Introductory Remarks

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting

June 28, 2016

NDA# 204629

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ODEII, OND, CDER, US Food and Drug Administration

Introduction

- The EMPA-REG outcomes study was required by the FDA to evaluate CV-risk
- The study is the **first** large prospective randomized controlled trial **to report a cardiovascular benefit** of an antidiabetic drug
- The committee was convened to discuss whether the findings **establish that empagliflozin is effective in reducing cardiovascular risk** such that a new use (indication) for this product should be added to the existing drug label

Indications

- **Old:** *In adult patients with type 2 diabetes mellitus and high cardiovascular risk to reduce the risk of all-cause mortality by reducing the incidence of cardiovascular death and to reduce the risk of cardiovascular death or hospitalization for heart failure*
- **New:** *In adult patients with type 2 diabetes mellitus and established cardiovascular disease, JARDIANCE is indicated to reduce the incidence of cardiovascular death*

Standard of Effectiveness

- The legal standard of effectiveness = "**substantial evidence of effectiveness**"
- **Substantial evidence =** "…evidence consisting of adequate and well-controlled investigation**s**, including clinical investigation**s**, …that the drug has the effect it purports or is represented to have under the condition of use prescribed …in the labeling or proposed labeling thereof"
- **Quality of evidence generally intended** = Adequate and well-controlled trials
- **Quantity of evidence generally intended =** at least two adequate and well-controlled studies

Quality of Evidence Necessary

Adequate and Well-Controlled Trial

Objectives of the investigation and methods of analysis are clearly stated

Design permits a valid comparison with a control to provide a quantitative assessment of drug effect.

Method of subject selection assures that subjects have the disease

Method of assignment to drug or comparator minimizes bias and assures comparability of the groups

Measures to minimize bias on the part of the subjects, observers, and analysts of the data are taken

Methods of assessment of subjects' response are well-defined and reliable

There is an analysis of the results of the study adequate to assess the effects of the drug

Quantity of Evidence Necessary

Circumstances When a Single Study Could Form the Basis for a New Claim

- The Agency may consider "data from **one adequate and well controlled clinical investigation** and **confirmatory evidence**" to constitute "substantial evidence" if FDA determines that such data and evidence are sufficient to establish effectiveness
- In some situations FDA has relied on a single adequate and well controlled efficacy study to support approval of a new drug or a new use (indication)
  - This has generally occurred **only** in cases in which a single multicenter study of **excellent design** provided **highly reliable** and **statistically strong evidence** of an **important clinical benefit**

Quantity of Evidence Necessary (cont.)

Characteristics of Single Trials used to Support an Efficacy Claim

The study is large and multi-center: Effect not driven by a few sites and is consistent across a majority of study sites

Consistency is observed across study subsets: Effect consistent across study subsets

Multiple studies in a single study: Factorial study prospectively analyzed as a series of pairwise comparisons that provides independent confirmation of the effect

Multiple endpoints involving different events: Study provides statistically persuasive evidence of a beneficial effects on different prospectively identified endpoints (e.g., CV death and non-fatal myocardial infarction)

Statistically very persuasive finding: a very low p-value indicating that the result is highly inconsistent with the null hypothesis of no treatment effect

Charge to the Committee

The committee was convened to

1. **Review the evidence generated from the EMPA-REG Outcome Study and**
2. **Advise the Agency on whether the study provides "substantial evidence of effectiveness" necessary to form the basis of a new claim for empagliflozin**

1. DISCUSSION

Discuss your interpretation of the EMPA-REG OUTCOME study conduct. Please comment on whether interim unblinding or changes made to the protocol, endpoint definitions, and analyses plan (e.g., specific exclusion of silent MI from the primary endpoint) during the course of the EMPA-REG OUTCOME study alter or do not alter your level of confidence in a conclusion that excess CV-risk was excluded and CV-benefit was established.

2. DISCUSSION

Please discuss the persuasiveness of the statistical results for the primary analysis. Please also comment on how results for the individual components in the primary composite endpoint impact your level of confidence in the study findings. Finally, comment on concerns you may have related to potentially incomplete ascertainment of some myocardial infarction events (i.e., silent MI) in this trial and whether these concerns, if any, alter your level of confidence in the results for the primary analysis.

3. DISCUSSION

Discuss the persuasiveness of the mortality findings in the EMPA-REG OUTCOME study. In your discussion, please address any potential limitations of these data including but not limited to:

- **Issues raised in Discussion Point #2**
- **The proportion of deaths that were determined "non-assessable" by adjudicators**
- **The lack of granular data on potentially important information such as baseline heart failure history and dose of relevant baseline and concomitant medications**
- **The lack of pre-specified alpha-adjustment for this endpoint**

4. DISCUSSION

Discuss the heart failure findings in the EMPA-REG OUTCOME study. Please comment on the potential limitations of these data, if any, and on whether the results of the study establish a benefit of empagliflozin on heart failure and heart-failure related outcomes.

5. DISCUSSION

Discuss the renal findings in the EMPA-REG OUTCOME study. Please comment on the potential limitations of these data, if any, and on whether the results of the study establish a benefit of empagliflozin on kidney disease related to diabetes.

1. VOTE

Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results have fulfilled the recommendations laid out in the 2008 Guidance for Industry by demonstrating that use of empagliflozin to improve glycemic control would not result in an unacceptable increase in cardiovascular risk?

A. If yes, please provide the rationale for your vote.

B. If no, please provide the rationale for your vote and comment on what additional data would be needed.

2. VOTE

Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results provide substantial evidence to establish that empagliflozin reduces cardiovascular mortality in the population studied?

A. If yes, please provide the rationale for your vote.

B. If no, please provide the rationale for your vote and comment on what additional data would be needed.

The EMPA-REG OUTCOME Study

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Rockville, MD
June 28, 2016

Andreea Lungu, M.D.
Division of Metabolism and Endocrinology Products
Office of New Drugs
Center for Drug Evaluation and Research

Overview

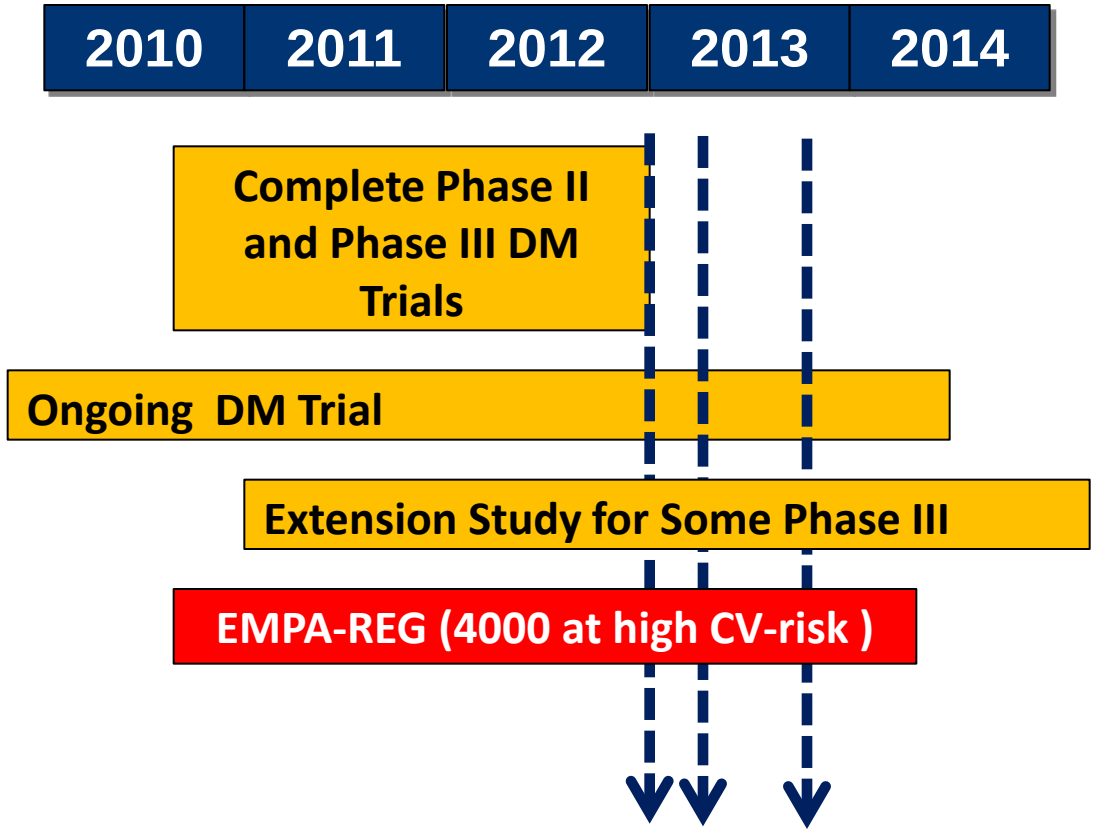
- **The EMPA-REG OUTCOME Study**
  - Regulatory history
  - Design and trial conduct
  - Population
- **Statistical Assessment**
  - Presented by Dr. Jennifer Clark
- **Clinical Discussion**
  - Factors affecting the interpretation of the primary endpoint
  - Exploratory endpoints
  - Non-cardiovascular safety
- **Summary**

EMPA-REG: Regulatory History

- Conducted as part of a plan to address the 2008 CV Risk Guidance
- Pre-approval
  - Exclude 1.8 from the upper bound of the two-sided 95% confidence interval
- Post-approval
  - Exclude 1.3 from the upper bound of the two-sided 95% confidence interval

CV = cardiovascular

CV-Risk Assessment Proposal 2009-2010



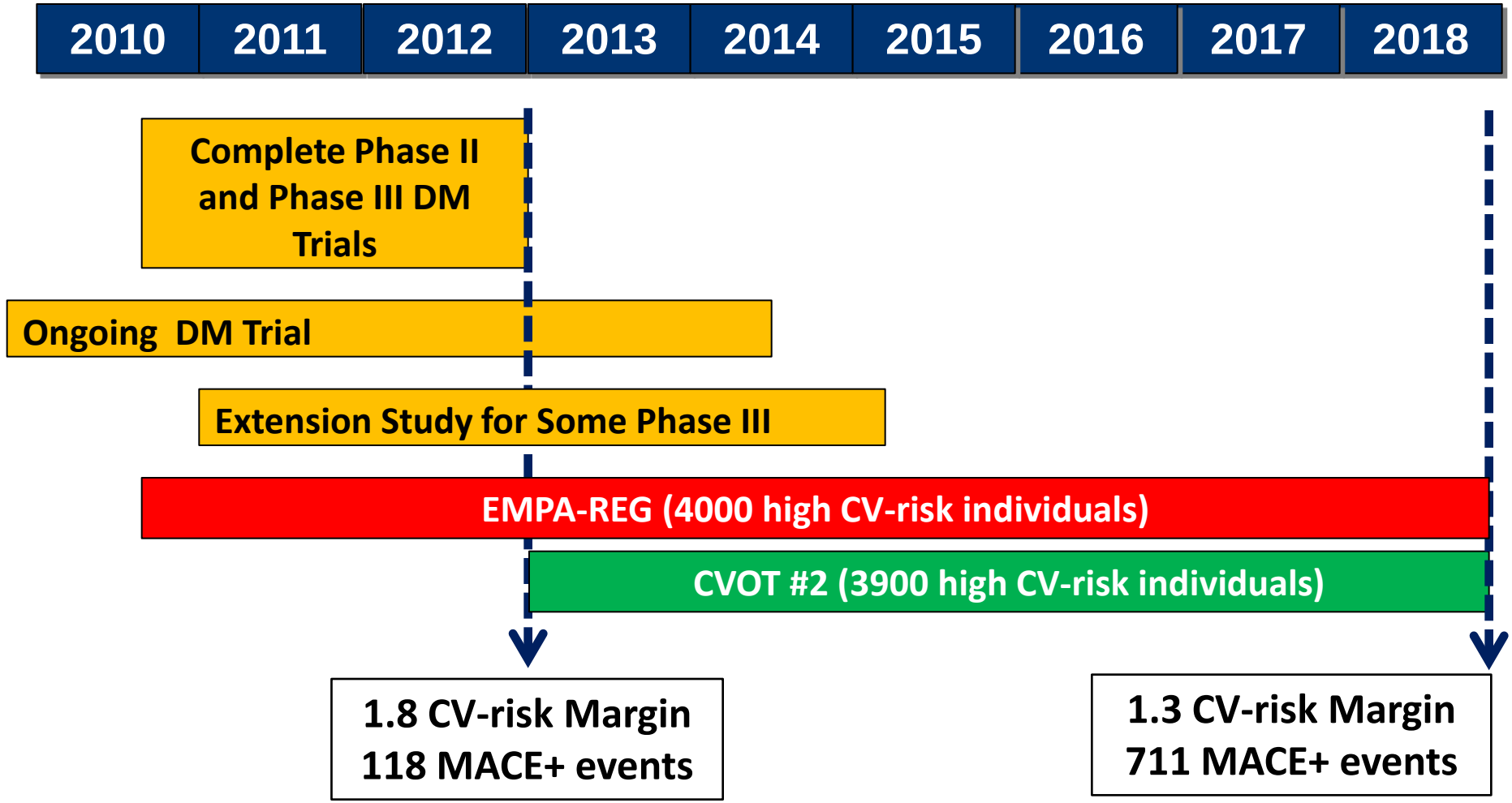
Proposed three "looks" for 1.8 based on MACE+

- **At completion of phase 3 DM trials**
- **At 60 events accrued**
- **At 152 events accrued**

1.3 margin not addressed in proposal

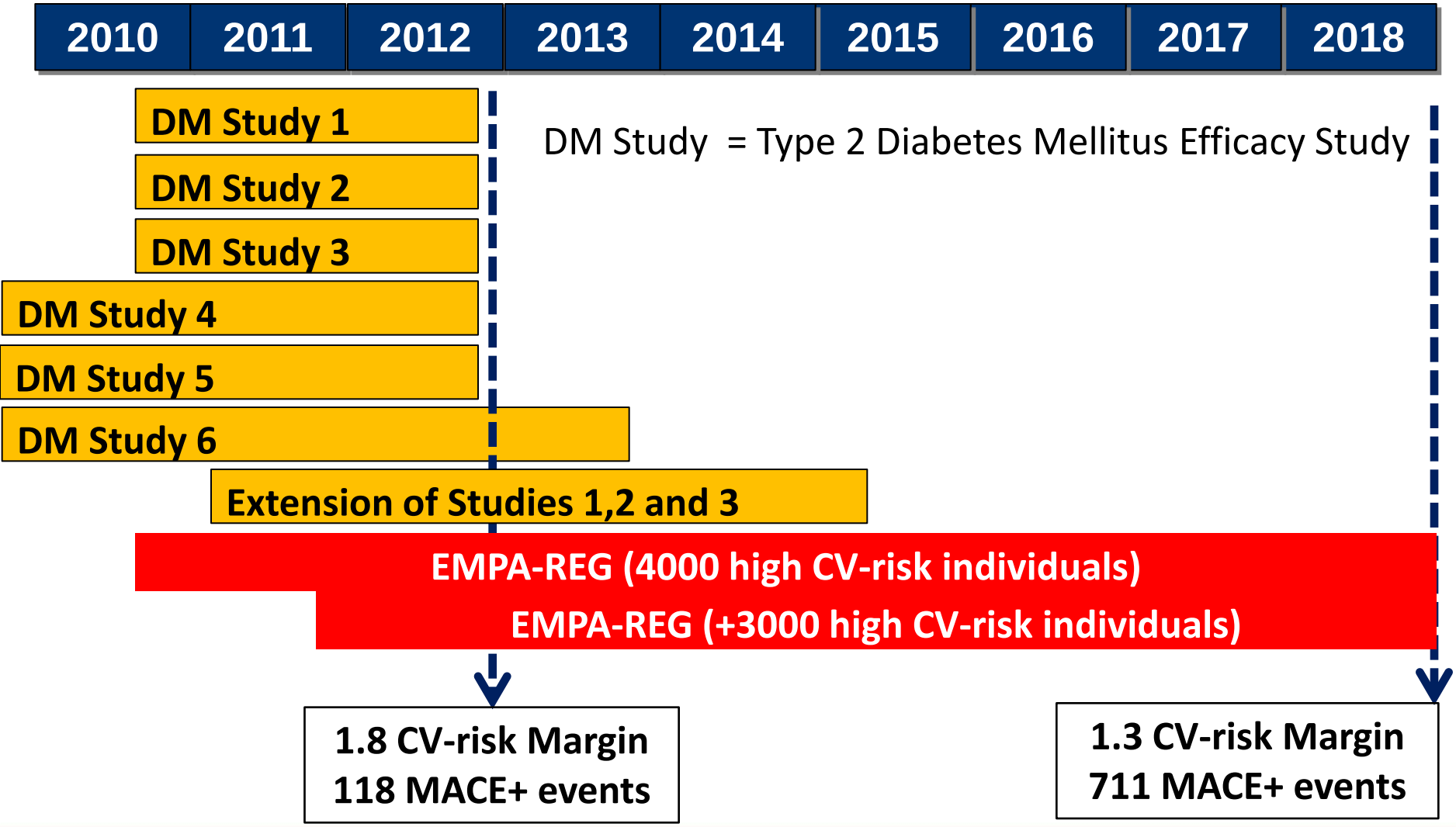
DM = diabetes mellitus; MACE+: Non-fatal MI, Non-fatal stroke, CV Death and Unstable Angina

