EMPA-KIDNEY Post-Trial Follow-Up
Data Analysis Plan (EDMS 7987)

Version History

Version	Description	Authors
1.0	First released version	Created by: William G. Herrington, Natalie Staplin, Jonathan Emberson, David Preiss, Colin Baigent and Richard Haynes (DEC2022-MAR2023) Review by Steering Committee (07MAR2023) and sponsor biostatistics and data science team (MAR-APR2023) Released for use by William G. Herrington (02MAY2023)

This is a controlled document. Distribution and approval is to be managed using the Electronic Document Management System or iPassport

TABLE OF CONTENTS

Contents

1 RELEVANT PROCEDURAL DOCUMENTS 3
2 ABBREVIATIONS 3
3 INTRODUCTION 3
4 PARTICIPANT FLOW & BASELINE CHARACTERISTICS 3
5 USE OF SGLT-2 INHIBITORS BY TIME 4
6 RANDOMIZED ASSESSMENTS 4
6.1 Hypotheses 4
6.2 Primary randomized assessment 4
6.3 Secondary randomized assessments 5
6.4 Tertiary randomized assessments 5
6.4.1 Mortality-based outcomes 5
6.4.2 *Subgroup analyses of the primary PTFU assessment* 5
6.5 Exploratory eGFR-based analyses 6
7 STATISTICAL METHODOLOGY 6
7.1 Methods of analysis 6
7.2 Subgroup analyses and tests for heterogeneity 6
7.3 Handling of missing and incomplete data 7
7.3.1 Handling of missing central eGFR values 7
7.4 Censoring schema for time-to-event endpoints 7
7.4.1 Date of censoring for intention-to-treat analyses 7
8 REFERENCES 7

1 RELEVANT PROCEDURAL DOCUMENTS

Document title	EDMS#
EMPA-KIDNEY Protocol	5434
EMPA-KIDNEY Post-Trial Follow-Up Protocol Supplement	7279
EMPA-KIDNEY Data Analysis Plan (SOP11)	6290

2 ABBREVIATIONS

Abbreviation	Definition
CKD	Chronic kidney disease
DAP	Data analysis plan
EDMS	Electronic document management system
eGFR	Estimated glomerular filtration rate
MMRM	Mixed model repeated measures
MRA	Mineralocorticoid receptor antagonist
PTFU	Post-trial follow-up
RAS	Renin-angiotensin system
SGLT-2	Sodium glucose co-transporter-2

3 INTRODUCTION

This document provides a Data Analysis Plan (DAP) for the EMPA-KIDNEY Post-Trial Follow-Up (PTFU) substudy. The substudy's aim is to continue follow-up of a subset of consenting and surviving EMPA-KIDNEY participants for at least 2 years after the end of the within-trial period in order to provide valuable information on the longer-term effects of empagliflozin 10 mg daily versus matching placebo on mortality and kidney disease progression. During this time, participants are not issued with any study treatment and no research samples for central analysis are collected: follow-up will be performed remotely for selected key pre-specified efficacy outcomes. However, participants may be prescribed a sodium glucose co-transporter 2 (SGLT-2) inhibitor by local clinicians. Wherever possible, participants and researchers remain blind to original study treatment allocation.

This DAP sets out the main analyses for the key publications of the EMPA-KIDNEY PTFU substudy. The nature of all analyses using PTFU data (randomized or observational) cannot be specified in detail but, where appropriate, a general analytical approach is set out. Approaches, wherever possible, should follow those set out in EMPA-KIDNEY's main DAP (SOP11; EDMS#6290).

4 PARTICIPANT FLOW & BASELINE CHARACTERISTICS

A CONSORT diagram will show participant flow and will include both the within trial and PTFU periods. It will count (by arm) the numbers of participants who:

- Were randomized

- Completed the within trial period of follow-up (with numbers who withdrew consent or were lost to follow-up)
- Were eligible for PTFU (i.e. survived and completed final follow-up)
- Entered PTFU (with reasons for exclusion [i.e. did not provide optional consent or the site was not included])
- Were lost to follow-up or withdrew consent during PTFU
- Were analysed (Note: all analyses follow the principle of intention-to-treat and will therefore include all participants)

Median follow-up among survivors will be calculated for the entire follow-up period, and separately for its two components (i.e. the within-trial and PTFU periods). Baseline characteristics of the participants who did not enter PTFU (e.g. due to non-provision of consent or exclusion of the site) will be provided alongside the baseline characteristics for the overall trial and those that did enter PTFU, using the categories set out in the main DAP.

