Protocol Supplement:
EMPA-KIDNEY Post-Trial Follow-Up

A post-trial observational substudy of EMPA-KIDNEY participants
followed for mortality and kidney disease progression

Short title: EMPA-KIDNEY PTFU

EDMS #7279

Table of contents

1. SUMMARY

This document provides the rationale and design of an EMPA-KIDNEY substudy which aims to continue to follow a subset of participants who provided supplemental consent at their original EMPA-KIDNEY Screening Visit to provide updated information about their health after the scheduled within-trial follow-up period. The substudy does not alter the main EMPA-KIDNEY trial Protocol in any respect.

Post-trial follow-up is purely observational (i.e. no study treatment will be issued) and will begin after their Final Follow-up Visit (i.e. after study treatment has been retrieved). EMPA-KIDNEY is a streamlined trial and the post-trial follow-up period will be even more streamlined with participants followed remotely to ascertain updates only on mortality and kidney disease progression. Participants will not be required to attend face-to-face study visits and will not need to provide any further blood/urine samples for central analyses. Ascertainment of mortality and kidney disease progression data will instead rely on reports from local clinicians, contacting participants (where necessary), registries, and retrieval of results of local creatinine blood testing collected for routine clinical monitoring.

2. BACKGROUND

The EMPA-KIDNEY randomized trial compares empagliflozin 10 mg once daily versus matching placebo in 6609 participants with established chronic kidney disease (CKD), with or without diagnosed diabetes mellitus. The primary outcome is a composite of kidney disease progression (defined end-stage kidney disease [ESKD: i.e. initiation of maintenance dialysis or receipt of a kidney transplant], a sustained estimated glomerular filtration rate [eGFR] <10 mL/min/1.73m², renal death, or a sustained ≥40% decline in eGFR from randomization) or cardiovascular death. The trial's treatment phase (referred to as the within-trial period) is planned to continue until 1070 first primary outcomes have accrued (expected in 2022 after a median of about 2.5 years follow-up[a]). The majority of the primary outcomes are predicted to be based on laboratory measurements of kidney function (i.e. eGFR) with about 310 ESKD outcomes and 270 cardiovascular deaths. This relatively small number of ESKD events during the treatment period is because CKD progression to ESKD can take many years. A post-trial observational study following consenting surviving participants

[a] An interim analysis is planned after about 150 ESKD events, and may lead to an early trial stop with slightly fewer primary outcomes than 1070 following trial completion.

once they have completed the trial enables assessment of whether any reductions in the risk of a sustained decline in eGFR during the treatment phase translate into long-term benefits on the clinically more important outcome of ESKD or cardiovascular death, or indeed, if effects regress. Such post-trial follow-up has been invaluable in assessing the long-term effects of simvastatin on mortality[1], and has suggested that intensive glucose-lowering may impart a legacy effect on risk of ESKD.[2,3] Long-term data from EMPA-KIDNEY would be particularly invaluable for direct assessments of health economic value, as dialysis and kidney transplantation are expensive and empagliflozin has the potential to substantially delay and perhaps even prevent development of ESKD, as well as reduce mortality. Accrual of further data would also improve the cohort's value for observational epidemiology.

EMPA-KIDNEY's streamlined design aimed to minimize extra work for collaborating doctors and hospitals, with only essential information collected. The trial focusses on readily identifiable and important clinical outcomes, with participant reported information recorded by participant interview and laboratory measured creatinine as the main sources of follow-up data. Post-trial follow-up is designed to follow this model and focus on ascertaining key efficacy data on mortality and kidney disease progression (i.e. it is even more streamlined).

Preparations for a possible post-trial follow-up observational study were made during the main EMPA-KIDNEY Protocol design. As described in the main Protocol (section 3.5.4), study staff at Local Clinical Centres (LCCs) or Regional Coordinating Centres (RCCs) may also attempt to follow participants (where appropriate consent and approvals are in place) by reviewing available information on routine healthcare systems and registries. Such information could also be used for long-term follow-up, alongside participant questionnaires administered by telephone, mail or electronically. Participants were asked at Screening Visits to provide Supplemental Consent to be contacted by the study coordinators to provide updated information about their health after the scheduled follow-up period. About 95% of randomized participants from the regions interested in contributing to this substudy have provided such consent. This document describes the planned processes for collecting additional clinical information from a subset of EMPA-KIDNEY participants following completion of the main treatment (i.e. the within trial) phase. This EMPA-KIDNEY post-trial follow-up Protocol supplement does not alter the main EMPA-KIDNEY Protocol in any respect.