CV-Risk Assessment Proposal 2011



CVOT = Cardiovascular Outcomes Trial

Final CV-Risk Assessment Plan Submitted Jan 2012



EMPA-REG: Regulatory History

- Protocol changes to address the final plan resulted in adequate power to independently exclude the 1.3 risk margin for MACE
  - Trial to stop after 691 MACE accrued
- Interim analysis planned after 118 events
  - Alpha-adjustment for 1.3 risk margin pre-specified to account for interim look
- Superiority testing only AFTER excluding 1.3 risk margin for MACE and MACE+

MACE: Non-fatal MI, Non-fatal stroke, CV Death
MACE+: Non-fatal MI, Non-fatal stroke, CV Death and Unstable Angina

EMPA-REG: Regulatory History

- NDA submitted in March 2013
- Database lock for interim analysis: August 21, 2012
  - 196 MACE, 142 from EMPA-REG
- Interim data from EMPA-REG were used to test both the 1.8 and 1.3 risk margins
  - At interim, ~5000 patients had been randomized
  - ~230 individuals unblinded to support US and other regulatory submissions

EMPA-REG: Regulatory History

- No signal of increased CV risk was identified in the overall empagliflozin development program
- Pre-approval exclusion of 1.8 risk margin for MACE+ was met
  - **Hazard Ratio 0.74 (95% CI: 0.57, 0.96)**
- Exclusion of 1.3 risk margin for MACE from interim analysis of EMPA-REG not met
  - **Hazard Ratio 0.74 (99.98% CI: 0.4, 1.4)**

CI = confidence interval

EMPA-REG: Regulatory History

- Empagliflozin approved in August 2014
- Required to perform post-approval evaluation of cardiovascular risk
  - EMPA-REG alone to exclude 1.3 for MACE
- Also collected additional information on non-cardiovascular safety

STUDY DESIGN AND CONDUCT

EMPA-REG – General Design

- **Design:** Randomized, double-blind, placebo-controlled
- **Population**: Adults with type 2 diabetes and high CV risk
- **Duration**: Event driven
- **Treatment**: Empagliflozin (10 mg and 25 mg) vs. Placebo
  - Randomized 1:1:1 as add-on to local standard of care
  - Pooled empagliflozin compared to placebo
- **Primary objective:** To evaluate ischemic cardiovascular risk associated with empagliflozin use
- **Primary outcome:** 3-point MACE
  - Cardiovascular (CV) death
  - Nonfatal myocardial infarction (MI)
  - Nonfatal stroke

Key Participants Involved in Study Conduct and Operations

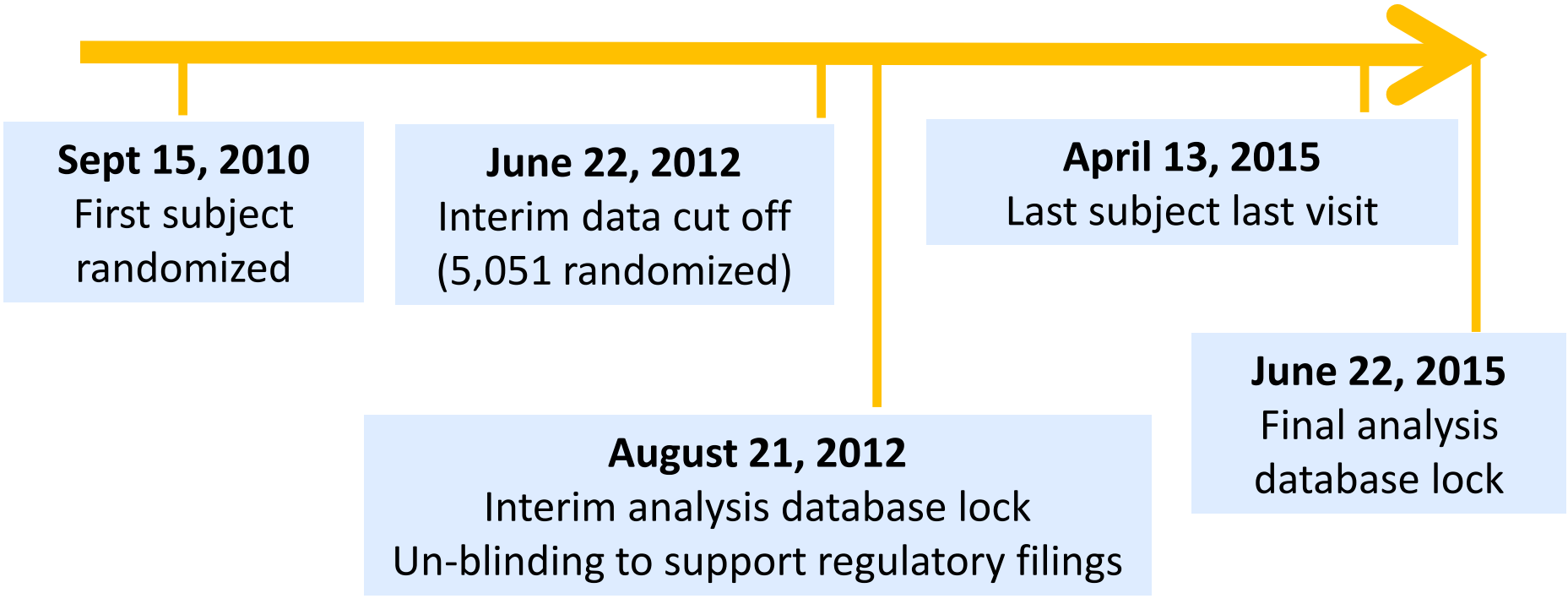
- Applicant
- Steering Committee
- Data Monitoring Committee (DMC)
- Clinical Event Committee (CEC)

Adjudication Process

- All events included in the primary endpoint were adjudicated by the CEC
- **Adjudication process flow**:
  - Events referred for adjudication based on investigator report in the electronic case report form or identified by third party vendor from the AE database
  - Source documents collected to support adjudication
  - Case reviewed by at least 2 members of CEC
  - Pre-specified definitions or totality of evidence + clinical judgment used to adjudicate
  - If no consensus, reviewed by additional members of CEC
  - Adjudication results communicated to sponsor

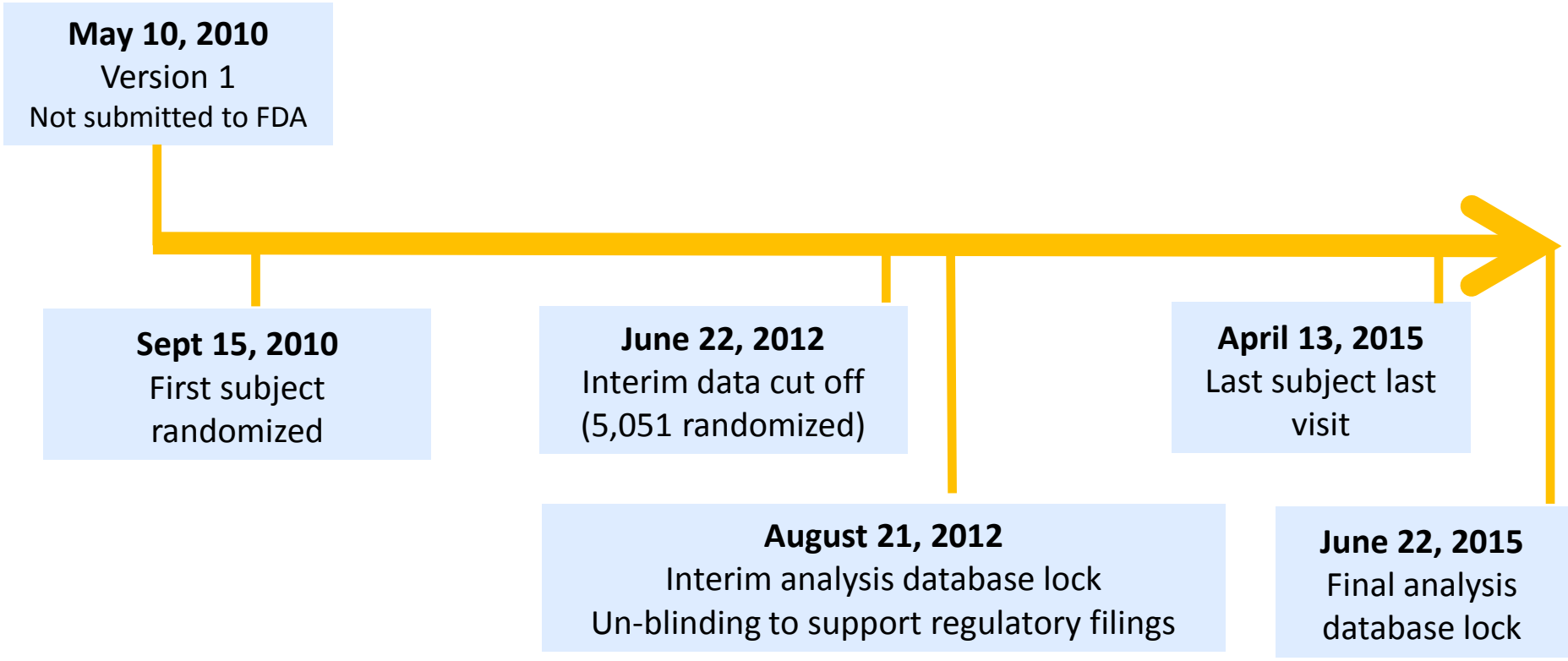
AE = adverse event

Major Milestones in Study Timeline

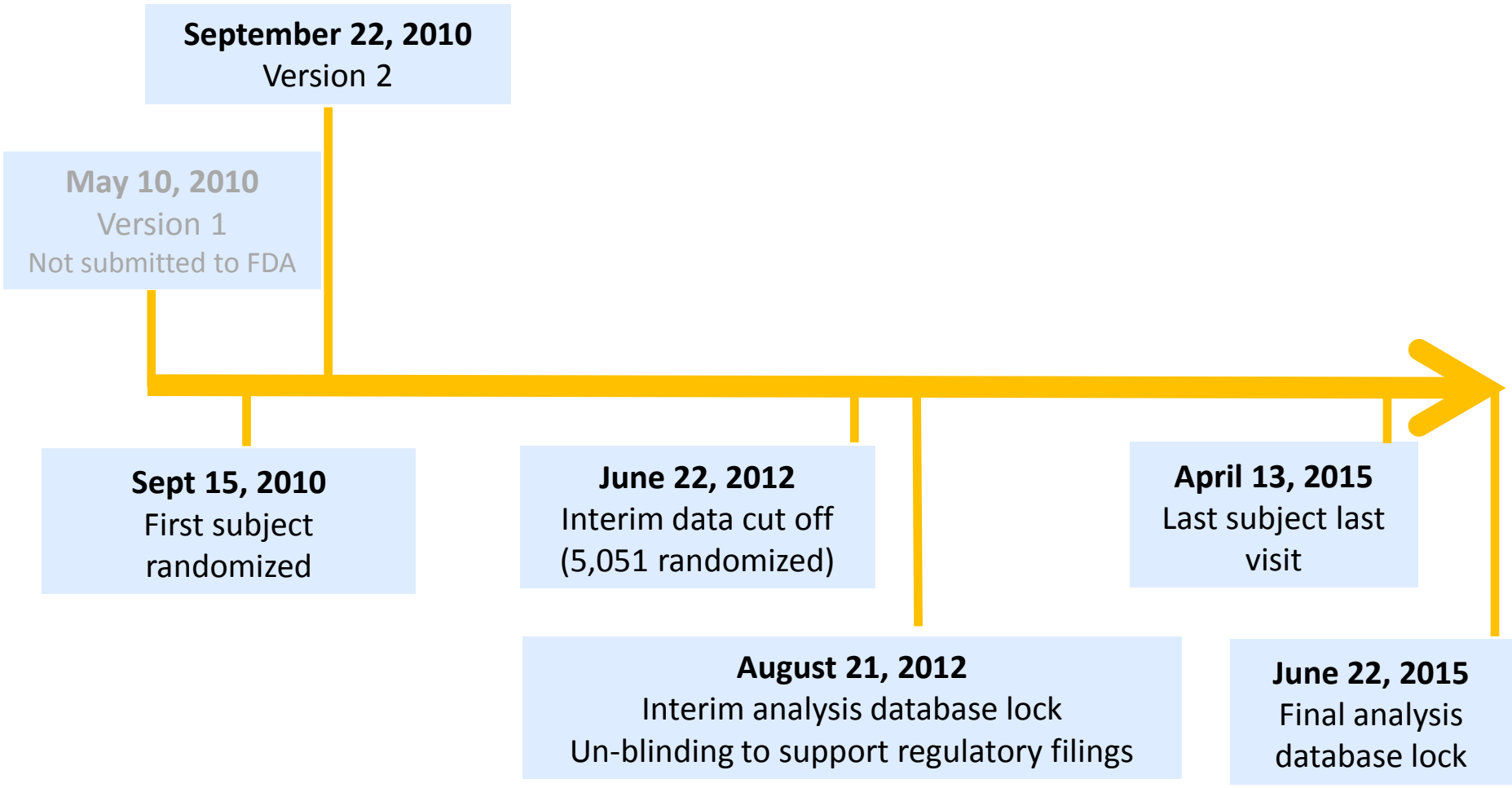


PROTOCOL CHANGES

Protocol Changes



Protocol Changes



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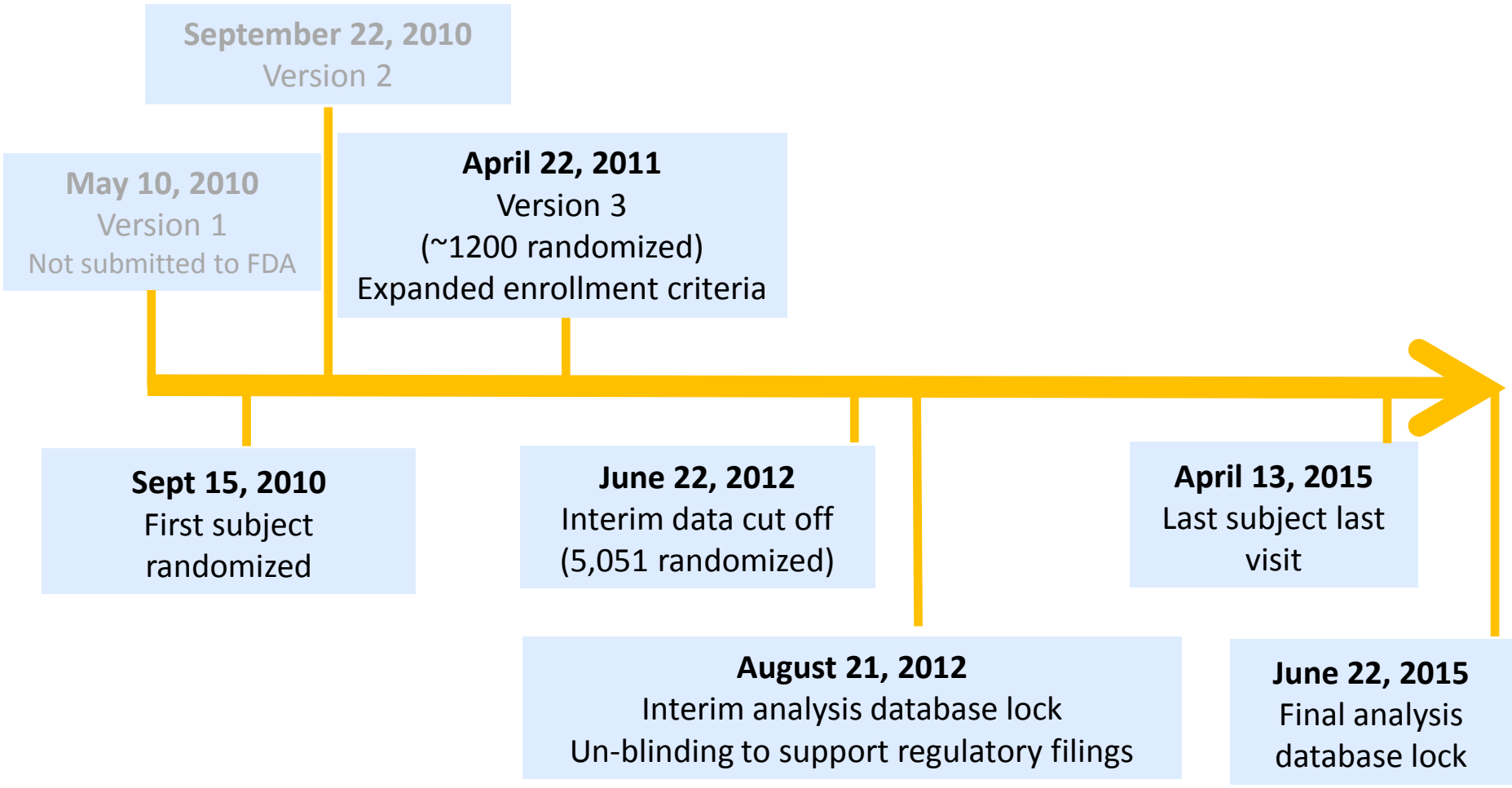

