EMPA-KIDNEY Magnetic Resonance Imaging Substudy Data Analysis Plan (EDMS #7662)

Version History

Version	Description	Authors
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1 RELEVANT PROCEDURAL DOCUMENTS

Document title	EDMS#
EMPA-KIDNEY Protocol	5434
EMPA-KIDNEY MRI Substudy Protocol Supplement	7083
EMPA-KIDNEY Data Analysis Plan (SOP11)	6290

2 ABBREVIATIONS

Abbreviation	Definition
ADC	Apparent diffusion coefficient
ASL	Arterial spin labelling
BOLD	Blood oxygen level dependency
CKD	Chronic kidney disease
EDMS	Electronic document management system
eGFR	Estimated glomerular filtration rate
MRI	Magnetic resonance imaging
MOLLI	Modified Look–Locker inversion recovery
SOP	Standard operating procedure
TKV	Total kidney volume
uACR	Urine albumin-to-creatinine ratio

3 INTRODUCTION

This document provides a Data Analysis Plan for the EMPA-KIDNEY magnetic resonance imaging (MRI) substudy, which has performed renal and cardiac MRI imaging in a subset of approximately 170 EMPA-KIDNEY participants recruited from the UK and Germany. An outline MRI data analysis plan was provided in the MRI substudy's Protocol Supplement. The purpose of this MRI Data Analysis Plan is to define, before unblinding of the treatment allocation, detail of pre-specified randomized analyses to be presented in initial publication(s) of the substudy. The nature of all analyses (randomized or observational) including those related to subsequent publications and exploratory analyses cannot be specified in detail but, where appropriate, a general analytical approach is set out. Approaches, wherever possible,

will follow those set out in EMPA-KIDNEY's main data analysis plan (to which this document should be considered supplementary) so are not repeated here.

4 BACKGROUND

The aim of this substudy is to evaluate the effect of empagliflozin 10mg versus matching placebo on markers of inflammation, fibrosis and perfusion of the kidney at around 18 months after randomization. Examples of MRI methods and what they assess are shown in Table 1.

MRI method	Target measure
Volumetry	Kidney size
T1 mapping (using Modified Look-Locker inversion recovery [MOLLI])	Fibrosis (scarring) and inflammation of kidney
Blood oxygen level dependent (BOLD) T2*	Kidney oxygenation
Phase contrast MRI	Renal flow and global perfusion
Diffusion-weighted imaging (DWI)	Fibrosis of kidney
Modified Dixon (mDIXON)	Fat content

Table 1: MRI methods and what they assess

Note: this pre-specified Data Analysis Plan re-orders the priority of some of the assessments set out in the MRI substudy Protocol Supplement. This follows a more detailed review of data whilst compiling this plan. This pre-specified Data Analysis Plan therefore supersedes the proposed assessments set out in the Protocol Supplement and prevails in the event of any discrepancies between the two documents.

5 BASELINE CHARACTERISTICS

In order to assess balance of baseline characteristics between randomized arms of the MRI substudy, the variables recorded at baseline listed in the main trial Data Analysis Plan will be presented for each of the empagliflozin and placebo groups.

6 DEFINITIONS OF KEY RANDOMIZED ASSESSMENTS

At participating centres (Oxford, Derby, Nottingham, Edinburgh, Würzburg), all randomized participants without an obvious contraindication for an MRI scan were invited during the course

of trial follow-up to have an MRI scan performed. Only those individuals that were able to have an MRI scan will be included in analyses (i.e. consented participants that were not scanned due to claustrophobia, or other contraindications will not be included). Therefore, unless otherwise specified, all analyses will involve an intention-to-treat comparison among all randomized participants with a valid MRI scan to assess the effects of allocation to empagliflozin versus placebo on MRI measurements obtained at about 18 months after randomization (i.e. all participants will be included irrespective of whether they take none, some or all of their allocated treatment).[1,2] Handling of missing individual MRI measurements is described in section 7.2.

