Supplementary Online Content

McGuire DK, Van de Werf F, Armstrong PW, et al; Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) Study Group. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial. *JAMA Cardiol*. Published online April 13, 2016. doi:10.1001/jamacardio.2016.0103.

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Prospective Statistical Analysis Plan for Analyzing Heart Failure-Related Outcomes in the TECOS Trial

TECOS is a multinational, placebo-controlled, double-blind, randomized, parallel-group pragmatic Phase III study to assess the impact of sitagliptin therapy on cardiovascular (CV) outcomes in a population with type 2 diabetes mellitus (T2DM) and inadequate glycemic control and a history of cardiovascular disease (CVD).

The primary Statistical Analysis Plan (SAP) of the study detailing the statistical methods for the analyses and summaries of efficacy, safety and other study data that are to be performed to help support the completion of the Clinical Study Report (CSR), has been written and approved on 12th September, 2014.[1]

The purpose of this memo is to describe the statistical considerations for additional exploratory analyses to further investigate the potential impact of sitagliptin on time to hospitalization due to congestive heart failure (CHF), a pre-specified and adjudicated endpoint in TECOS, and to provide further clarification on background, rationale and details of the analyses. This document is a supplement to the CHF hospitalization analyses in the protocol and the primary SAP, and is merely intended to specify 'hypothesis-generating analyses' further noting that the study has not been prospectively designed or powered to formally address these questions.

Additional exploratory analyses may be conducted based upon the results of the pre-specified analyses of time to CHF hospitalizations. If the hazard for the time to event for CHF hospitalization is altered in a potentially clinically relevant or statistically significant manner by sitagliptin, further analyses may be conducted to clarify and enhance the understanding of the time to event results.

1. Background and Rationale

Time to hospitalization for congestive heart failure (CHF) defined as time from randomization to a confirmed event of hospital admission for CHF (i.e., an event meeting adjudication criteria that include requiring treatment with intravenous diuretics, inotropes, or vasodilator therapy, and confirmed by the CEC) is a pre-specified TECOS secondary endpoint. All reported hospital admissions for CHF will be CEC adjudicated.

CEC-adjudicated events of hospitalization for CHF are recognized as a standard component in CHF 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 CHF hospitalizations is expected to be driven by acute decompensations and correlate with general CHF disease progression in a given cohort. However, although generally accepted by the clinical community, it is recognized that this endpoint has a number of limitations. For example, it does not incorporate outpatient CHF-related events (e.g., CHF treatment initiation or modification), or events not requiring intravenous diuretic use, and may also be subject to other influences not related to the incidence/severity of the CHF event such as regional differences in hospitalization and CHF treatment standards.

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 (SAVOR-TIMI 53) trial,[2] a 27% (3.5% vs. 2.8%, HR: 1.27; 95% CI, 1.07 to 1.51; p=0.007) increase for the secondary outcome "time to hospitalization for heart failure" was reported for saxagliptin as compared to placebo. In addition, the limited data available from the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) showed a non-statistically significant, numerically greater number of cases of congestive heart failure hospitalization (within the primary composite endpoint) for the alogliptin treated group (HR 1.07, 95% CI: 0.79-1.46).[3]

In view of the CHF hospitalization trends seen in SAVOR-TIMI 53 and EXAMINE, the following additional analyses on CHF hospitalizations will be specified before the data base lock occurs.

2. Analysis of CHF hospitalizations

The TECOS protocol and primary SAP include time to CHF hospitalization as a pre-specified secondary outcome, which will be analyzed both in the intention-to-treat (ITT) and the per protocol (PP) populations.

For the time to confirmed CHF hospitalization analysis, the primary SAP states that the treatment effect will be evaluated using a Cox proportional hazards model that includes treatment as an explanatory factor, region as a stratification factor, and history of CHF and CVD status at baseline as other factors. See Section 5.6 in the primary SAP.