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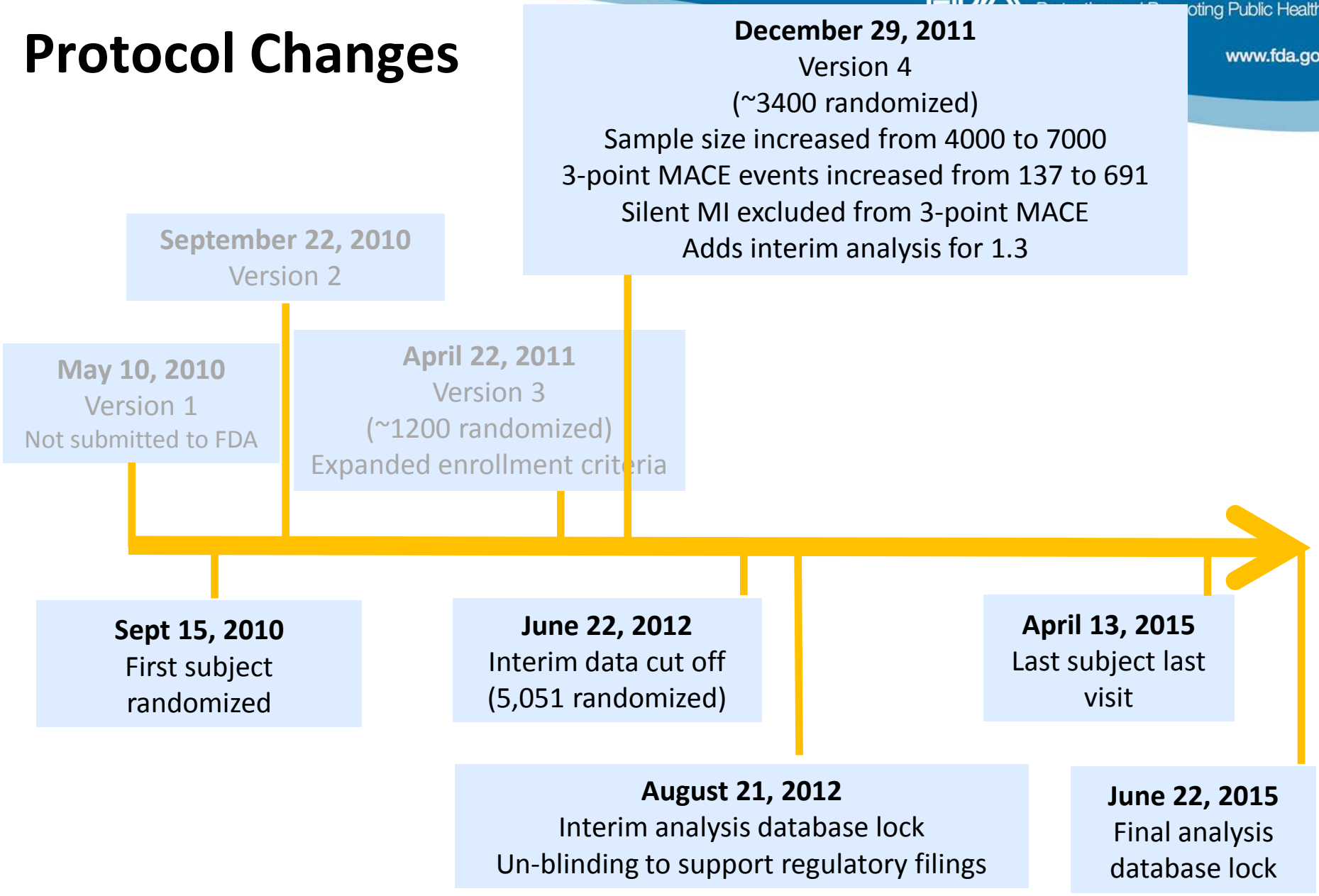

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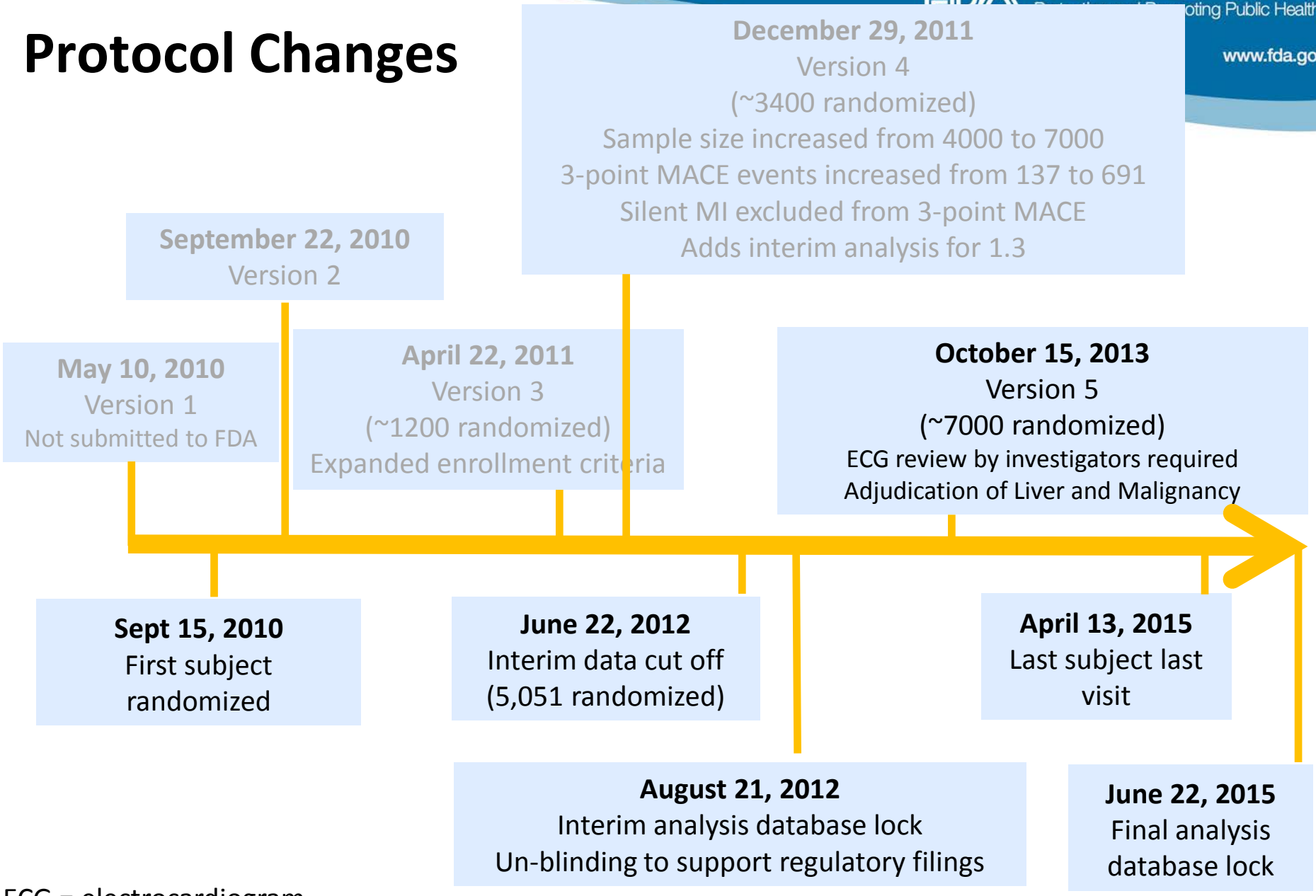
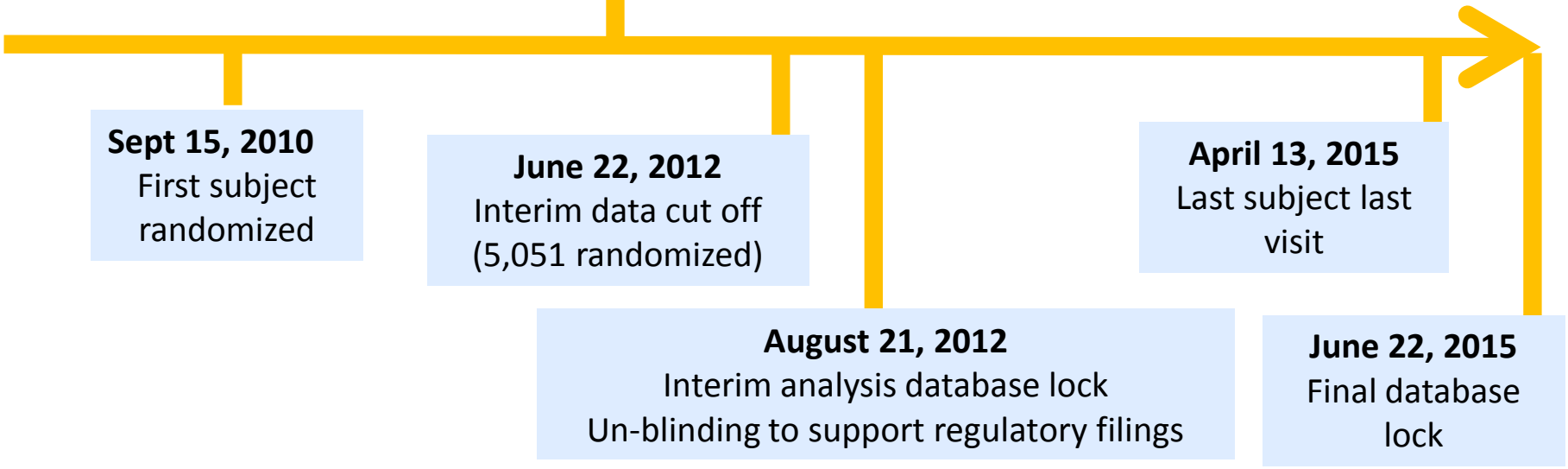


ECG = electrocardiogram

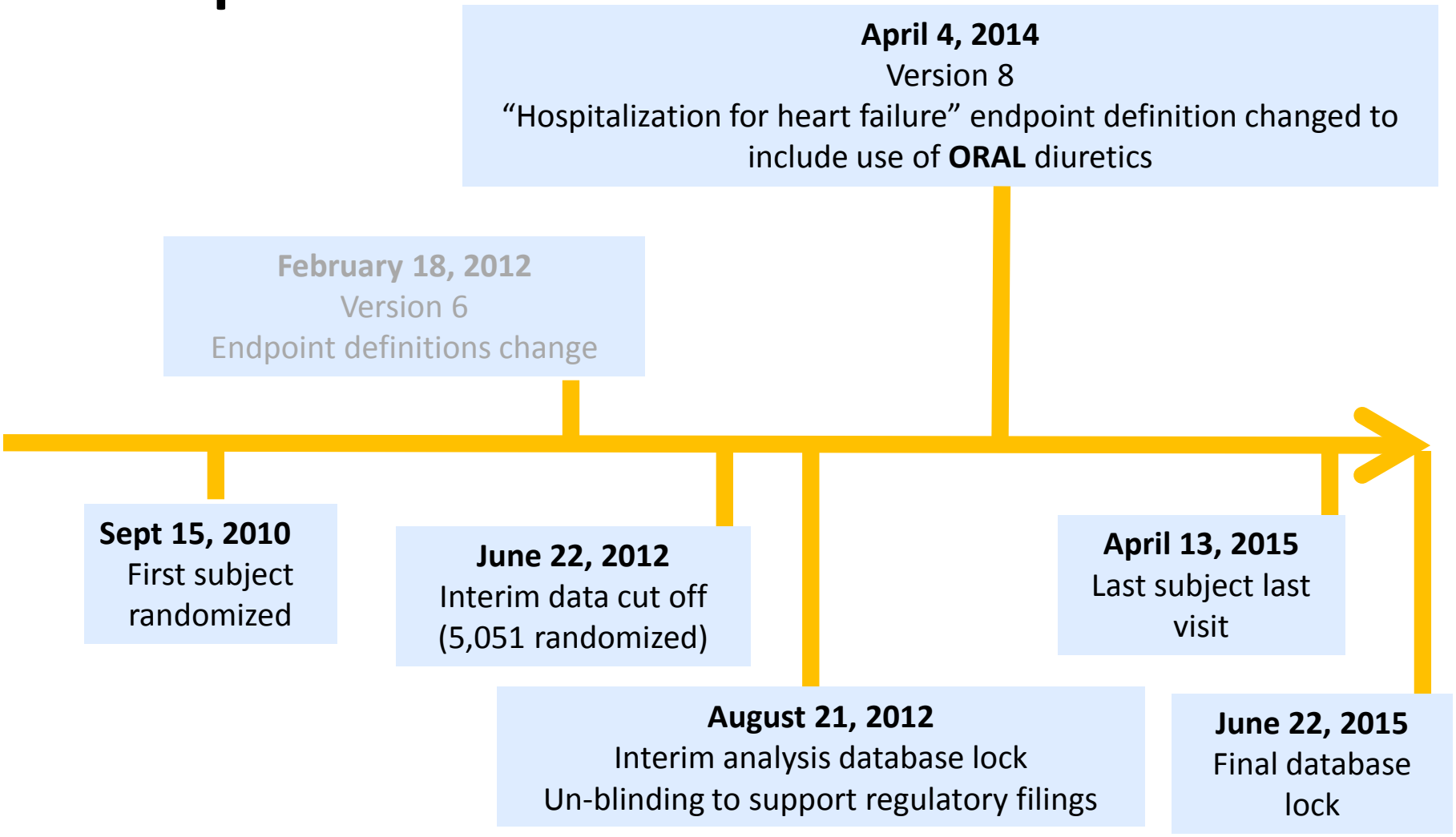
CLINICAL EVENT COMMITTEE (CEC) CHARTER AND ENDPOINT DEFINITION CHANGES

CEC Charter and Changes to Endpoint Definitions

- MI definition expanded to include symptoms and only one supportive criterion (imaging, ECG, biomarker)
- Hospitalization for unstable angina and hospitalization for heart failure liberalized to include overnight admissions to the chest pain units