6.1 Hypotheses

For all statistical tests (other than tests for heterogeneity or trend), the null hypothesis will be that the effect of allocation to empagliflozin on a given MRI measurement in the target population is the same as the effect of allocation to placebo (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).

6.2 Primary randomized assessment

The primary assessment will be the effect of allocation to empagliflozin versus placebo on kidney cortical T1 mapping as measured by MOLLI at about 18 months after randomization measured using MRI. The details of all analysis methods are described in section 7.2 Methods of analysis.

6.3 Secondary randomized assessments

The secondary assessments, at about 18 months after randomization, are:

Kidney measures:

- Kidney size (measured by total kidney volume [TKV])
- Kidney arterial flow (measured using mean of left and right renal arterial flow)
- Kidney global perfusion (measured by phase contrast MRI correct for TKV)
- Kidney diffusion (measured by apparent diffusion coefficient [ADC])
- Kidney oxygenation (measured by BOLD T2*)
- Kidney fat content mapping (measured by mDIXON)

Cardiac measures:

- Left ventricular mass index (i.e., normalised to body surface area),
- Left ventricular ejection fraction

- Cardiac fibrosis measured by T1 MOLLI (mean of measurements at apex, wall and base of left ventricle)
- Diastolic dysfunction (measured by left ventricular strain, left ventricular global longitudinal strain, left ventricular diastolic strain rate, and left ventricular volume)

6.4 Tertiary randomized assessments including subgroup analyses

Tertiary assessments include:

i. Subgroup analyses of effects of empagliflozin 10mg versus matching placebo on T1 mapping by baseline feature (age, sex, diabetes status, eGFR and uACR).

ii. Amongst the proportion of participants with a baseline MRI scan, assessments of the effects of empagliflozin 10mg versus matching placebo on follow-up MRI measurements adjusted for baseline.

7 STATISTICAL METHODOLOGY

7.1 Handling of missing MRI data

Participants included in the MRI substudy with a particular missing MRI measurement, will still be included in analyses and these values will be imputed using multiple imputation, using 20 imputed data sets, with results across imputations being combined using the methods of Rubin.[3] The imputation procedure will take into consideration each participant's key baseline characteristics, treatment allocation and other available MRI measurement parameters. Results from the imputed analyses will be compared with those from equivalent "complete-case" analyses, but primary emphasis will be placed on the results after multiple imputation. All multiple imputation analyses will be implemented using the multiple imputation procedure in SAS version 9.4 (SAS Institute, Cary NC), using the expectation-maximization algorithm (which assumes a multivariate normal distribution) to impute values. In sensitivity analyses conducted in participants with baseline scans, missing baseline MRI measurement parameters will be imputed with the median observed value (in both treatment groups combined). For participants with missing baseline characteristics required for analyses of outcomes (e.g. for subgroup analyses), the median value will be imputed.

7.2 Methods of analysis

All MRI measurements will be analysed as a continuous variable. Differences in MRI measurements between treatment groups will be assessed using a linear regression approach adjusted for the elements included in the minimization algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and uACR [but not region as the MRI substudy was

only conducted in Europe]). If outcomes are not normally distributed then appropriate transformations (e.g. log transformation) will be made.

7.3.1 Subgroup analyses

Subgroup analyses will be conducted by fitting relevant interaction terms for subgroups in linear regression models with the aim of assessing whether the effects in specific subgroups are statistically different from the overall effect.

7.3.2 Sensitivity analyses

Among those with both a baseline and follow-up MRI scan, sensitivity analyses will additionally be adjusted for the baseline MRI estimates by fitting a linear regression model.

8 REFERENCES

1. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *British journal of cancer* 1976; **34**(6): 585-612.
2. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *British journal of cancer* 1977; **35**(1): 1-39.
3. Rubin D. Multiple imputation for non-response in surveys.: New York: John Wiley; 1987.