3. PLAN OF INVESTIGATION

This plan was formulated and agreed while the Executive and Steering Committees, funders, and investigators were blind to the main trial results. Alterations to this plan, including the proposed

outcome collection, may be recommended by the trial Steering Committee, once the main trial results become available.

3.1. Eligibility

Any randomized EMPA-KIDNEY participant from a contributing region/site who consented to be contacted to provide updated information about their health after the scheduled follow-up period, and was known to be alive at Final Follow-up.

3.2. Aims

The aim of extended post-trial follow-up is to continue follow-up of a subset of 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 on mortality and kidney disease progression in people with CKD (see Figure). During this time, participants will not be issued with any study treatment and no research samples will be collected: follow-up will be performed remotely for selected key pre-specified efficacy outcomes.

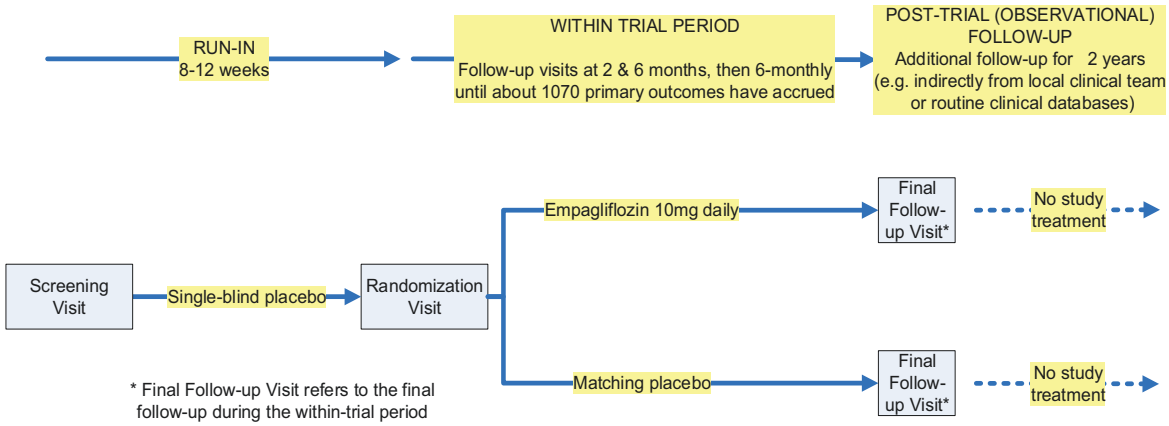

Figure: *Outline of main within-trial and post-trial follow-up schedule*

3.3. Data Analysis Plan

All assessments will involve intention-to-treat comparisons among all randomized participants of the effects of allocation to empagliflozin versus placebo on the trial's primary outcome of kidney disease progression or cardiovascular death, and separately on the secondary outcomes, and the mortality-based tertiary outcome of cause-specific mortality. Assessments using time-to-event approaches will use a Cox model adjusting for each of the minimization variables (see main Protocol) and be irrespective of whether the outcome occurred during the within- or post-trial follow-up period.

Specifically, the primary assessment will be the time to the first occurrence of:

(i) Kidney disease progression (defined as ESKD, a sustained decline in eGFR to <10 mL/min/1.73m^2, renal death, or a sustained decline of ≥40% in eGFR from randomization); or

(ii) Cardiovascular death.

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 the primary outcome at the point local eGFR measurements are unavailable (i.e. 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). See the main Protocol for definitions of 'sustained'. This definition will remain unchanged irrespective of whether eGFR measurement was performed during the within- or post-trial period. As central samples are not being collected during post-trial follow-up, all eGFR-based assessments will be relative to the local eGFR measurement at randomization (or shortly before if unavailable at randomization).

The key secondary assessments are time to first occurrence of:

a) Kidney disease progression; and

b) Death from any cause or ESKD

The other secondary outcome assessment is time to first occurrence of ESKD

The tertiary outcomes are time to death from any cause and, separately, death from cardiovascular and non-cardiovascular causes. Cardiovascular causes include coronary death, other cardiac (including heart failure and sudden cardiac death not known to be coronary), stroke, other cardiovascular and presumed cardiovascular. Non-cardiovascular includes renal, infection, cancer, other medical, and non-medical causes.