2.1 Composite of CHF hospitalization or CV-related death

A composite endpoint of confirmed CHF hospitalization or CV-related death will also be assessed for both the ITT and the per protocol populations. A time to event analysis using the Cox proportional hazards model described earlier will be performed for the following endpoints to explore the potential impact of sitagliptin on confirmed events for

- Composite of CHF hospitalization or CV-related death
- CHF hospitalization (described in the primary SAP)
- CV related death (described in the primary SAP)

A supportive analysis for the composite and components of the composite will be performed in the subset of patients with history of CHF at baseline (~18%/n~2600). The time to first confirmed event will be modeled with treatment, region and baseline CVD status as factors.

2.2 Total events (composite of CHF hospitalization or CV related 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 the first event has occurred. At the time of authoring the memo, preliminary, blinded data on CHF hospitalization based on site-reported data (inpatient hospitalization records) indicated that the total number of patients with CHF hospitalization events is about 571 (414 patients with 1 event only, 99 patients with 2 events only, 58 patients with ≥ 3 events). These numbers are likely to be reduced after adjudication, since not all events are likely to be confirmed as meeting all criteria for hospitalization for CHF. Similar numbers of CV deaths were seen (n=539) from blinded data.

An analysis will be performed to explore the effect of sitagliptin when used as part of usual care compared to usual care without sitagliptin on total events including the first and subsequent events in the composite endpoint. The Andersen–Gill[4] method will be used to analyze multiple occurrences of the composite endpoint (1 event, 2 events, ≥ 3 events) with treatment as an explanatory factor, region as a stratification factor, and history of CHF and CVD status at baseline as other factors. A point estimate and two sided 95% confidence interval for the hazard ratio and the resulting p value will be reported.

2.3 Other Statistical Considerations

It is important to recognize that the endpoints outlined in this memo are additional to those planned at the start of the trial (added based upon new results from other DPP4 inhibitors available only after initiation of TECOS), and not analyzed under strict hierarchical statistical testing planned for key endpoints associated with hypotheses. Therefore results need to be interpreted carefully since these exploratory analyses are not adjusted for multiplicity; only unadjusted p values will be reported.

The time to event analysis (Cox regression) relies on the assumption of non-informative censoring. To examine this assumption, variables that may be related to patient dropout, e.g., the most frequent major protocol deviation, certain AEs, etc. will be explored as indicated in Sections 4.4 and 4.5 of the primary SAP.

Note that the above post-hoc analyses will be exploratory and are only intended to help in the understanding of an increase, if an increase is observed.

eAppendix 2. Clinical Events Committee Charter Definition of Congestive Heart Failure (CHF) Requiring Hospitalization

All episodes of suspected CHF requiring hospitalization will be reported by the site investigator on the eCRF. CHF events that meet the following criteria will be study endpoints

1. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that result in at least a 12 hour stay (or a date change if the time of admission/discharge is not available).

AND

2. Clinical manifestation of CHF including at least one of the following: New or worsening: dyspnea, orthopnea, paroxysmal nocturnal dyspnoea, edema, pulmonary basilar crackles, jugular venous distension, or radiological evidence of worsening heart failure.

AND

3. Additional / increased therapy
    a. Intravenous treatment with diuretic, inotrope, or vasodilator therapy

    OR

    b. Mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function) or the use of ultrafiltration, hemofiltration or dialysis that is specifically directed at treatment of heart failure.

Congestive Heart Failure (CHF) events will be reviewed using the following approach:
(Please note that validation of the algorithm will be done by a clinician (CECC coordinator or CECC MD)

1. Data will be collected on the eCRF based on the endpoint definition
2. A Computer Algorithm will be created to assess the data on the eCRF
3. The algorithm will be a series of logic statements evaluating the eCRF data to determine if the data provided is consistent and supports the endpoint criteria.
4. If the data are consistent and data are complete on the eCRF then the algorithm will determine if an endpoint CHF event did or did not occur. If the data are nonconsistent or data are not complete despite query process, then the algorithm will not make a determination and the event will be reviewed by one CECC MD and a determination made about whether an endpoint CHF event did or did not occur.
5. The algorithm will be validated by a clinician. The clinician will review the algorithmic determinations about whether a CHF event did or did not occur for those that a decision is made for the first 25 events.
6. If there are discrepancies found in the algorithm the CECC coordinator will note these to the data manager and have all CHF events reviewed manually until the discrepancy is resolved.