5 USE OF SGLT-2 INHIBITORS BY TIME

SGLT-2 inhibitor use will be estimated by year of follow-up, with SGLT-2 inhibitor use defined as a record of taking an open-label SGLT-2 inhibitor, or reporting taking at least 80% of study treatment (during the within trial period only). A separate estimate of "average" use over the within-trial and relevant PTFU periods of follow-up will be provided. Supplementary analyses using a similar approach will provide information on RAS inhibitor and MRA use over time.

6 RANDOMIZED ASSESSMENTS

All primary, secondary and tertiary assessments will follow the principle of intention-to-treat and will consider the entire follow-up period (i.e. will combine the within trial and PTFU periods).

6.1 Hypotheses

For statistical tests (other than tests for heterogeneity or trend), the null hypothesis will be that the effect of allocation to empagliflozin on the parameter of interest in the target population is the same as the effect of allocation to placebo for the entire follow-up period which includes both within trial and PTFU periods combined (and hence the alternative hypothesis will be that the effect of allocation to empagliflozin is not the same as the effect of allocation to placebo for the entire follow-up period).

6.2 Primary randomized assessment

The primary assessment will be the effect of allocation to empagliflozin on the time to the first EMPA-KIDNEY primary composite outcome event of kidney disease progression or cardiovascular death for the entire follow-up period. Whether the effect of allocation to empagliflozin versus placebo on the primary outcome differs by year since randomization will be explored enabling interpretation of PTFU results in the context of the changing use of SGLT-2 inhibitors with time.

The EMPA-KIDNEY main Protocol (EDM#5434) and main DAP (SOP11; EDMS#6290) provide full details of the definitions for the trial's primary composite outcome and its components, which were based on central eGFR measurements wherever possible. As central samples are not being collected during PTFU, all eGFR-based assessments for the PTFU period will necessarily be relative to the local eGFR measurement at randomization (or the measurement shortly before, if unavailable at randomization).[1] For the primary PTFU assessment, the main results of the trial's primary outcome from the within trial period will be carried over,[2] including the eGFR-based outcomes (i.e. any eGFR-based outcome recorded at the within trial period's Final Follow-up Visit without a confirmatory result will still be accepted as "sustained" despite the availability of eGFR measurements in the PTFU period). A sensitivity analysis using only local eGFR measurements collected throughout the entire follow-up period will be conducted and this analysis will not differentiate the within versus PTFU periods (i.e. in this sensitivity analysis, a locally-measured eGFR recorded at the last PTFU will be designated as the "last scheduled visit" for the purposes of "sustained" definitions).

6.3 Secondary randomized assessments

The key secondary assessments for the entire follow-up period (i.e. the within trial plus PTFU periods combined) are time to first occurrence of:

a) Kidney disease progression; and

b) Death from any cause or end-stage kidney disease (ESKD)

The other secondary outcome for the entire follow-up period is time to first occurrence of ESKD (with detail of the other components of kidney disease progression presented for completeness).

6.4 Tertiary randomized assessments

6.4.1 Mortality-based outcomes

The tertiary outcomes for the entire follow-up period are time to death from any cause and, separately, death from cardiovascular and non-cardiovascular causes.

6.4.2 *Subgroup analyses of the primary PTFU assessment*

The primary assessment will be assessed among subgroups of participants based on data recorded at baseline. These will focus on four subgroups: the three key subgroups of interest by: (a) diabetes status, (b) baseline eGFR, and (c) baseline urinary albumin-to-creatinine ratio, plus (d) by primary kidney disease (using definitions specified in the main DAP).

[1] Local eGFR measurements are considered to be sufficiently reliable for PTFU assessments as sensitivity analyses for the within trial primary outcome analysis and eGFR slope analyses using these local records provided similar results to central sample based analyses. Results of EMPA-KIDNEY's primary outcome and tertiary eGFR slope-based outcome re-analysed using only local (rather than central) eGFR results will be provided as supplementary materials for the main PTFU publication, if not already published in another peer reviewed manuscript.

[2] Any data errors may be subject to data changes leading to minor differences between publications (which will be explained in footnotes, if necessary).