CEC Charter and Changes to Endpoint Definitions



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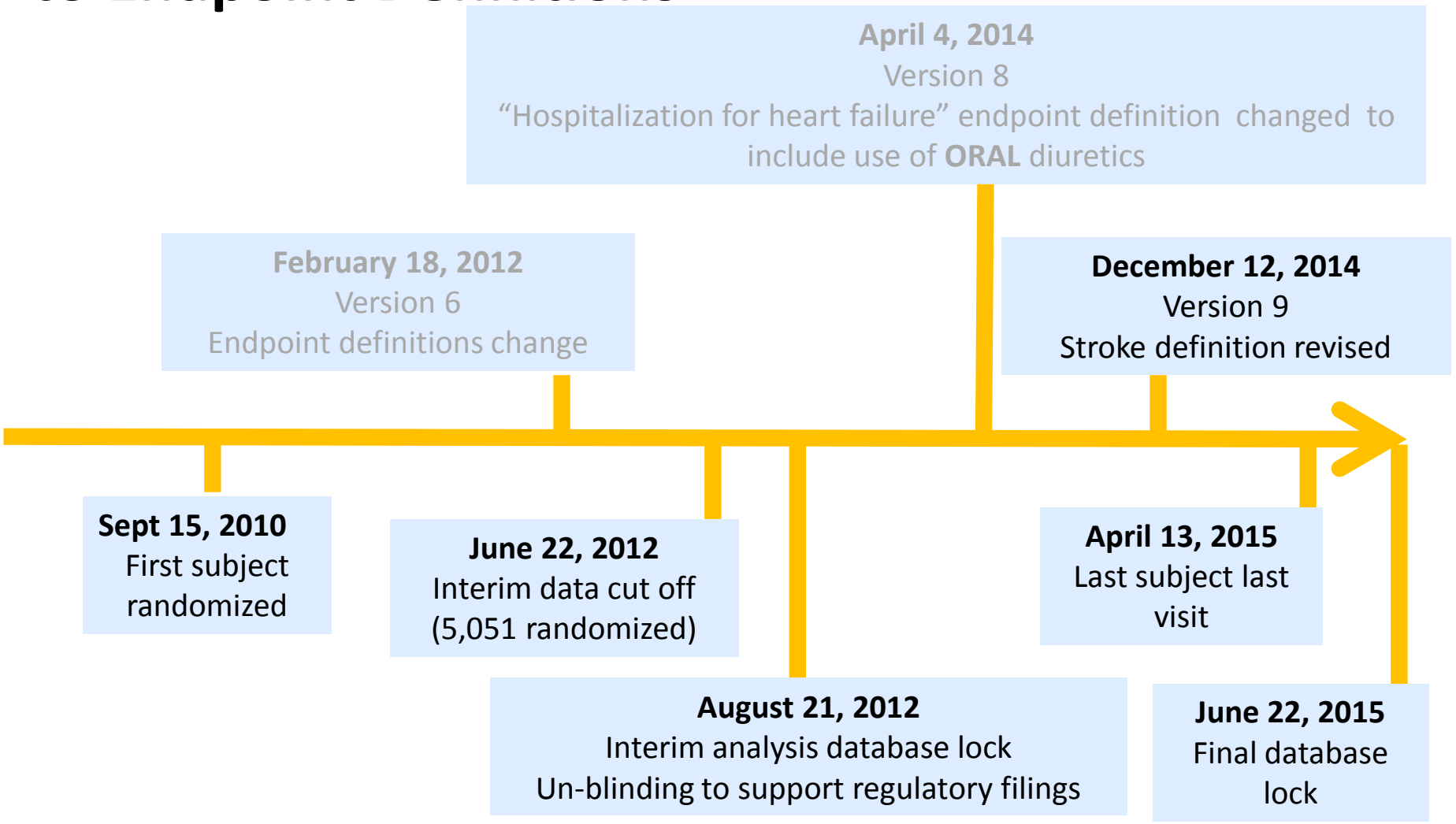
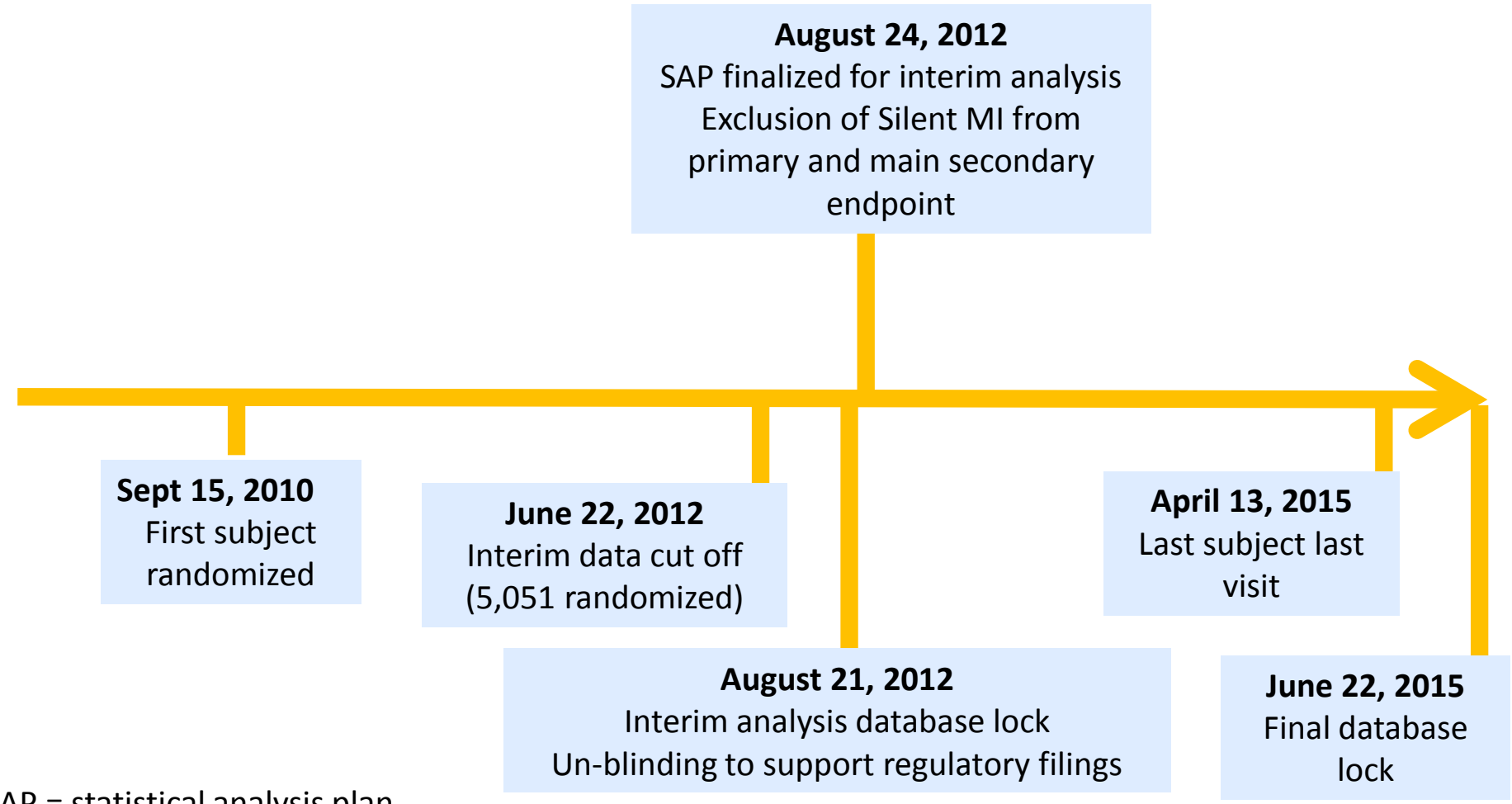


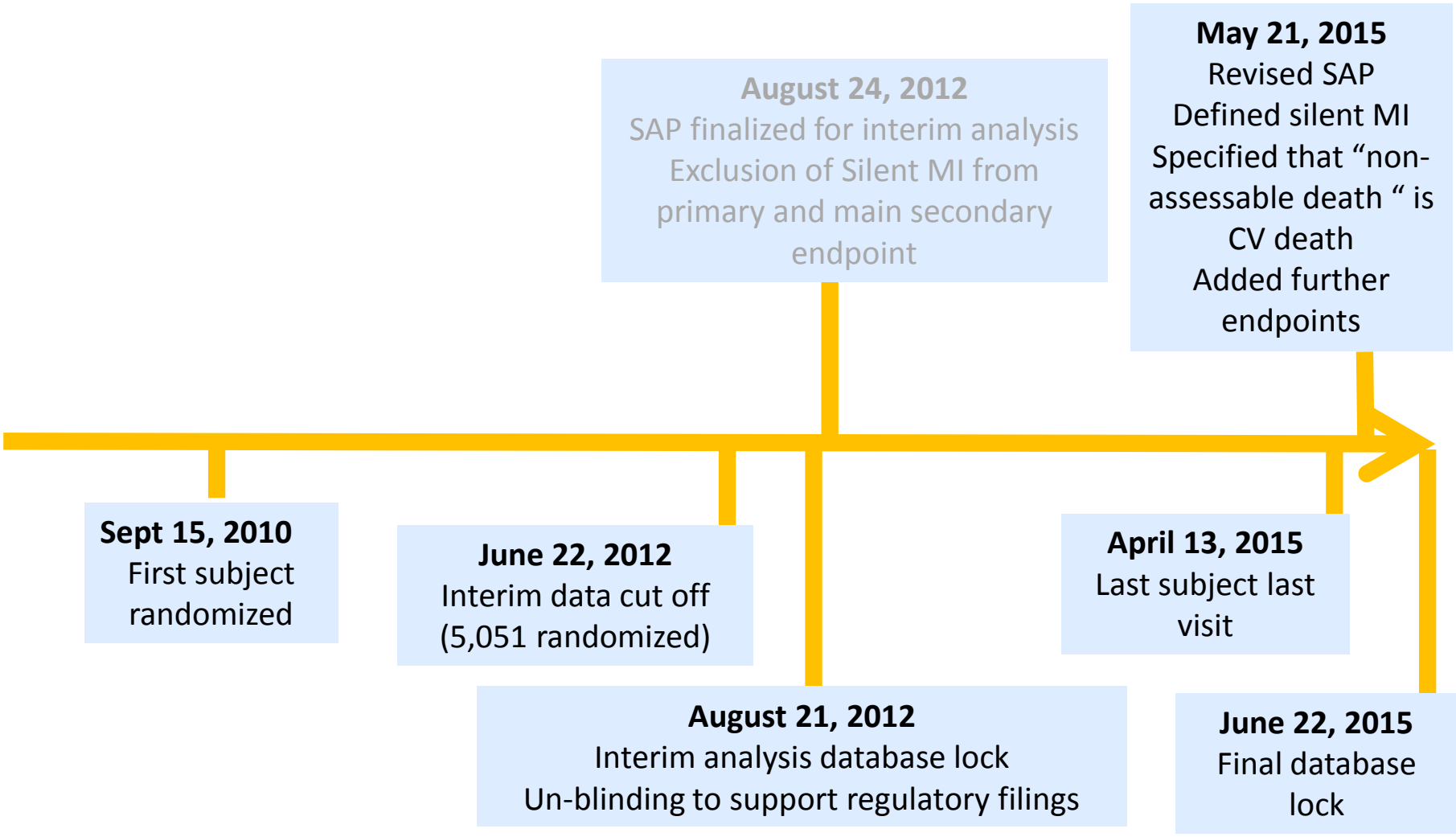
STATISTICAL ANALYSIS PLAN CHANGES

Statistical Analysis Plan Changes



SAP = statistical analysis plan

Statistical Analysis Plan Changes



STUDY POPULATION AND DISPOSITION

Study Population

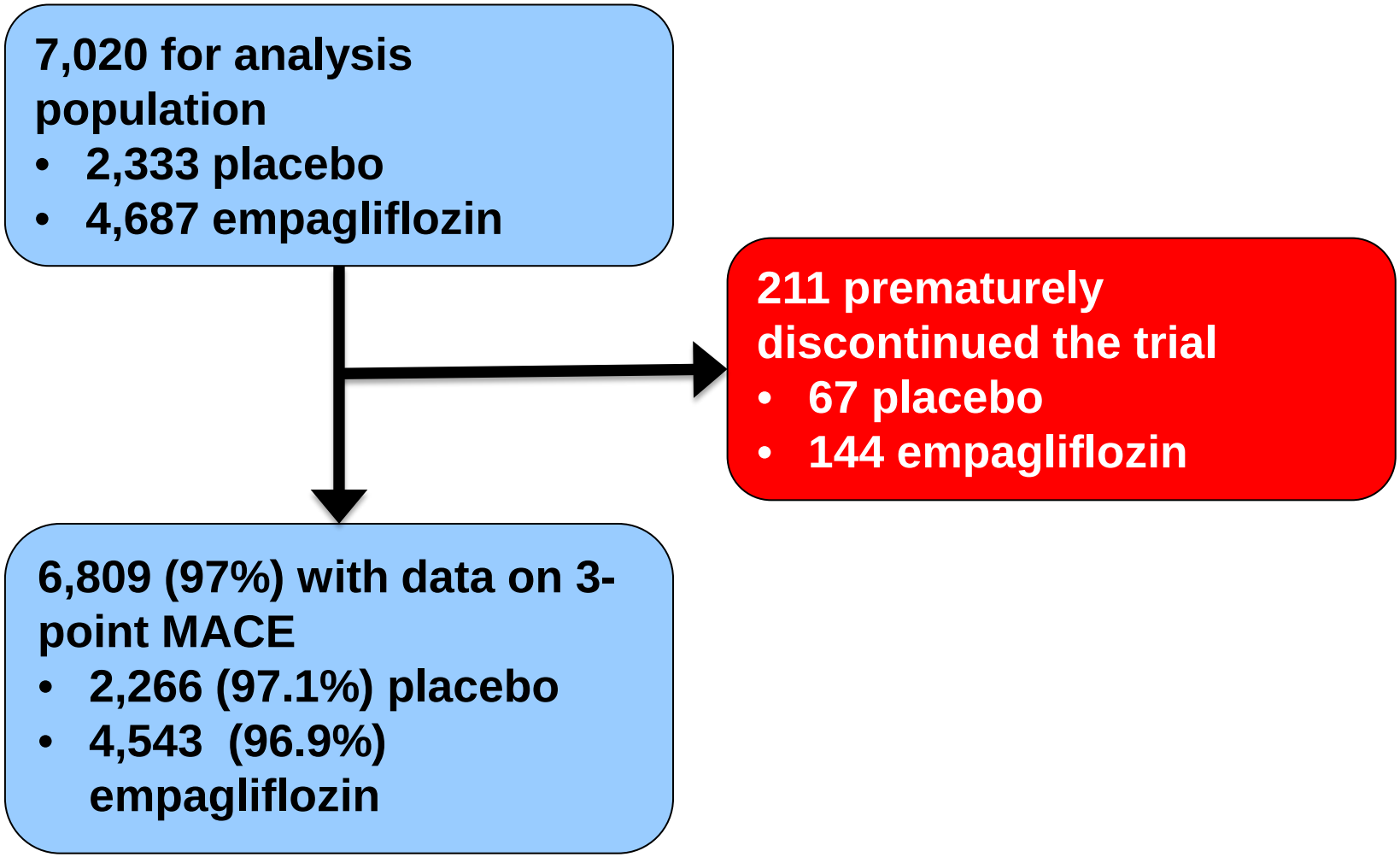
	Placebo N=2333	Empagliflozin N=4687
Mean age (years)	63.2	63.1
Mean HbA1c (%)	8.1	8.1
Time since diagnosis of T2DM		
5 to 10 years	24.5%	25.1%
> 10 years	57.4%	57%
Diabetic complications		
Diabetic neuropathy	31.2%	31.4%
Diabetic retinopathy	22.4%	21.8%
Diabetic nephropathy	20%	19.3%

T2DM = type 2 diabetes mellitus

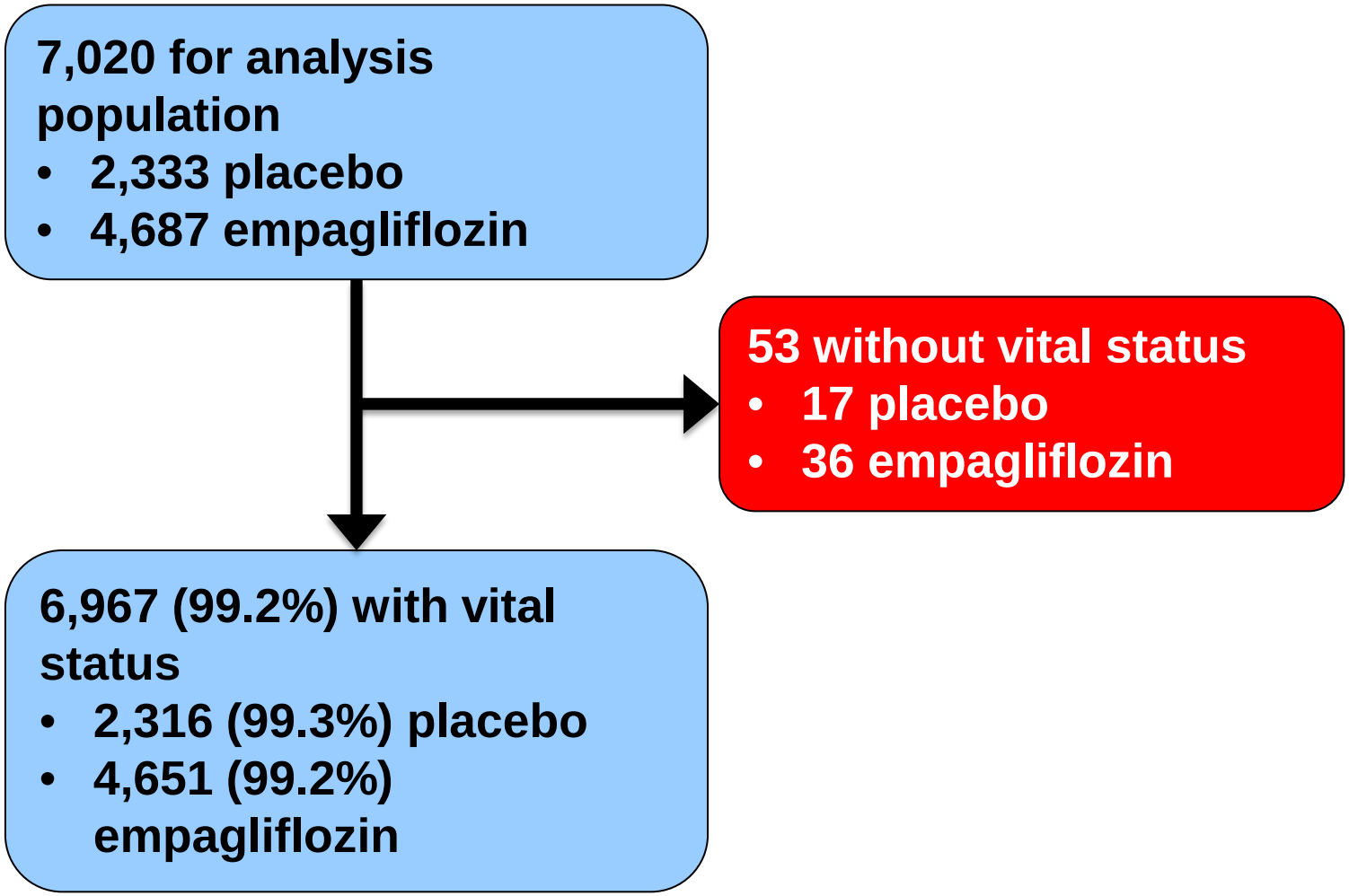
Study Population

	Placebo N=2333	Empagliflozin N=4687
High CV risk	98.9%	99.4%
Coronary artery disease	75.6%	75.6%
Multi-vessel CAD	47.1%	46.5%
History of MI	46.4%	46.7%
History of CABG	24.1%	25.1%
Single vessel CAD	10.2%	10.6%
History of stroke	23.7%	23.1%
Peripheral artery disease	20.5%	21%

Disposition – 3-point MACE



Disposition – Vital Status



Statistical Assessment of the EMPA-REG OUTCOME Safety Trial

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Rockville, MD
June 28, 2016

Jennifer Clark, PhD
Office of Biostatistics (OB)
Office of Translational Science (OTS)

Presentation Outline

- EMPA-REG Overview
- Trial Results
- 3-Point MACE Components
- Death
- Follow-up

EMPA-REG Overview

- Required to rule out a 30% increase in cardiovascular (CV) risk
- No precedent for diabetes safety trials with superiority
- <5 year follow-up
  - First Randomization: September 15, 2010
  - Last Randomization: April 19, 2013
  - Trial Completion Visit at or after December 15, 2014

Primary Objective

- Safety of empagliflozin vs. placebo for MACE
  - Rule out a 30% increased risk

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Pre-specified testing hierarchy

1. Non-inferiority: 3-Point MACE
2. Non-inferiority: 4-Point MACE
3. Superiority: 3-Point MACE
4. Superiority: 4-Point MACE