A clinician will validate the algorithm on the next 10 CHF events after the discrepancy has been resolved to ensure that it supports the endpoint criteria.

eTable 1. Baseline Characteristics of Patients in the TECOS Intention-to-Treat Population With Prior Heart Failure at Baseline Stratified by Randomized Treatment Assignment

	Sitagliptin n=1303	**Placebo n=1340**
Age, years	66.7 (8.1)	66.9 (8.2)
Women, %	36.1	34.8
Race/ethnicity, %		
White	82.3	83.8
Black	1.8	1.8
Asian	5.8	4.9
Other	10.0	9.6
Not Hispanic or Latino	87.0	85.8
Hispanic or Latino	13.0	14.2
Region, %		
North America	12.1	11.6
Latin America	10.9	12.0
Western Europe	11.7	11.3
Eastern Europe	55.5	57.2
Asia Pacific/other	9.8	7.8
Duration of diabetes, years	11.3 (8.1)	11.7 (8.6)
Qualifying A_{1c}, %	7.2 (0.5)	7.2 (0.5)
Qualifying A_{1c} categories, %		
<7%	34.9	37.8
≥7-<7.5%	29.6	29.1
≥7.5%	35.5	33.1
eGFR, mL/min/1.73m^2	72.5 (22.0)	70.6 (21.0
Prior vascular disease, %	99.5	99.6
Coronary artery disease	82.4	82.8
Cerebrovascular disease	25.4	25.1
Peripheral artery disease	14.4	12.9
Prior myocardial infarction	59.4	60.7
NYHA heart failure class, %		
I	21.9	18.7
II	49.0	50.3
III	12.8	14.4
IV	0.3	0.7
Not available	16.0	16.0
Systolic blood pressure, mmHg	135.4 (17.1)	135.6 (17.2)
Diastolic blood pressure, mmHg	78.5 (10.5)	78.6 (10.5)
Weight, kg	90.0 (19.0)	89.7 (18.8)
Body mass index, kg/m^2	31.8 (5.7)	31.7 (5.5)
Cigarette smoking, %		
Current	11.1	10.5
Former	38.7	40.4
Never	50.3	49.0
Antihyperglycemic therapies, %		
Metformin	72.1	73.6
Sulfonylurea	42.3	43.0
Thiazolidinedione	1.3	1.6
Insulin	29.6	28.6
Cardiovascular medications, %		

Statins	76.7	76.9
Aspirin	74.7	75.9
Non-aspirin anti-platelet agents	17.6	17.9
ACE inhibitors/angiotensin receptor blockers	85.0	85.1
Beta blockers	78.0	77.8
Diuretics	59.9	59.5
Calcium channel blockers	34.5	34.3

