to the Screening visit (V1) or Coronary Artery Bypass Graft (CABG) at least 3 months (90 days) prior to the Screening visit (V1); **OR**

   c. Ischemic (presumed thrombotic) cerebrovascular disease as indicated by a history of ischemic stroke (hospitalized with a final diagnosis of non-hemorrhagic stroke [includes completion of a standard evaluation for stroke in an acute care facility or stroke clinic without hospital admission] with the most recent event occurring at least 3 months (90 days) prior to the Screening visit (V1) or a history of carotid revascularization at least 3 months (90 days) prior to the Screening visit (V1); OR

   d. Peripheral arterial disease as indicated by:

      1. Angiographically-documented peripheral vascular disease; **or**

      2. Resting ankle/brachial index (ABI) of <0.85 (measured by a certified vascular laboratory) plus symptoms of claudication; **or**

      3. Amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia occurring at least 3 months (90 days) prior to the Screening visit (V1).

Blinded data sample based in AVD CRF:

Table 14.1.2.11 (Ertugliflozin Protocol MK-8835-004/B1521021)
Subject Characteristics: Baseline CV Risk Factors, Diabetes Characteristics and Other Factors
CV ITT

	Placebo n	(%)	Ertugliflozin 5 mg n	(%)	Ertugliflozin 15 mg n	(%)	All Ertugliflozin n	(%)	Total n	(%)
Subjects in population	2754		2783		2709		5492		8246	
Albuminuria (mg/g)										
Normal-albuminuria (<30)	1592	(57.8)	1587	(57.0)	1584	(58.5)	3171	(57.7)	4763	(57.8)
Micro-albuminuria (≥30 to ≤300)	820	(29.8)	870	(31.3)	796	(29.4)	1666	(30.3)	2486	(30.1)
Macro-albuminuria (>300)	268	(9.7)	242	(8.7)	244	(9.0)	486	(8.8)	754	(9.1)
Unknown	74	(2.7)	84	(3.0)	85	(3.1)	169	(3.1)	243	(2.9)
History of Hypertension										
No	230	(8.4)	253	(9.1)	242	(8.9)	495	(9.0)	725	(8.8)
Yes	2524	(91.6)	2530	(90.9)	2467	(91.1)	4997	(91.0)	7521	(91.2)
History of Dyslipidemia										
No	686	(24.9)	703	(25.3)	680	(25.1)	1383	(25.2)	2069	(25.1)
Yes	2068	(75.1)	2080	(74.7)	2029	(74.9)	4109	(74.8)	6177	(74.9)
History of Coronary Artery Disease										
No	680	(24.7)	670	(24.1)	640	(23.6)	1310	(23.9)	1990	(24.1)
Yes	2074	(75.3)	2113	(75.9)	2069	(76.4)	4182	(76.1)	6256	(75.9)
History of Cerebrovascular Disease										
No	2135	(77.5)	2126	(76.4)	2094	(77.3)	4220	(76.8)	6355	(77.1)
Yes	619	(22.5)	657	(23.6)	615	(22.7)	1272	(23.2)	1891	(22.9)
History of Peripheral Artery Disease										
No	2199	(79.8)	2290	(82.3)	2215	(81.8)	4505	(82.0)	6704	(81.3)
Yes	555	(20.2)	493	(17.7)	494	(18.2)	987	(18.0)	1542	(18.7)
History of Diabetic Microvascular Disease										

Data in Background publication - presented based on Medical History Blinded data:

Table 14.2.12.12.1 (Ertugliflozin Protocol MK-8835-004/B1521021)
Selected Baseline CV Conditions
CV ITT