Population

- Primary Analysis Population: Treated Set (N=7020)
  - Placebo: 2333
  - Empagliflozin 10 mg: 2345
  - Empagliflozin 25 mg: 2342

- 7065 Total
  - 8 Randomized, not treated : (4 Placebo, 2 Empa 10mg, 2 Empa 25mg)
  - 37 Started treatment, excluded for site non-compliance or other issues: (15 Placebo, 12 Empa 10mg, 10 Empa 25mg)

- Pooled Empagliflozin Arm: 4687

Methods

- Cox proportional hazards model
  - Pooled empagliflozin arms vs. placebo
  - Adjusting baseline covariates

    Age, sex, BMI, HbA1c, eGFR, and geographic region
  - Hazard Ratio (HR)

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- Adjustment for Interim Analysis
  - 95.02% Confidence Intervals (CI)

Trial Results

MACE Results, Hazard Ratio (95.02% CI)

- Non-inferior to placebo (Safety)
  - Upper Bound<1.3

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- 3-Point MACE

  0.86 (0.74, 0.99)

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Non-inferiority
3-Point MACE
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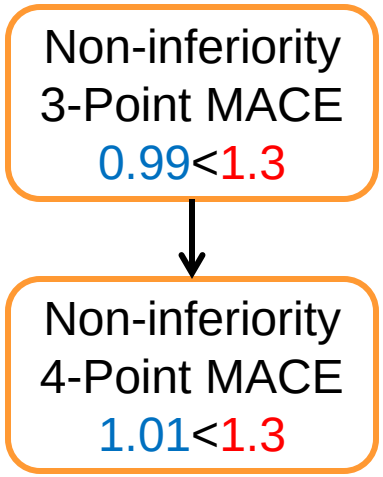

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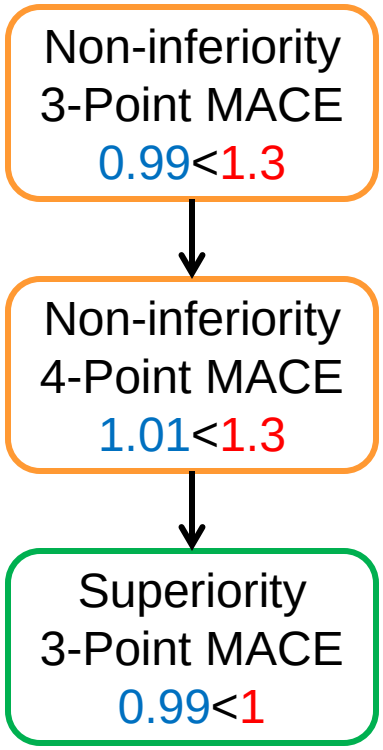

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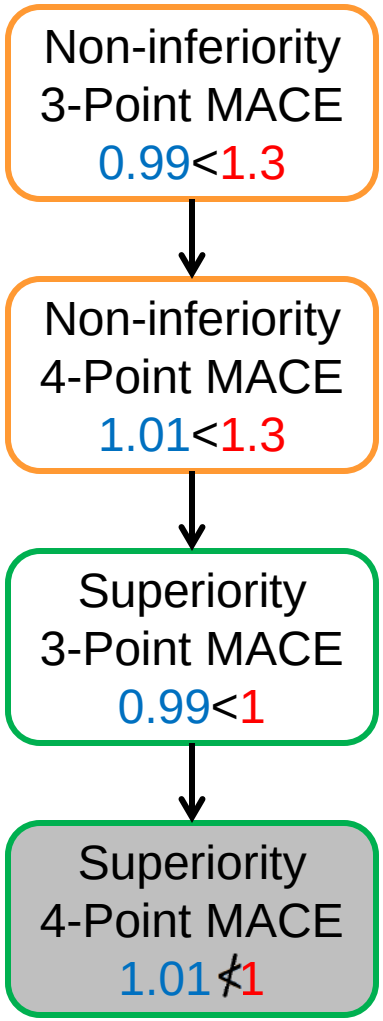
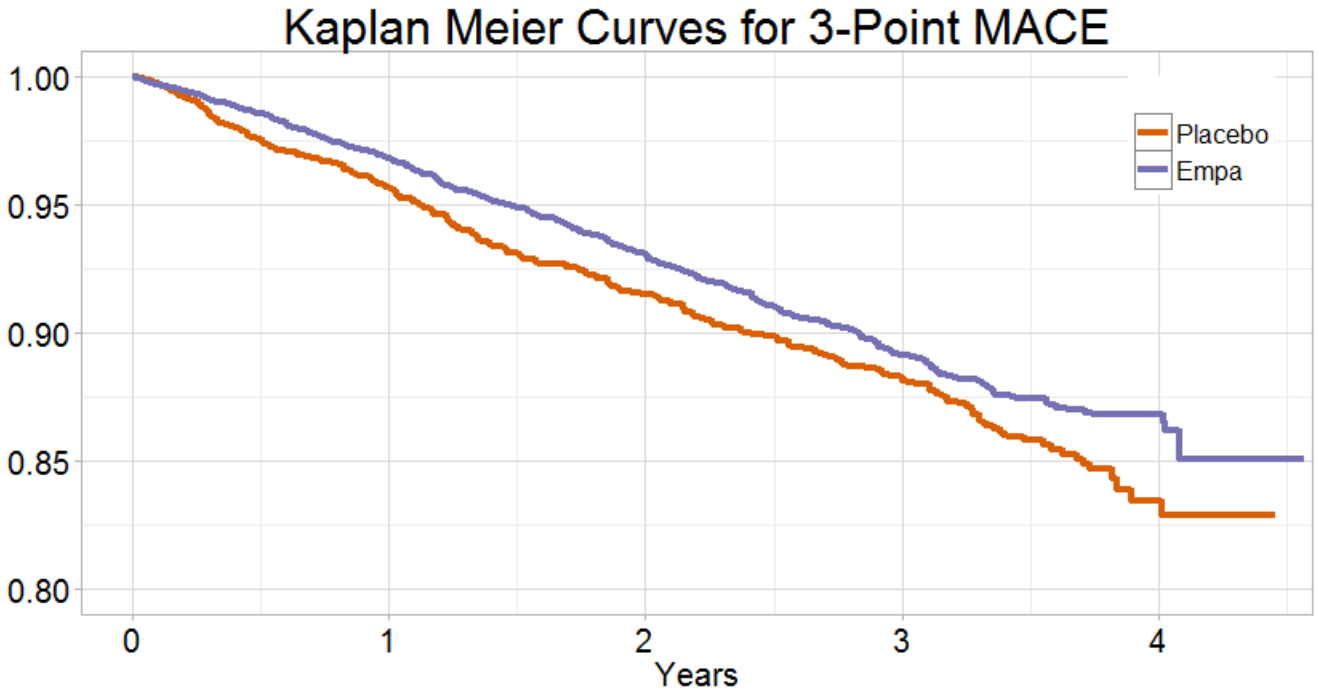


3-Point MACE Kaplan-Meier



Number at risk by time

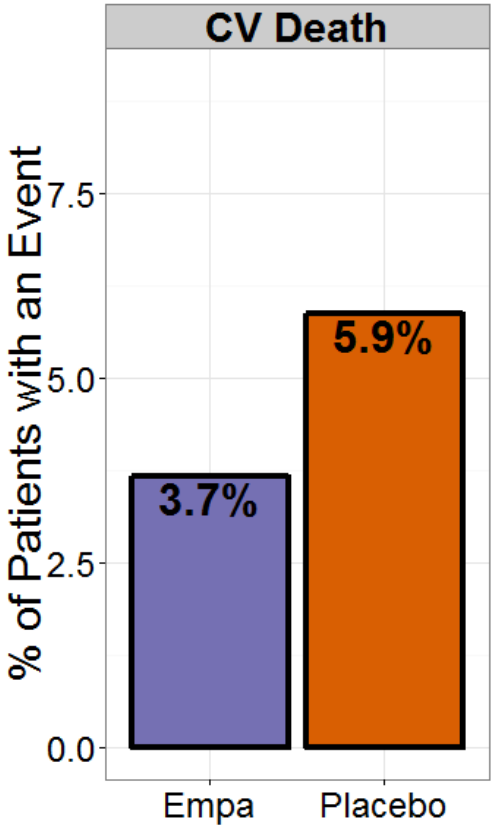
	0	1	2	3	4
Placebo	2333	2192	1866	1075	154
Empa	4687	4451	3818	2186	332

Years

Patients with 3-Point MACE	
Placebo, N=2333	282 (12.1%)
Empa, N=4687	490 (10.5%)

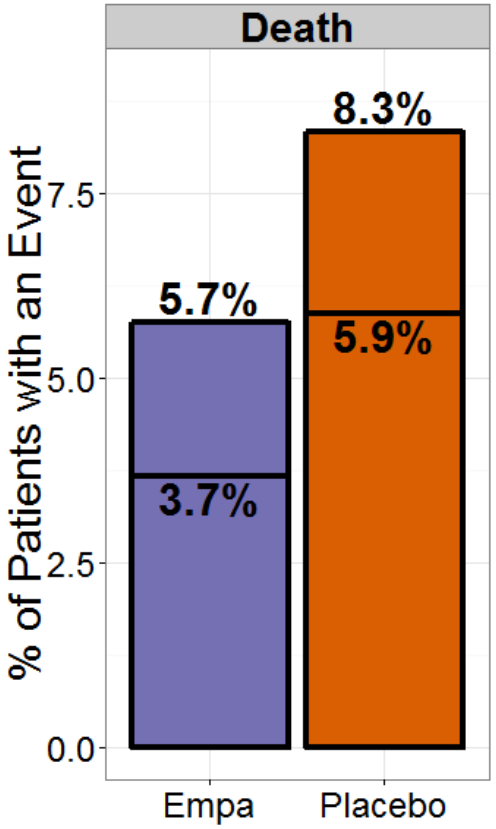
3-Point MACE Components

Proportion of Patients with Events



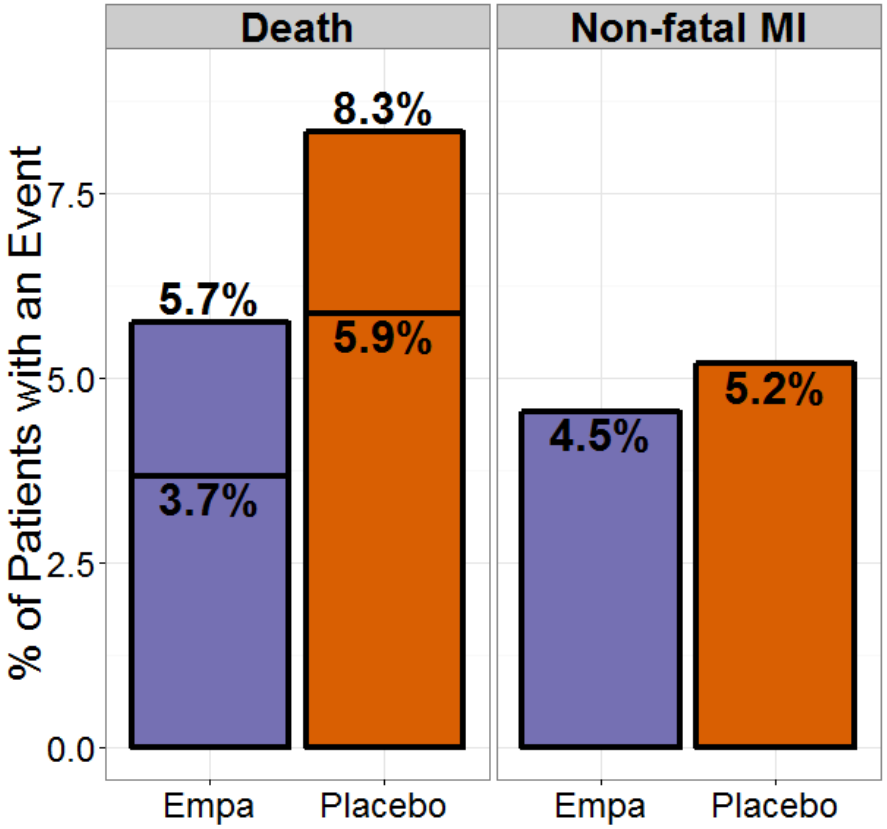
	Placebo N=2333	Empa N=4687
CV Death	137	172

Proportion of Patients with Events



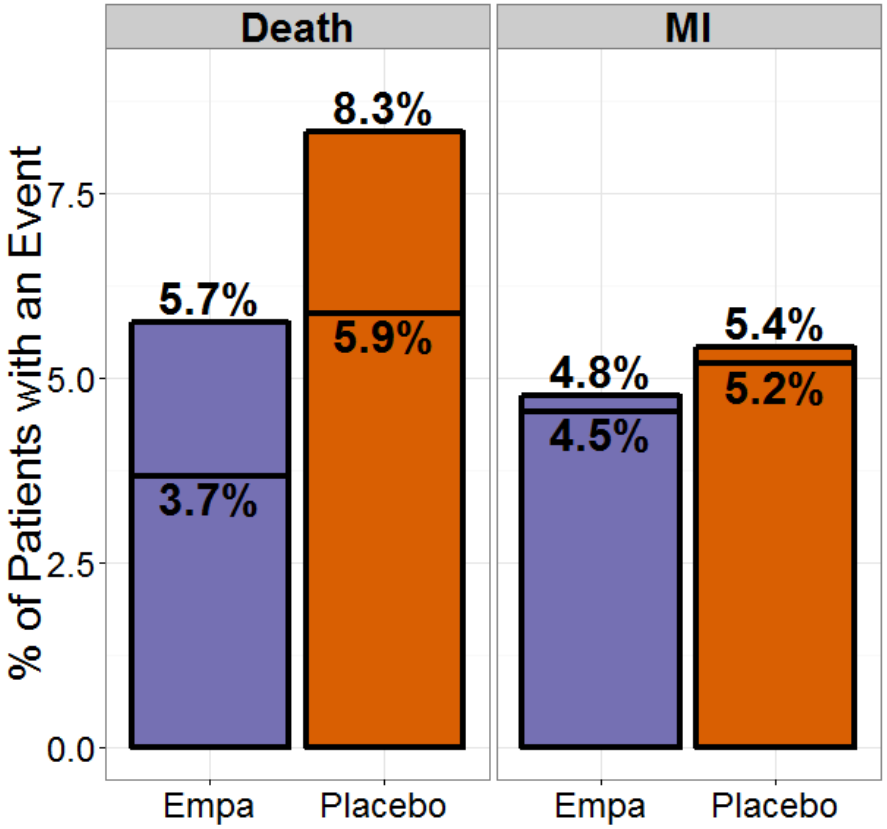
	Placebo N=2333	Empa N=4687
CV Death	137	172
Death	194	269

Proportion of Patients with Events



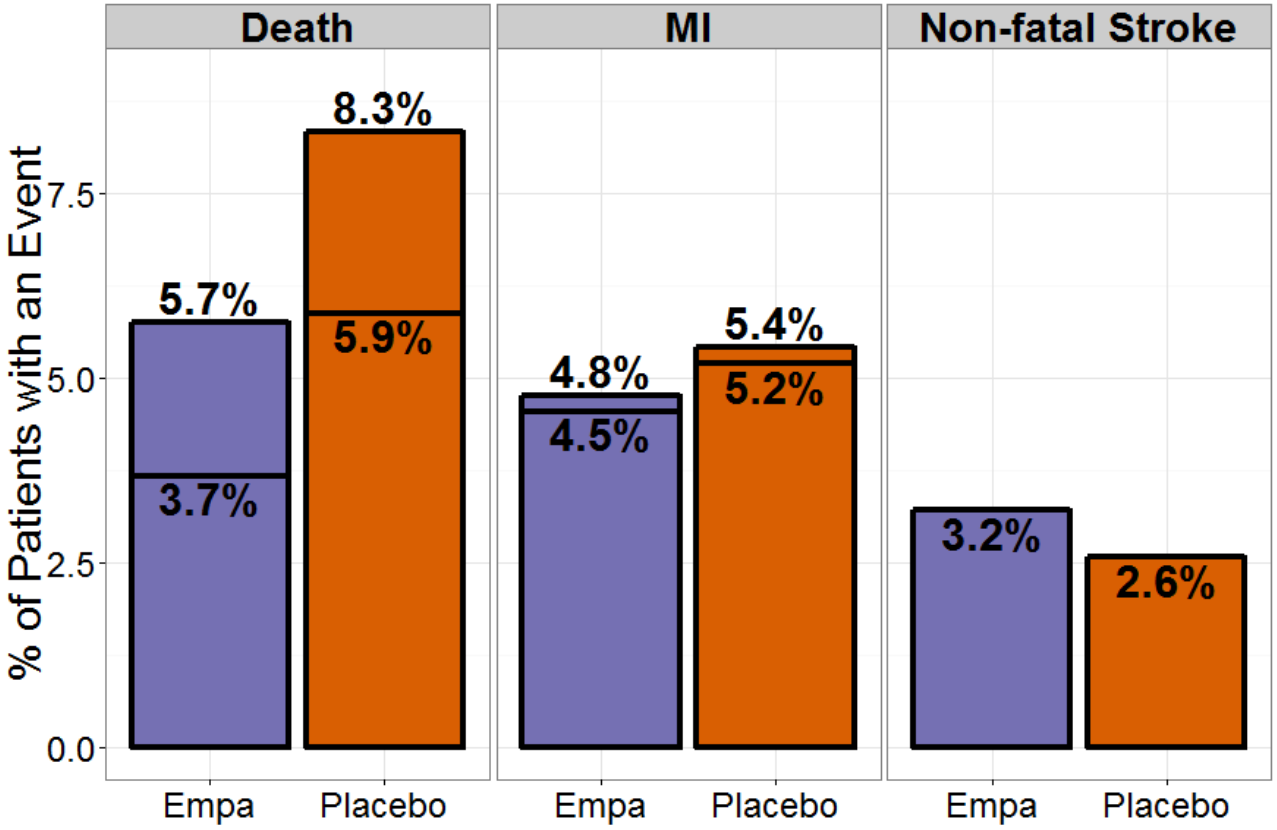
	Placebo	Empa
	N=2333	N=4687
Non-fatal MI	121	213