In addition, exploratory assessments will include analyses of the effects of empagliflozin on:

a) The primary outcome among particular subgroups of participants based on data recorded at the randomization visit. The subgroup analyses of the primary composite outcome which are of key interest remain those involving subdivision by baseline: (a) diabetes status, (b) eGFR, and (c) urinary albumin:creatinine ratio (as specified in the main Protocol). Other subgroups analyses of interest include by baseline primary renal disease (as specified in the main trial Data Analysis Plan [SOP11]).

b) Annual rate of change in eGFR calculated for the whole within- and post-trial follow-up period (combined) for the overall population and among the key subgroups. Methods for

these, and all the assessments above, will follow the principles and methods set out in the pre-specified main study Data Analysis Plan (SOP11), but will be formalized in a separate EMPA-KIDNEY PTFU Data Analysis Plan which will include any additional analyses needed to account for specific post-trial follow-up considerations (e.g. reversal of any acute effects on eGFR on cessation of study treatment and approaches to controlling for type 1 errors).

c) Additional healthcare costs per ESKD and per death avoided using previously established methods and formalized in a separate Data Analysis Plan.[5]

As no study treatment is issued during the post-trial follow-up phase and the safety of empagliflozin is already well characterised, there are no pre-specified assessments of Serious Adverse Events (SAEs) or other biochemical data from the post-trial observational follow-up period (other than those specified above).

3.4. Study Duration

Wherever possible, post-trial follow-up of all surviving randomized participants will continue for at least 2 years beyond the end of the within-trial period in order to provide valuable information on the longer-term effects of the study treatment (with assessments performed after about a median of about 1 year's post-trial follow-up (i.e. an interim assessment) and again after about 2 years.

4. SUMMARY OF PRACTICAL PROCEDURES

4.1. Data Collection

During post-trial follow-up, only information on the selected efficacy outcomes and cause-specific mortality will be sought for all surviving and consenting EMPA-KIDNEY participants (see Appendix I). The main method of follow-up will be indirect from local clinical teams or from registries/routinely collected healthcare data. Direct follow-up of participants by telephone (or mail or web) will only be considered where other data are unavailable (see Appendix II). No face-to-face study visits are planned. Information collected will be entered directly into the study's computer-based system with no other requirement for the LCCs to retain other sources of information (e.g. medical notes used to completed follow-up or paper copies of laboratory results) and no planned specific monitoring. However, if there are inconsistencies or concerns about the quality of data identified by Central Coordinating Office (CCO) or Regional Coordinating Centre (RCC) staff, random checks may be performed (e.g. a request for a subsample of local laboratory results to be shared by the LCC for checking with the RCC or CCO by secure remote methods). A copy of the data entered by each LCC will also be stored on a 3rd party server under the control of the Local Lead Investigator (analogous to the main trial's data entry collection methods).

Substudy assessments are limited to mortality and kidney disease progression. Information on these outcomes will be captured in a streamlined fashion and full SAE reports will not be collected. However, if a local investigator considers an adverse event to be related to randomized treatment received during the within-trial period (restricted to adverse events of specialist interest [AESI] or SAE as defined in 2.5.1.1 of the main Protocol), CCO-based clinicians will collect additional information as per standard AESI and Suspected Serious Adverse Reaction reporting (including the details specified in section 2.5.1.3 of the main Protocol). These reports will be provided to the Sponsor within 24 hours.

4.1.1. Record Linkage to Routine Clinical Databases

Wherever possible and with relevant approvals, information on death and renal status (i.e. dialysis or kidney transplantation) will be collected long-term through linkage to available sources of health information, including electronic healthcare records systems, national registries and clinical audit databases (see Appendix II). For example, in the UK, information will be sought from NHS Digital, the UK Renal Registry and equivalents in the devolved nations.

4.1.2. 6-monthly LCC Assessments

Follow-up assessments of surviving participants are to be performed by trained LCC staff about every 6 months (or by the RCC or delegated organization should LCC follow-up be infeasible). At each assessment, interview of the local clinical team or review of participant's medical records will be performed to collect details about current renal status (i.e. dialysis and transplantation), latest local creatinine/eGFR measurement, and any current use of relevant co-medication (limited to SGLT-2 inhibition, renin-angiotensin system inhibition, or mineralocorticoid receptor antagonism – and not a full list of co-medications). Contact details of participants, their local doctor and their relative/carer will also be checked and stored according to local requirements, as will any identifiers required for linkage. Such data will be recorded at the LCC, RCC and/or CCO, as per local permissions.

Where contact by the local clinical team is not possible, follow-up information may be collected directly from participants or indirectly through discussion with a relative or carer or primary care physician, using telephone, mail-based or other electronic means. Such follow-up could be conducted by the CCO or RCC (or an appropriate delegate [e.g. another LCC]), as per local permissions.

4.2. Study Treatment and Unblinding

At the final main study visit, all participants are to stop study treatment and are to be advised to contact their own doctor to discuss the appropriate use of SGLT-2 inhibition and other treatments for kidney disease as part of routine ongoing treatment. During the post-trial follow-up period, no study treatment will be issued to participants. However, participants may receive open-label SGLT-2 inhibition from their own doctor.