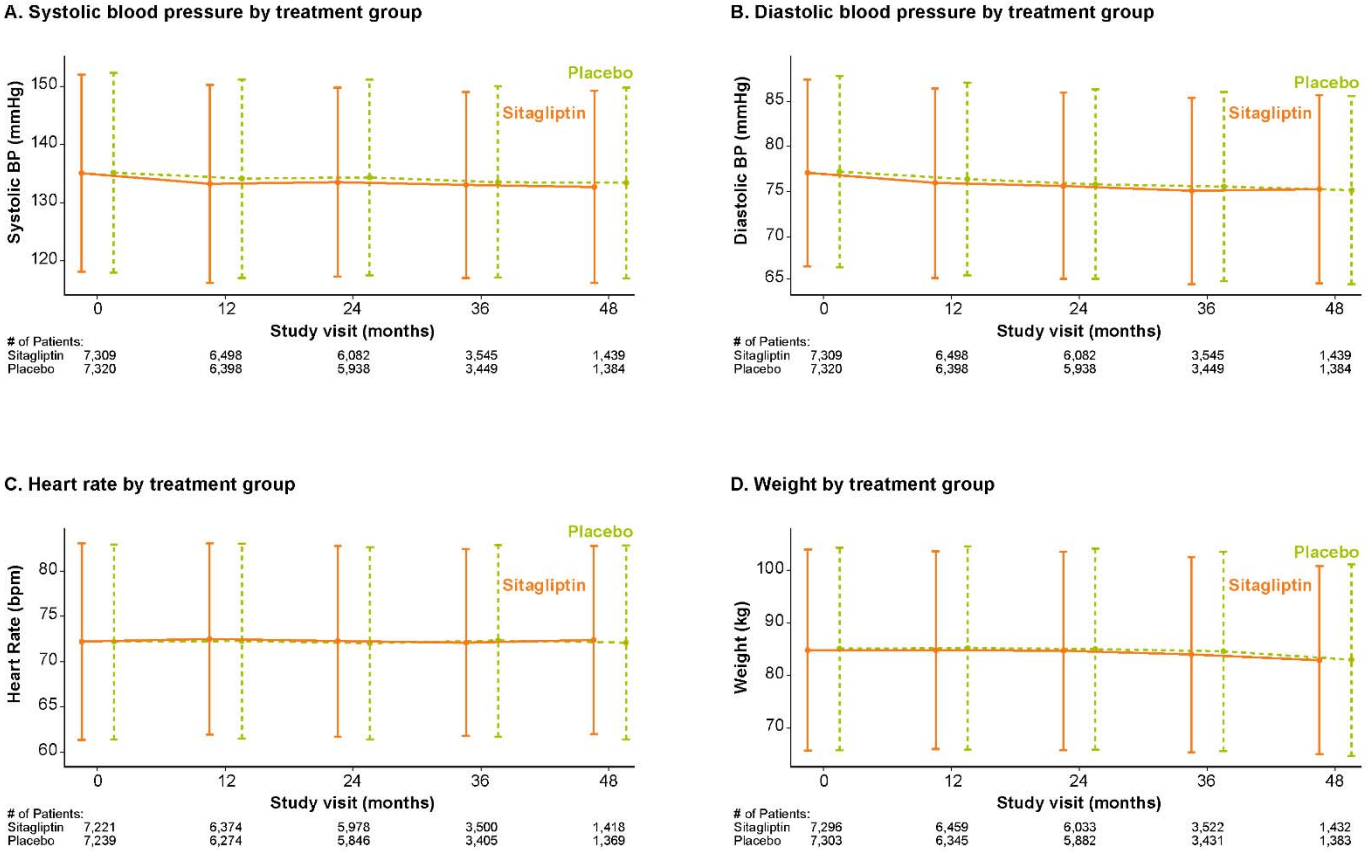
Data are mean (SD) or %. A_{1c} indicates glycated hemoglobin; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme.

eTable 2. Selected Baseline Characteristics From the EXAMINE, SAVOR-TIMI 53, and TECOS Cardiovascular Outcomes Trials of DPP4 Inhibitors[2,5-7]