Proportion of Patients with Events



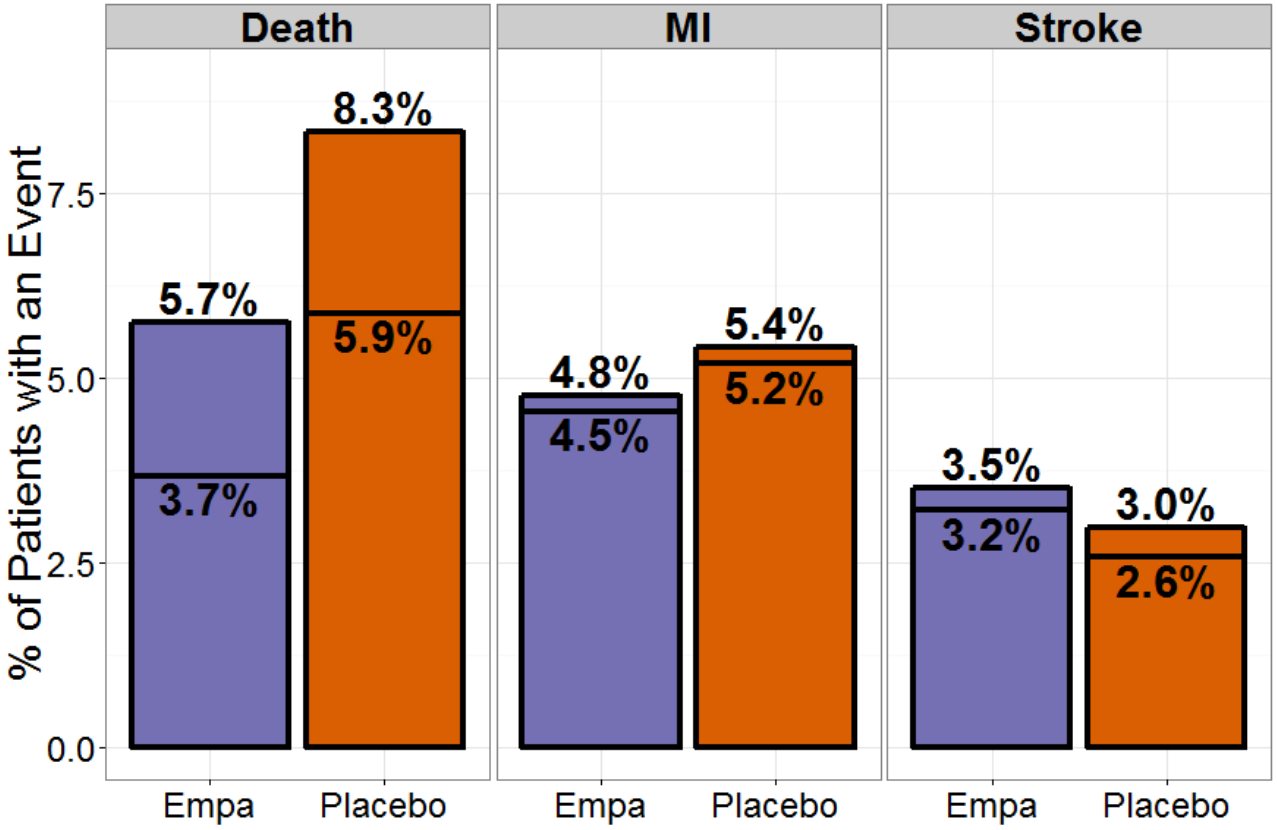
	Placebo N=2333	Empa N=4687
Non-fatal MI	121	213
MI	126	223

Proportion of Patients with Events



	Placebo N=2333	Empa N=4687
Non-fatal Stroke	60	150

Proportion of Patients with Events



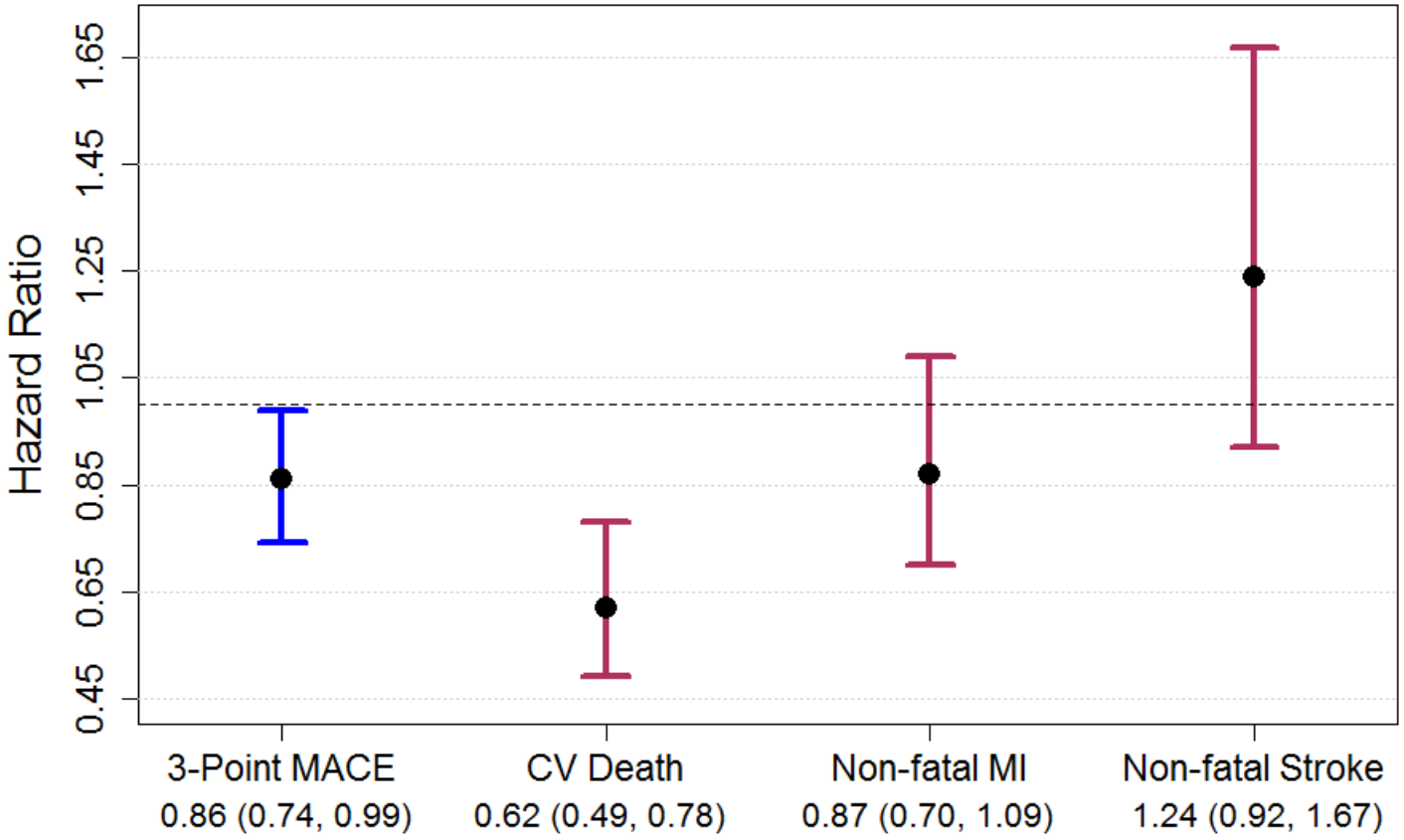
	Placebo N=2333	Empa N=4687
Non-fatal Stroke	60	150
Stroke	69	164

Estimated Incidences

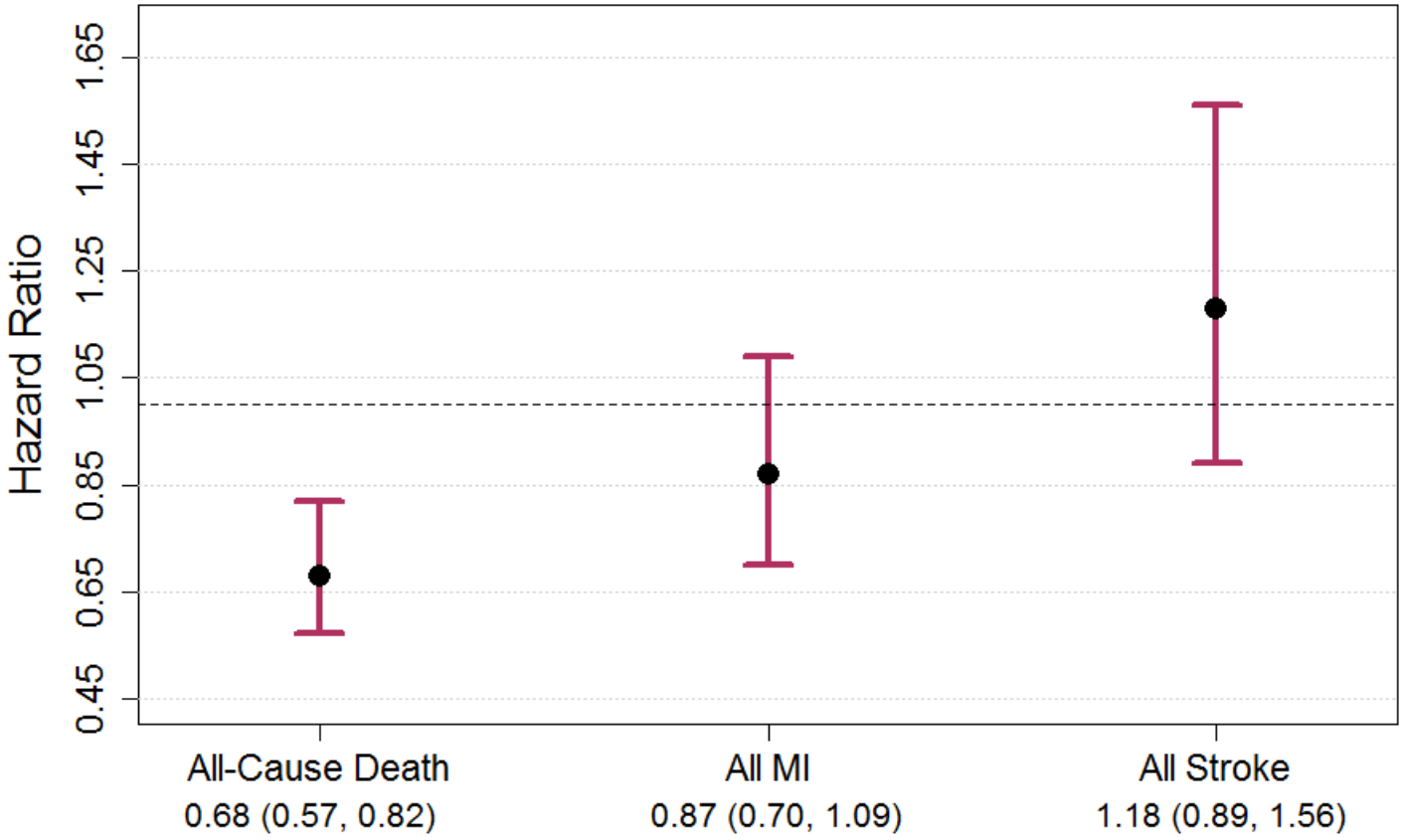
Estimated Incidence per 100 patient years

	Placebo	Empa
	N=2333	N=4687
3-Point MACE	4.39	3.74
CV Death	2.02	1.24
Death	2.86	1.94
Non-fatal MI	1.85	1.6
MI	1.93	1.68
Non-fatal Stroke	0.91	1.12
Stroke	1.05	1.23

3-Point MACE Components, HR (95% CI)



Related Outcomes, HR (95% CI)



Analyses on CV Death and All-Cause Death

Including All-Cause Death with 3-Point MACE

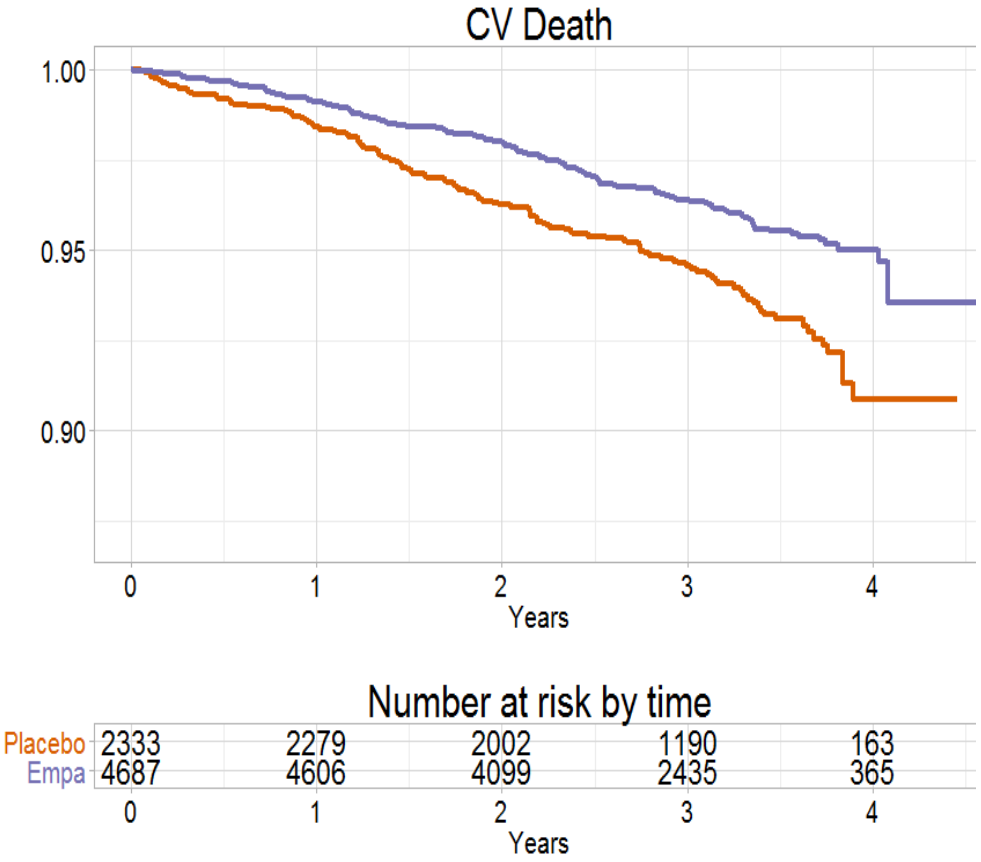
- Primary Analysis assumption
  - Time till MACE after non-CV death equivalent to those censored alive in the same treatment arm
    - Bias favors placebo

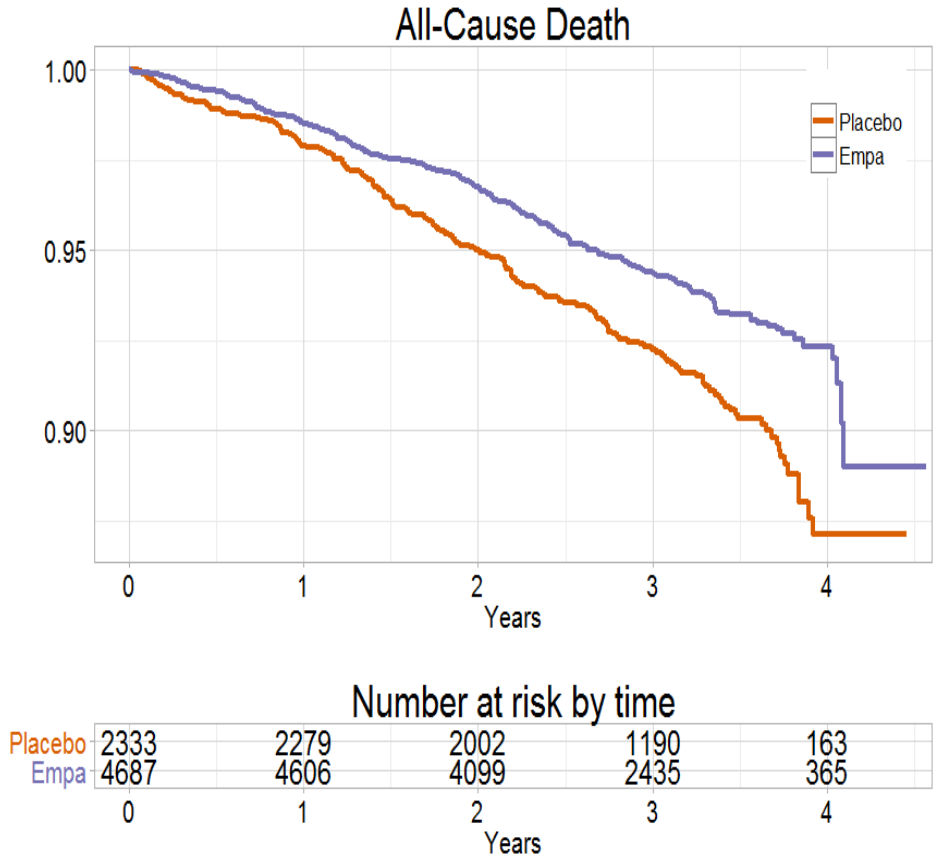
Including All-Cause Death with 3-Point MACE