6.5 Exploratory eGFR-based analyses

The acute reversible dips in eGFR on commencing an SGLT-2 inhibitor make eGFR slope analyses more complex. The PTFU period will start with systematic discontinuation of study treatment (including "rebounds" of acute dips) among those allocated to the empagliflozin group followed by non-systematic initiation of SGLT-2 inhibitors in participants in both groups. In addition, there will be considerable between-person variation in the number of years from randomization to the end of the trial period (i.e. the 'within-trial' period will vary between participants) so the impact of these eGFR rebounds on mean eGFR in each group will average across a distribution of times since randomization. Consequently, eGFR slope analyses will be problematic to model and interpret. eGFR-based analyses by time will therefore all be exploratory with sensitivity analyses used to assess the robustness of findings. The key eGFR-based explorations will involve mixed model repeated measures (MMRM) approaches to estimate mean eGFR at each follow-up time point throughout the entire follow-up period and will emphasize results from local laboratory measurements. This will enable characterisation of the nature of any PTFU eGFR rebounds and dips that may occur, as well as the nature of the subsequent rates of change in eGFR. The MMRM model will be calculated overall and in the 4 subgroups described in section 6.4.2.

7 STATISTICAL METHODOLOGY

7.1 Methods of analysis

Cox proportional hazards regression adjusted for the variables specified in the protocol for the minimization algorithm (age, sex, prior diabetes, eGFR, urinary albumin-to-creatinine ratio, and region) will be used to estimate the hazard ratio associated with allocation to empagliflozin versus placebo (with the Wald chi-square statistic used to both test significance and generate an asymptotic 95% confidence interval).(1) Any ties will be handled using Breslow's method. If any regression models fail to converge, the approaches set out in the main DAP will be followed.

Kaplan-Meier estimates for the time to each of the primary and secondary assessments will also be calculated. Plots will include indicators of median within-trial and entire follow-up durations. To explore whether the effect of allocation to empagliflozin versus placebo on the primary outcome differs over time, follow-up time will be split into categories by year since randomization and the significance of the time x treatment allocation interaction will be assessed.

In addition to the pre-specified comparisons, other post-hoc analyses may be performed with due allowance for their exploratory and, perhaps, data-dependent nature. For example, how well estimates from eGFR-slope analyses using the methods specified in the DAP visually fit with MMRM estimates of eGFR by time will be possible.

7.2 Subgroup analyses and tests for heterogeneity

Tests for heterogeneity of effects observed in subgroups will follow the methods set out in the main DAP. Interpretation of results will take into account the number of statistical tests performed.

7.3 Handling of missing and incomplete data

Missing eGFR values will be handled as detailed below. Participants with missing values relevant to subgroup analyses will be included in the subgroup containing the median value.

7.3.1 Handling of missing central eGFR values

Methods will follow the approaches from the main DAP, with the exception of when local eGFR measurements are used in preference to central samples in the relevant analyses (e.g. section 6.2 and 6.5). eGFR will be estimated using the same CKD-EPI formula as the main DAP analyses,(2) and will use the DAP defined follow-up windows and the principles of the algorithm to define sustained. If multiple local eGFR measurements are available in any one follow-up window, then the eGFR closest to the ideal follow-up day will be used to define the eGFR for that particularly window. If there are two eGFRs recorded at the last follow-up, the last of these eGFRs will be included in analyses, and will be included irrespective of whether or not it is the eGFR closest to the ideal follow-up day. This may result in two eGFRs in the last follow-up window.

7.4 Censoring schema for time-to-event endpoints

7.4.1 Date of censoring for intention-to-treat analyses

It is the aim at each follow-up to ascertain all components of the primary outcome. Censoring dates for those who withdraw consent or who are lost to follow-up will be derived from information collected at their most recent follow-up before consent withdrawal or loss to follow-up. For those that did not consent to PTFU, the censoring will be the same as their within trial date. Otherwise, the censoring date will be the date of death or the date of the last follow-up (using the date of last known to be alive). Note that all participants will contribute to the primary outcome irrespective of whether post-trial eGFRs were available, with participants censored for the eGFR-based components of outcomes at the point local eGFR measurements are unavailable (e.g. participants remain at risk of the ESKD and cardiovascular death components of the primary composite outcome even in the absence of post-trial eGFR measurements).

8 REFERENCES

1. Cox DR. Regression Models and Life-Tables. J R Stat Soc B. 1972;34(2):187-+.

2. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.