In order to minimize the potential for biased reporting of clinical events, participants and their doctors will not be unblinded to the original treatment allocation routinely at the end of the main study. However, because it is conceivable that knowledge of the original treatment allocation could materially influence the medical management of a participant, should unblinding be requested, it will remain available via the CCO. Other options for RCCs to support non-urgent unblinding will also be available.

4.3. Consent, and its withdrawal

At about the time of Final Follow-up for the within-trial phase, or sometime shortly thereafter, EMPA-KIDNEY participants who have provided supplemental consent for contact after the trial will be provided with information about post-trial follow-up. This will include contact details of their local

study team should they wish to change their consent. The post-trial information leaflet will include an explanation about the purpose of post-trial follow-up and the planned ongoing access to their medical records and/or linkage to registries. It will be possible for the post-trial information leaflet to be provided by hand, sent by mail, or read to participants. It will not be necessary for participants to re-attend study clinics and sign any document to join post-trial follow-up because they have already provided consent at entry into EMPA-KIDNEY. Unlike the within-trial consent form, any signatures from LCC staff/patients (e.g. on Notification of Information to Participants [NIP] forms) will not be subject to central monitoring during the post-trial follow-up phase.

As per the main Protocol, participants are free to withdraw consent for some or all aspects of follow-up at any time. Participants will be asked to specify which aspect(s) of the study consent is being withdrawn: for example, direct contact with the participant, collection of information from non-study doctors or use of routine data sources. The date of consent withdrawal will be recorded onto the study's computer-based system. Note that, in accordance with FDA guidance, data that have already been collected and incorporated into the study database will continue to be processed.

4.4. Confirmation and Verification of Clinical Events

As per the main Protocol, outcomes based on laboratory values (e.g. sustained ≥40% decline in eGFR) and ESKD will not be adjudicated. Local Investigators will be asked to confirm changes in renal status. The CCO/RCCs may seek additional documentation (e.g. hospital notes, autopsy results) for reported information (e.g. for deaths where there is uncertainty as to whether a death was the result of cardiovascular or non-cardiovascular cause). The RCC will be responsible for coordinating the collection of relevant supporting information (with assistance from the LCC, where appropriate), with clinicians based at or overseen by the CCO providing the final assessment. Any adjudication will be conducted in accordance with the relevant section of the main trial's adjudication SOP (SOP9b) and will be conducted blind to the original study treatment allocation.

5. Appendix I – Visit Schedule and Procedures

Task	Activity	Record linkage[a]	6-monthly LCC assessments (local clinical team interview +/- review of local records)	6-monthly participant assessments[b] (by telephone, mail or web)
Demographics	Check and update contact details and identifiers		✓	**(✓)**
Medication	Record current SGLT-2 inhibitor use, and any co-prescription of renin-angiotensin system inhibitor or mineralocorticoid receptor antagonist	**(✓)**	✓	**(✓)**
Outcomes	Record death (with cause) and renal status	**(✓)**	✓	**(✓)**
	Record latest local creatinine/eGFR measurement (performed as part of routine clinical care)	**(✓)**	✓	**(✓)**

✓=likely main source of follow-up information; **(✓)=**sources of follow-up information that will be sought, where necessary (see footnotes below)

[a] Where feasible, data are to be collected through linkage to available sources of health information, including electronic healthcare records systems, national registries (death and renal) and clinical audit databases. If sufficient data are available from record linkage, 6-monthly assessments may be discontinued and record linkage remain the sole source of follow-up in such regions.

[b] Where record linkage and LCC assessments are not possible, direct contact with participants or their relatives and carers will be performed ideally by telephone, but alternative means of follow-up (e.g. mail, web- or smartphone based methods) may be used when telephone follow-up fails.

6. Appendix II – Feasibility Assessment

Country	LCC assessments (local clinical team interview +/- review of local records)		Record linkage			
	Relevant current medication, renal status or death	Latest creatinine/ eGFR	Relevant current medication	Renal status	Death	Latest creatinine/ eGFR
UK	✓	✓	(✓)	✓	✓	(✓)
Japan	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)
Malaysia	✓	✓	×	✓	✓	×
Germany	✓	✓	×	×	×	×
Italy	✓	✓	×	×	×	×
USA	✓	✓	×	(✓)	(✓)	×
Canada	✓	✓	(✓)	(✓)	(✓)	(✓)
China	✓	✓	×	×	×	×

✓=possible; **(✓)=**may be possible in all or a subset of participants; ×=not possible at time of protocol writing. Exact arrangements may vary according to local requirements. Participants with access to their laboratory data may also be able to provide creatinine results.

7. REFERENCES

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