- Primary Analysis assumption
  - Time till MACE after non-CV death equivalent to those censored alive in the same treatment arm
    - Bias favors placebo

- 3-Point MACE + All-cause Death
  - 135 Additional Events
    - Placebo: 51
    - Empa: 84
  - Results: 0.85 (0.74, 0.97)

Kaplan-Meier, Death





Follow-Up

Premature Discontinuation from Follow-up

	Placebo	Pooled Empa
	N=2333	N=4687
MACE	67 (2.87%)	144 (3.07%)
Death	17 (0.73%)	36 (0.77%)

FDA Analyses Addressing Missing Data

- MACE
  - Multiple imputation for missing follow-up
  - Event rate: Estimated incidence for retrieved dropouts by arm
  - Average Imputed Events
    - Placebo: 10
    - Empa: 20
  - Results relatively unchanged: 0.86 (0.744, 0.996)

FDA Analyses Addressing Missing Data

- MACE
  - Multiple imputation for missing follow-up
  - Event rate: Estimated incidence for retrieved dropouts by arm
  - Average Imputed Events
    - Placebo: 10
    - Empa: 20
  - Results relatively unchanged: 0.86 (0.744, 0.996)

- CV Death and Death
  - Assume patients on empa had an event at censoring
  - Upper bounds remain below 1

Conclusions

- Single CVOT required for new diabetes drugs to show non-inferiority for cardiovascular endpoints
- Trial results showed superiority for 3-Point MACE but not 4-Point MACE
- Currently no precedent when safety studies show superiority
- Superiority due to differences in CV death
  - Premature discontinuation did not affect results

Clinical Assessments

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Rockville, MD
June 28, 2016

Andreea Lungu, M.D.
Division of Metabolism and Endocrinology Products
Office of New Drugs
Center for Drug Evaluation and Research

Additional Considerations Related to the Persuasiveness of the Results and Level of Evidence Necessary to Form the Basis for a New Claim

Considerations Related to Evidence Necessary to Form the Basis for a Claim

- Single study, not specifically designed for efficacy and mostly focused on evaluating atherosclerotic CV risk
- p-value for superiority for 3-point MACE was 0.04
- Primary endpoint driven by effect on CV mortality, lack of effect on stroke or MI component
- Issues related to the handling of silent MI in the trial
- CV death – 'non-assessable' deaths

ISSUES IN HANDLING OF SILENT MYOCARDIAL INFARCTION

Silent MI Infarction

Reasons to Include

- Associated with poor prognosis
- May be particularly important and frequent in a population of patients with diabetes

Challenges

- Challenging endpoint to capture, fully ascertain and analyze in a time to event trial

These events have not always been included as part of the primary composite endpoint in CV outcomes studies evaluating antidiabetic therapies

'Silent MI' in EMPA-REG

- Study design suggested intent to collect silent MI events
  - Central ECG vendor
  - Case report form had silent MI as an outcome event
  - Silent MI was a trigger term for adjudication
  - Clinical silent MI definition was included as a secondary endpoint in the original protocols
- Initially unclear whether it was to be part of 3-point MACE
  - Version 4 of the protocol specified that it was excluded
  - Final SAP defined silent MI purely on ECG
- CEC meeting minutes suggest there was uncertainty about what to do with silent MIs

Limitations of 'Silent MI' Analyses

- ECG criteria only
- Identified events were not reviewed or adjudicated to verify whether it was a silent MI
- Subject to missing data
  - Only about half of patients could be analyzed for this endpoint due to baseline ECG abnormalities, absence of post-baseline evaluation, or intervening ECG changes unrelated to event

'Silent MI' in EMPA-REG

- 3,589 of the 7,020 subjects included in analysis for 'silent MI'
  - 15/1211 (1.2%) 'silent MIs' in placebo group
  - 38/2378 (1.6%) 'silent MIs' in empagliflozin group

	HR (95% CI)
'Silent MI' alone	1.28 (0.70, 2.33)
3-point MACE including 'silent MI'	0.91 (0.73, 1.13)

CV DEATH

CV Death

	Placebo N=2333	Empagliflozin N=4687
CV death	5.9%	3.7%
Sudden CV death	1.6%	1.1%
Death due to MI	0.5%	0.3%
Death due to heart failure or cardiogenic shock	0.9%	0.3%
Death due to stroke	0.5%	0.3%
Other CV death	2.4%	1.6%
Non-assessable	2.3%	1.5%

Information on Non-Assessable Death

	Placebo (n=53)	Empagliflozin (n=71)
Death certificate or proof of death available	19	31
Other	34	40

- No autopsy records

Cardiovascular Death

- Analyses excluding 'non-assessable death' from CV death

	Incl. 'non-assessable'	Excl. 'non-assessable'
3-point MACE (HR [95% CI])	0.86 (0.74, 0.99)	0.9 (0.77, 1.06)
CV Death (HR [95% CI])	0.62 (0.49, 0.77)	0.59 (0.44, 0.79)

Additional Exploratory Endpoints

- Heart Failure
- Renal Endpoints

HEART FAILURE

Hospitalization for Heart Failure

- One of many exploratory endpoints
  - No control for type 1 error
  - Multiple changes to the definition as study was ongoing

Adjudicated Heart Failure Events

	Placebo N=2333	Empagliflozin N=4687	HR (95% CI)
HHF	4.1%	2.7%	0.65 (0.50, 0.85)
HHF or heart failure death	4.5%	2.8%	0.61 (0.47, 0.79)

HHF = hospitalization for heart failure

Hospitalization for Heart Failure

- Study not designed to explore effect in heart failure
  - Baseline heart failure reported in 10.1% of subjects
  - Data on heart failure not collected
- Concomitant medications and doses were not well captured

	Placebo N=2333	Empagliflozin N=4687
ACE-inhibitor/ARB	80.1%	81%
β-blockers	64.2%	65.2%

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker

EXPLORATORY RENAL ENDPOINTS

Issues with the Renal Endpoints

- Exploratory, no control of type 1 error
- Endpoints substantially modified over the course of the trial
  - Endpoints to be used in the final analyses first defined in revised SAP submitted after end of trial
- Endpoints used differ from those traditionally used to establish efficacy and support approval of drugs marketed to treat diabetic nephropathy
- Not clear that the endpoints captured an irreversible effect on renal function or are reliable surrogates for a clinically significant effect on renal outcomes

Exploratory Renal Endpoints

- New onset albuminuria
  - UACR ≥ 30 mg/g
- New onset macroalbuminuria
  - UACR ≥300 mg/g
- Composite of 'new or worsening nephropathy'
  - New onset macroalbuminuria
  - Doubling of serum creatinine and eGFR ≤ 45
  - Initiation of 'continuous renal replacement therapy'
  - Death due to renal disease

UACR = urine albumin to creatinine ratio

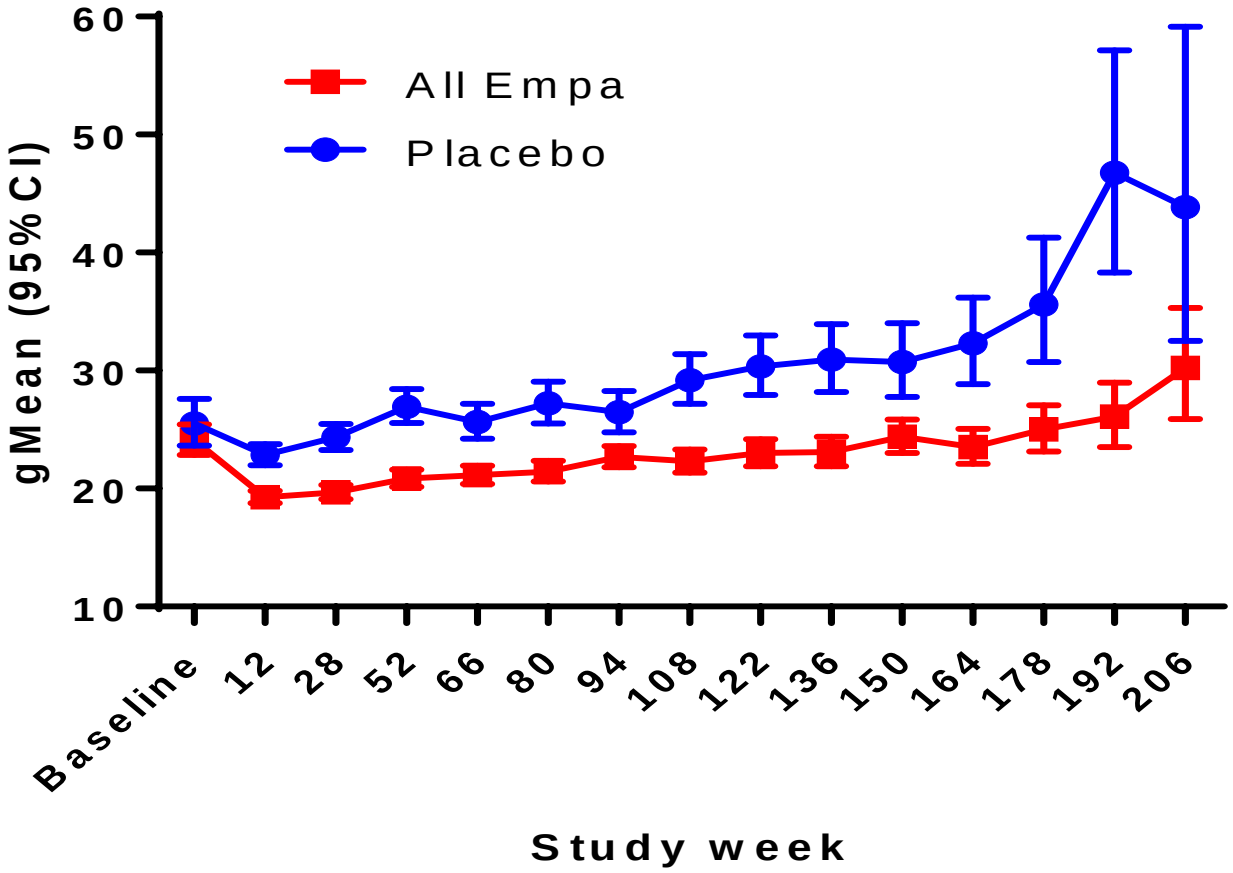
Exploratory Renal Endpoints

Albuminuria-related endpoints

- Only required a single UACR value above the threshold and could include small, transient, and/or reversible changes

	Placebo	Empagliflozin
Subjects without albuminuria at baseline	N=1374	N=2779
• New onset albuminuria	51.2%	51.5%
Subjects without macroalbuminuria at baseline	N=2033	N=4091
• New onset macroalbuminuria	16.2%	11.2%

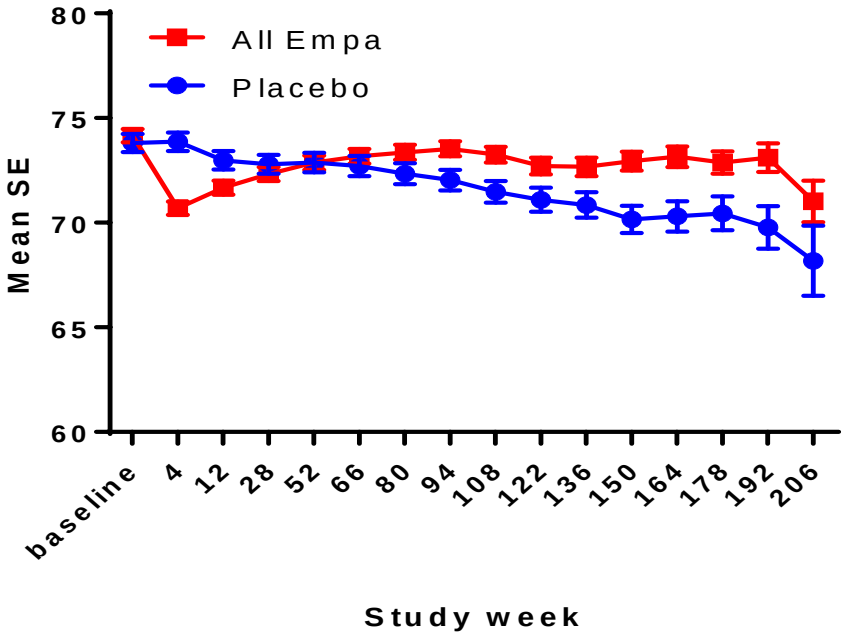
Spot UACR (mg/g) Over Course of Trial



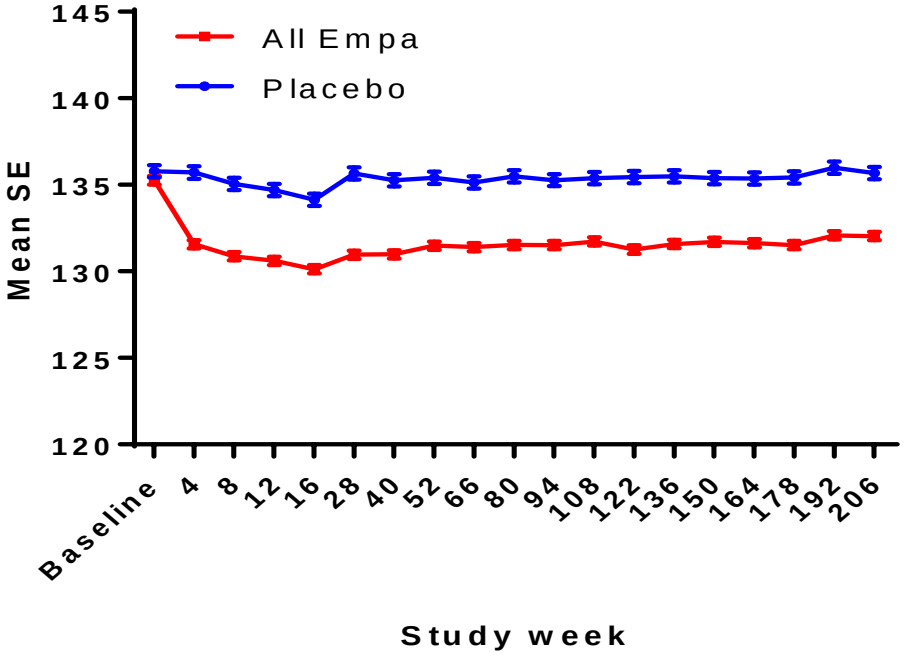
gMEAN = geometric mean

Changes in eGFR and SBP Suggest Hemodynamic Effect on Albuminuria

eGFR (ml/min/1.73m^2)

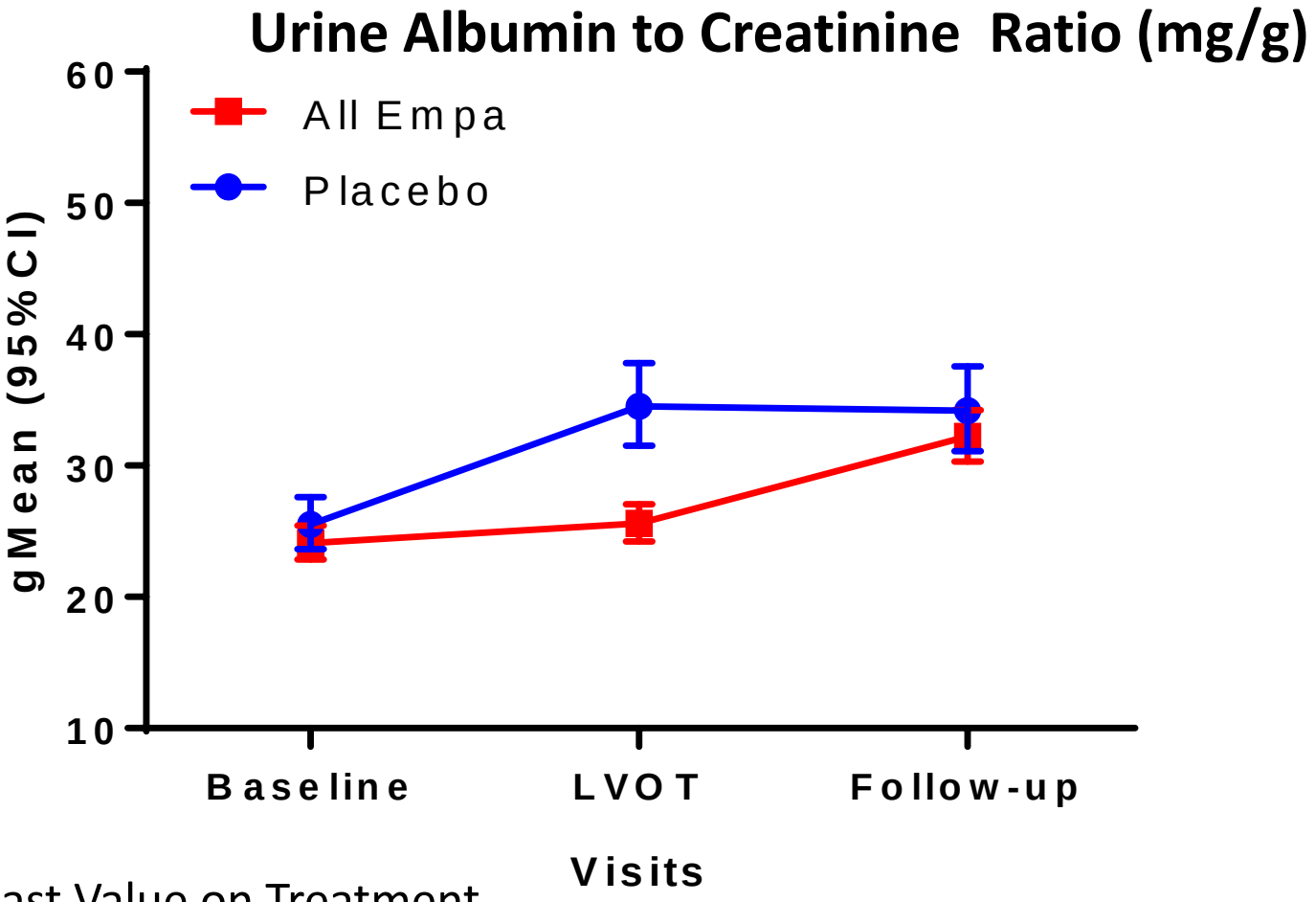


SBP (mmHg)



eGFR = glomerular filtration ratio; SBP = Systolic blood pressure; SE = standard error