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	2754		2783		2709		5492		8246	
Established CV disease										
No	19	(0.7)	22	(0.8)	18	(0.7)	40	(0.7)	59	(0.7)
Yes	2735	(99.3)	2761	(99.2)	2690	(99.3)	5451	(99.3)	8186	(99.3)
MI (Cardiac SOC)	**1293**	**(46.9)**	**1346**	**(48.4)**	**1315**	**(48.5)**	**2661**	**(48.5)**	**3954**	**(48.0)**
Acute myocardial infarction	222	(8.1)	236	(8.5)	224	(8.3)	460	(8.4)	682	(8.3)
Myocardial infarction	1084	(39.4)	1117	(40.1)	1103	(40.7)	2220	(40.4)	3304	(40.1)
Silent myocardial infarction	5	(0.2)	10	(0.4)	9	(0.3)	19	(0.3)	24	(0.3)
Coronary revascularization (Procedures SOC)	**1598**	**(58.0)**	**1587**	**(57.0)**	**1605**	**(59.2)**	**3192**	**(58.1)**	**4790**	**(58.1)**
CABG	**602**	**(21.9)**	**621**	**(22.3)**	**592**	**(21.9)**	**1213**	**(22.1)**	**1815**	**(22.0)**
PCI	**1162**	**(42.2)**	**1151**	**(41.4)**	**1176**	**(43.4)**	**2327**	**(42.4)**	**3489**	**(42.3)**
Coronary angioplasty	273	(9.9)	292	(10.5)	266	(9.8)	558	(10.2)	831	(10.1)
Coronary arterial stent insertion	491	(17.8)	461	(16.6)	514	(19.0)	975	(17.8)	1466	(17.8)
Coronary endarterectomy	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)	1	(0.0)
Coronary revascularisation	56	(2.0)	57	(2.0)	69	(2.5)	126	(2.3)	182	(2.2)
Percutaneous coronary intervention	471	(17.1)	493	(17.7)	485	(17.9)	978	(17.8)	1449	(17.6)
Other	**61**	**(2.2)**	**61**	**(2.2)**	**74**	**(2.7)**	**135**	**(2.5)**	**196**	**(2.4)**
Stroke (Nervous system disorders)	**562**	**(20.4)**	**615**	**(22.1)**	**562**	**(20.7)**	**1177**	**(21.4)**	**1739**	**(21.1)**
Brain stem infarction	0	(0.0)	4	(0.1)	1	(0.0)	5	(0.1)	5	(0.1)
Brain stem stroke	0	(0.0)	2	(0.1)	1	(0.0)	3	(0.1)	3	(0.0)

HF population - defined based on medical history – presented based on narrow Cardiac Failure SMQ

Table 14.2.12.12.1 (Ertugliflozin Protocol MK-8835-004/B1521021)
Selected Baseline CV Conditions
CV ITT

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Cerebellar infarction	1	(0.0)	3	(0.1)	4	(0.1)	7	(0.1)	8	(0.1)
Cerebral infarction	24	(0.9)	32	(1.1)	31	(1.1)	63	(1.1)	87	(1.1)
Cerebrovascular accident	60	(2.2)	59	(2.1)	64	(2.4)	123	(2.2)	183	(2.2)
Ischaemic cerebral infarction	2	(0.1)	4	(0.1)	3	(0.1)	7	(0.1)	9	(0.1)
Ischaemic stroke	486	(17.6)	531	(19.1)	471	(17.4)	1002	(18.2)	1488	(18.0)
Lacunar infarction	9	(0.3)	9	(0.3)	5	(0.2)	14	(0.3)	23	(0.3)
Thalamic infarction	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Heart Failure	**654**	**(23.7)**	**652**	**(23.4)**	**627**	**(23.1)**	**1279**	**(23.3)**	**1933**	**(23.4)**
Acute left ventricular failure	1	(0.0)	2	(0.1)	0	(0.0)	2	(0.0)	3	(0.0)
Acute pulmonary oedema	2	(0.1)	4	(0.1)	1	(0.0)	5	(0.1)	7	(0.1)
Cardiac asthma	0	(0.0)	1	(0.0)	2	(0.1)	3	(0.1)	3	(0.0)
Cardiac failure	9	(0.3)	8	(0.3)	14	(0.5)	22	(0.4)	31	(0.4)
Cardiac failure acute	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)	1	(0.0)
Cardiac failure chronic	630	(22.9)	631	(22.7)	593	(21.9)	1224	(22.3)	1854	(22.5)
Cardiac failure congestive	8	(0.3)	7	(0.3)	5	(0.2)	12	(0.2)	20	(0.2)
Cardiogenic shock	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Chronic left ventricular failure	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Cor pulmonale	0	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)	1	(0.0)
Cor pulmonale chronic	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)
Ejection fraction decreased	1	(0.0)	0	(0.0)	1	(0.0)	1	(0.0)	2	(0.0)
Left ventricular failure	8	(0.3)	7	(0.3)	12	(0.4)	19	(0.3)	27	(0.3)
Pulmonary oedema	6	(0.2)	6	(0.2)	7	(0.3)	13	(0.2)	19	(0.2)
Ventricular failure	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