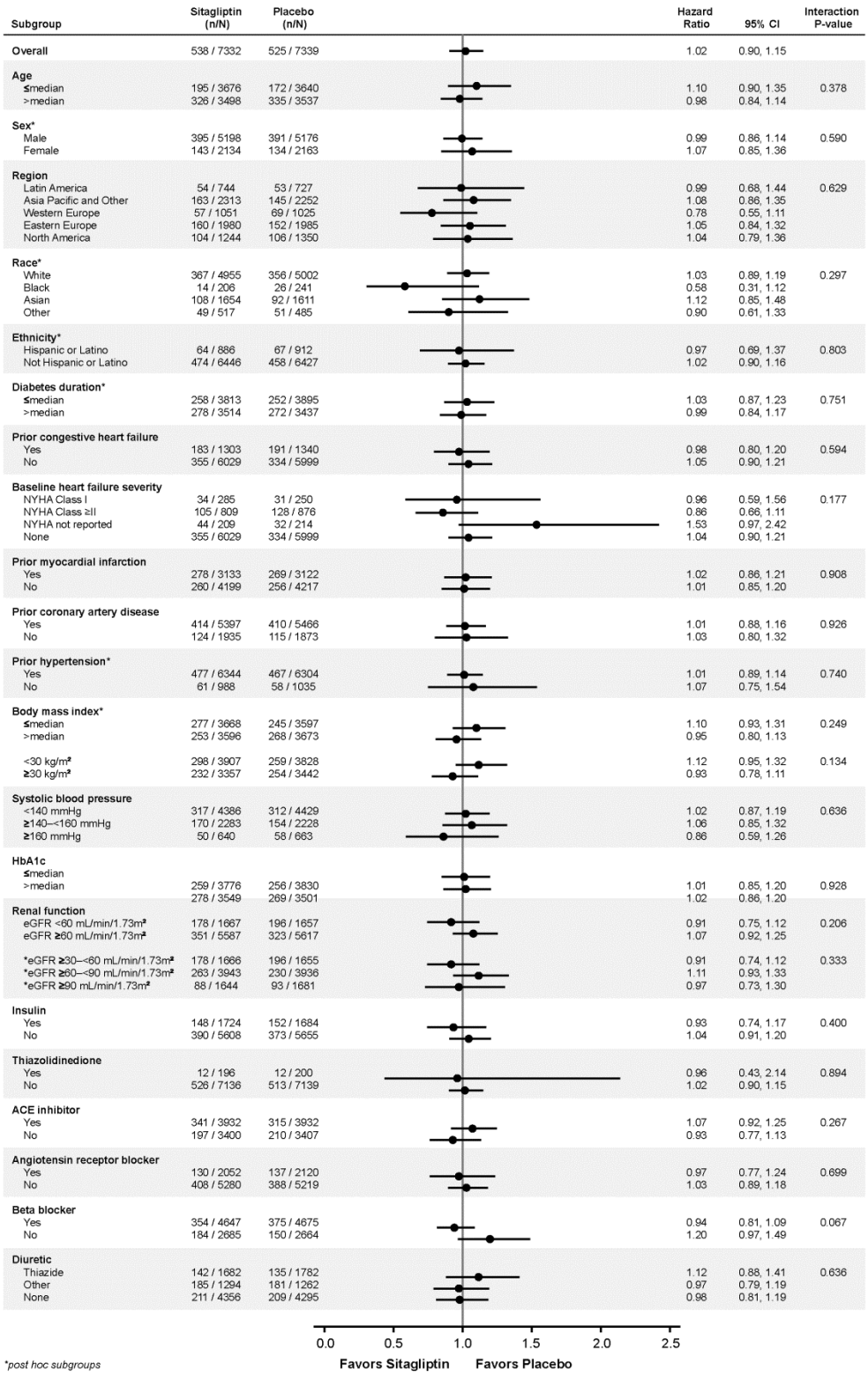
	EXAMINE	SAVOR-TIMI 53	TECOS
Mean age, years	61	65	66
Median duration of DM	7.3	10.3	10.0
Mean A_{1c}, %	8.0	8.0	7.2
Hypertension, %	83	82	86
Mean blood pressure, mmHg	Not reported	137/79	135/77
Dyslipidaemia, %	Not reported	71	77
Mean LDL-cholesterol, mg/dl	78.7	Not reported	91
Current smoker, %	14	Not reported	11
Previous heart failure, %	28	13	18
Median duration of follow-up, years	1.5	2.1	3.0
Aspirin, %	90.3	75.3	78.5
Statin, %	90.5	78.4	79.9
RAAS blockade*, %	82.0	82.2	78.8
Beta-blocker, %	82.0	61.6	63.5

*SAVOR-TIMI 53 estimated by adding reported ACE inhibitor + angiotensin receptor blocker.

eFigure 1. Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, and Weight by Treatment Group



eFigure 2. Forest Plot of Stratified Analyses for Sitagliptin vs. Placebo on the Composite Outcome of Hospitalization for Heart Failure or Cardiovascular Death



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