Effect on Albuminuria Reflects a Pharmacodynamic Effect



LVOT = Last Value on Treatment

Exploratory Renal Endpoints

'Nephropathy' endpoint

	Placebo	Empagliflozin
Subjects analyzed for 'new or worsening nephropathy'	N=2061	N=4124
• 'New or worsening nephropathy'	18.8%	12.7%
Components of composite		
• New onset macroalbuminuria	16.2%	11.2%
• Doubling of serum creatinine and eGFR ≤ 45 ml/min/1.73 m^2	2.6%	1.5%
• 'Continuous renal replacement therapy'	0.6%	0.3%
• Death due to renal disease	0%	0.1%

Issues with 'Doubling of Serum Creatinine'

- Only required single elevated creatinine value without requiring confirmation that the decline in function persisted after a specified time period as is typically done

	Placebo N=2323	Empagliflozin N=4645
Doubling of serum creatinine	60 (2.6)	70 (1.5)
Events confirmed at ≥30 days	29 (1.2)	25 (0.5)

Issues with 'Continuous Renal Replacement Therapy'

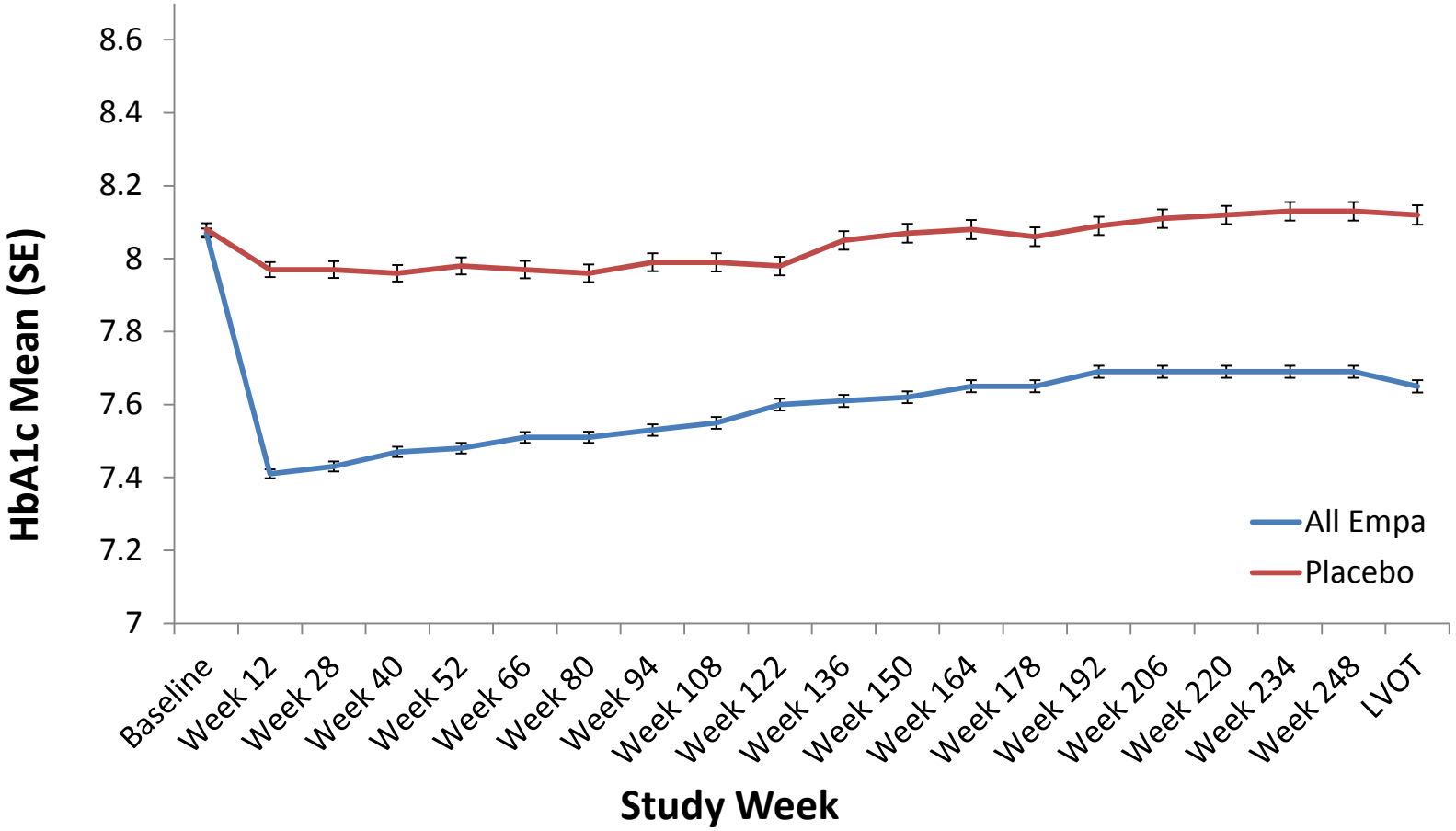
- Identified by searching adverse event and concomitant medication datasets
- Definition not clear: 5/27 narratives reviewed
- **Events do not represent the "end-stage" disease that is typically captured in efficacy endpoints for trials of diabetic nephropathy**
  - Four cases of acute kidney injury requiring temporary dialysis associated with sepsis following aortic valve surgery, terminal heart failure, unstable angina requiring angioplasty, and hyperkalemia
  - One case of acute kidney injury associated with inoperable mesenteric ischemia for which a dialysis catheter was placed but the subject died before receiving dialysis

Conclusions on Exploratory Renal Endpoints

- Renal endpoints were exploratory - no control of type 1 error
- The endpoints selected differ from those typically used to establish efficacy of drugs to treat diabetic nephropathy or to assess effects on irreversible loss of renal function
- Endpoints were re-defined during trial, and processes to identify and confirm renal events were not defined
- Effects on albuminuria appear to be a reversible hemodynamic effect and this may not predict treatment effects on renal outcomes

DIFFERENCES BETWEEN TREATMENT ARMS

Glycemic Control



Glycemic Control

	Placebo N=2333	Empagliflozin N=4687
Increase in dose of background antidiabetic medication	39.9%	23.3%
Addition of antidiabetic medication	27%	14.8%
• Insulin	9.5%	4.2%
• DPP-4 inhibitor	6.5%	4.1%
• Sulfonylurea	6.3%	3%

DPP-4 = dipeptidyl peptidase-4

Other Differences

- Lipids
  - Small dose dependent increase in mean cholesterol
- Hemoglobin and hematocrit
  - Small increases in mean values
  - More likely to shift from normal to above upper limit of normal
- Medications
  - More antihypertensives added in placebo
  - More lipid lowering drugs added in placebo

Cardiovascular Safety

Stroke

- Adjudication of event based on available data
  - No formal assessments specified to be performed at the time of the event
- Criteria:
  - Rapid onset of focal/global neurological deficit
  - Duration ≥ 24 hours (unless therapeutic intervention, imaging shows new infarct or hemorrhage, or death)
  - No readily identifiable non-stroke cause for presentation
  - Confirmation by specialist, imaging, or lumbar puncture

Stroke

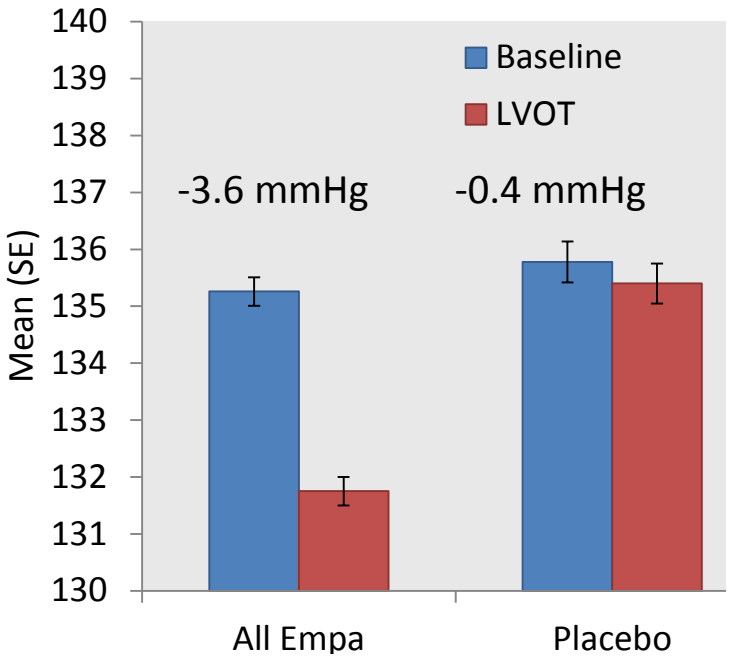
- 233 strokes (fatal and nonfatal)
  - 69/2333 placebo vs. 164/4687 empagliflozin
- 210 nonfatal strokes
  - 60/2333 placebo vs. 150/4687 empagliflozin

	Placebo N=2333	Empagliflozin N=4687	HR (95% CI)
Stroke (fatal and nonfatal)	3%	3.5%	1.18 (0.89, 1.56)
Nonfatal stroke	2.6%	3.2%	1.24 (0.92, 1.67)

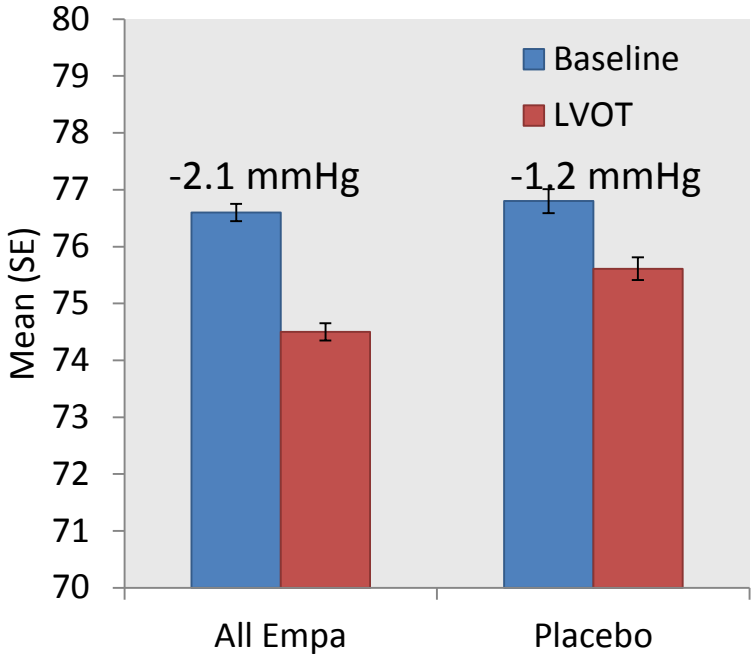
Stroke

- Blood pressure differences between groups

Systolic Blood Pressure



Diastolic Blood Pressure



LVOT=Last value on treatment, SE=Standard error

NON-CARDIOVASCULAR SAFETY

Non-Cardiovascular Safety

- Fractures
- Hepatic injury
- Malignancies
- Venous embolic and thromboembolic events
- Ketoacidosis
- Hypersensitivity reactions
- Urinary tract infections
- Genital infections
- Volume depletion
- Hypoglycemia
- Renal impairment/acute kidney injury

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Fractures

	Placebo N=2333	Empagliflozin N=4687
Any fracture	3.9%	3.8%
• Upper limb fracture[1]	0.5%	1%
• Lower limb fracture[2]	1.1%	0.7%
Serious fracture adverse event	1.5%	1.2%
Fracture event leading to discontinuation	0.6%	0.3%

[1]includes 'humerus fracture', 'radius fracture', 'upper limb fracture', 'wrist fracture', and 'forearm fracture'; [2] includes 'ankle fracture', 'hip fracture', 'tibia fracture', 'femoral neck fracture', 'femur fracture', 'fibula fracture', and 'lower limb fracture'

'Osteoporosis': 0.1% placebo vs. 0.5% empagliflozin

Hepatic Injury

	Placebo N=2333	Empagliflozin N=4687
Hepatic event referred for adjudication	0.5%	0.9%
• 'Probably related'	0	0
• 'Possibly related'	0	0.1%
• 'Unlikely related'	0.5%	0.8%
• 'Indeterminate'	0	< 0.1%

Hy's Law laboratory test profile: 1 (< 0.1%) placebo vs. 6 (0.1%) empagliflozin

Hy's Law profile (elevation in transaminases >3x ULN, total bilirubin > 2x ULN without findings of cholestasis) may suggest potential for drug-induced liver injury if no alternative etiology identified.

Malignancy

- Overall incidence of malignancy balanced
  - 4.4% with placebo, 4.8% with empagliflozin

	Placebo N=2333	Empagliflozin N=4687
Lung cancer	11	19
Bladder cancer	4	10
Renal cancer	5	9
Pancreatic cancer	1	8
Breast cancer	3	7
Melanoma	2	7

Venous Embolic and Thromboembolic Events

- Concerned due to increased hemoglobin and hematocrit
- Based on reported adverse events, **excluding** stroke

	Placebo N=2333	Empagliflozin N=4687
Venous embolic/thromboembolic events	0.9%	0.6%
• Serious events	0.6%	0.5%
• Leading to discontinuation	0.1%	< 0.1%

Summary

- Empagliflozin was non-inferior and superior to placebo for 3-point MACE
  - HR 0.86; 95% CI 0.74, 0.99; p = 0.04 for superiority
  - **Statistical significance appears to be entirely driven by CV death**

- Empaglifozin was non-inferior but not superior to placebo for 4-point MACE
  - HR 0.89; 95% CI 0.78, 1.01; p = 0.08 for superiority

- The review of the non-cardiovascular safety data from the EMPA-REG OUTCOME trial did not raise any new safety concerns.

Summary - Limitations

- Factors that could affect interpretability of the study results and the robustness of our conclusions
  - Single safety study, p value 0.04
  - Handling of silent MI
  - The components of 3-point MACE are not consistent
  - Most CV deaths are non-assessable, unclear what is driving the CV death endpoint

Back-up Slides Shown

Endocrinologic and Metabolic Drugs Advisory Committee

June 28, 2016

EMPA-REG OUTCOME TRIAL: Key Factors Affecting the Interpretation of the Efficacy Findings

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Karen A. Hicks, M.D., FACC
Medical Officer
Division of Cardiovascular and Renal Products

June 28, 2016

Primary Endpoint: Silent MI - 2

- The trial used an algorithm for silent MI that likely did not identify all potential events
- Time to event data were unreliable
- There was reportedly no oversight by the CEC of these events
- Some patients in the trial lacked baseline 12-lead electrocardiograms (ECGs)

Unlikely led to differential ascertainment. Silent MI findings are likely unreliable.

Undetermined Cause of Death - 1

"Undetermined Cause of Death refers to a death not attributable to one of the categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to 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. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few patients in well-run clinical trials.

Hicks KA, Hung HM, Mahaffey KW, Mehran R, Nissen SE, Stockbridge NL, Targum SL, Temple R. Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials. Draft Definitions for CDISC August 20, 2014.

Undetermined Cause of Death - 2

"A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the CV category (e.g., presumed CV death, specifically 'death due to other CV causes').
Nevertheless, the appropriate classification and analysis of undetermined causes of death depends on the population, the intervention under investigation, and the disease process. The approach should be prespecified and described in the protocol and other trial documentation such as the endpoint adjudication procedures and/or the statistical analysis plan."

Hicks KA, Hung HM, Mahaffey KW, Mehran R, Nissen SE, Stockbridge NL, Targum SL, Temple R. Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials. Draft Definitions for CDISC August 20, 2014.

Primary Endpoint: CV Death - 2

- **Common analytic approach to presume that all undetermined deaths are CV deaths BUT**
  - **Should be prespecified**
  - **The number of undetermined deaths should be few → missing data**
- **Effect on CV death still robust when undetermined deaths are excluded (HR 0.59; 95% CI 0.44, 0.79)**