NYHA – collected in subjects with HF at baseline – data collected retrospectively:

Table 14.2.12.12.1 (Ertugliflozin Protocol MK-8835-004/B1521021)
Selected Baseline CV Conditions
CV ITT

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
NYHA Functional Classification										
Class I	157	(5.7)	149	(5.4)	155	(5.7)	304	(5.5)	461	(5.6)
Class II	436	(15.8)	448	(16.1)	407	(15.0)	855	(15.6)	1291	(15.7)
Class III	50	(1.8)	49	(1.8)	44	(1.6)	93	(1.7)	143	(1.7)
Class IV	1	(0.0)	1	(0.0)	1	(0.0)	2	(0.0)	3	(0.0)

Every subject is counted a single time for each applicable specific condition. A subject with multiple conditions within a bolded category is counted a single time for that bolded category.
Data cut date: 14Oct2019
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 12DEC2019 Date of Table Creation: 09JAN2020(8:46)
Source: [P004MK8835: adam-adsl; adcf; admh]

EF collection: data collection in all subjects if available. In case of multiple historical measurements in the same patient, sites were asked to repost EF based on the test obtained closest to randomization (prior to):

Table 14.2.12.15 (Ertugliflozin Protocol MK-8835-004/B1521021)
Classification of Ejection Fraction Prior to Randomization
CV ITT

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	2754		2783		2709		5492		8246	
In the full CV ITT population										
Subjects with EF data prior to randomization	1678	(60.9)	1685	(60.5)	1642	(60.6)	3327	(60.6)	5005	(60.7)
0-1 year prior to randomization	582	(21.1)	602	(21.6)	593	(21.9)	1195	(21.8)	1777	(21.5)
EF reduced: ≤ 40%	69	(2.5)	57	(2.0)	73	(2.7)	130	(2.4)	199	(2.4)
EF preserved: > 40%	513	(18.6)	545	(19.6)	520	(19.2)	1065	(19.4)	1578	(19.1)
0-2 year prior to randomization	915	(33.2)	901	(32.4)	851	(31.4)	1752	(31.9)	2667	(32.3)
EF reduced: ≤ 40%	104	(3.8)	96	(3.4)	99	(3.7)	195	(3.6)	299	(3.6)
EF preserved: > 40%	811	(29.4)	805	(28.9)	752	(27.8)	1557	(28.4)	2368	(28.7)
0-3 year prior to randomization	1105	(40.1)	1086	(39.0)	1046	(38.6)	2132	(38.8)	3237	(39.3)
EF reduced: ≤ 40%	123	(4.5)	122	(4.4)	125	(4.6)	247	(4.5)	370	(4.5)
EF preserved: > 40%	982	(35.7)	964	(34.6)	921	(34.0)	1885	(34.3)	2867	(34.8)
0-5 year prior to randomization	1347	(48.9)	1335	(48.0)	1263	(46.6)	2598	(47.3)	3945	(47.8)
EF reduced: ≤ 40%	151	(5.5)	152	(5.5)	149	(5.5)	301	(5.5)	452	(5.5)
EF preserved: > 40%	1196	(43.4)	1183	(42.5)	1114	(41.1)	2297	(41.8)	3493	(42.4)
Any time prior to randomization	1678	(60.9)	1685	(60.5)	1642	(60.6)	3327	(60.6)	5005	(60.7)
EF reduced: ≤ 40%	179	(6.5)	173	(6.2)	189	(7.0)	362	(6.6)	541	(6.6)
EF preserved: > 40%	1499	(54.4)	1512	(54.3)	1453	(53.6)	2965	(54.0)	4464	(54.1)

Table 14.2.12.15 (Ertugliflozin Protocol MK-8835-004/B1521021)
Classification of Ejection Fraction Prior to Randomization
CV ITT

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
In subjects with a history of heart failure †										
Subjects with EF data prior to randomization ‡	498		492		476		968		1466	
0-1 year prior to randomization	204	(41.0)	208	(42.3)	211	(44.3)	419	(43.3)	623	(42.5)
EF reduced: ≤ 40%	42	(8.4)	37	(7.5)	46	(9.7)	83	(8.6)	125	(8.5)
EF preserved: > 40%	162	(32.5)	171	(34.8)	165	(34.7)	336	(34.7)	498	(34.0)
0-2 year prior to randomization	319	(64.1)	312	(63.4)	289	(60.7)	601	(62.1)	920	(62.8)
EF reduced: ≤ 40%	61	(12.2)	63	(12.8)	60	(12.6)	123	(12.7)	184	(12.6)
EF preserved: > 40%	258	(51.8)	249	(50.6)	229	(48.1)	478	(49.4)	736	(50.2)
0-3 year prior to randomization	359	(72.1)	362	(73.6)	338	(71.0)	700	(72.3)	1059	(72.2)
EF reduced: ≤ 40%	70	(14.1)	71	(14.4)	73	(15.3)	144	(14.9)	214	(14.6)
EF preserved: > 40%	289	(58.0)	291	(59.1)	265	(55.7)	556	(57.4)	845	(57.6)
0-5 year prior to randomization	433	(86.9)	419	(85.2)	392	(82.4)	811	(83.8)	1244	(84.9)
EF reduced: ≤ 40%	81	(16.3)	83	(16.9)	86	(18.1)	169	(17.5)	250	(17.1)
EF preserved: > 40%	352	(70.7)	336	(68.3)	306	(64.3)	642	(66.3)	994	(67.8)
Any time prior to randomization	498	(100.0)	492	(100.0)	476	(100.0)	968	(100.0)	1466	(100.0)
EF reduced: ≤ 40%	93	(18.7)	91	(18.5)	99	(20.8)	190	(19.6)	283	(19.3)
EF preserved: > 40%	405	(81.3)	401	(81.5)	377	(79.2)	778	(80.4)	1183	(80.7)

Subjects with EF data are classified in all applicable time periods based on the most recent EF results prior to randomization.
† History of heart failure is defined as baseline condition coding to narrow heart failure SMQ.
‡ Used as the denominator for all categories below.
EF = ejection fraction.
Data cut date: 14Oct2019
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 08JAN2020 Date of Table Creation: 08JAN2020(17:48)
Source: [P004MK8835: adam-adsl; adbase]

Reference points from publications:

DAPA HF-NEJM (contribution of urgent visits was minimal to overall endpoints pool)

Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

Variable	Dapagliflozin (N=2373)		Placebo (N=2371)		Hazard or Rate Ratio or Difference (95% CI)	P Value
	values	*events/100 patient-yr*	*values*	*events/100 patient-yr*		
Efficacy outcomes						
Primary composite outcome — no. (%)†	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)	<0.001
Hospitalization or an urgent visit for heart failure	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59 to 0.83)	NA
Hospitalization for heart failure	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)	NA
Urgent heart-failure visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)	NA
Cardiovascular death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)	NA