Statistical Analysis Plan

A Phase 2b Randomized, Double-blind, Placebo-controlled, Multi-centre Study to Evaluate the Efficacy and Safety of MEDI3506 in Subjects with Diabetic Kidney Disease

Protocol Number: D9183C00001

Version: 6.0

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REVISION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	09JAN2020	Initial document	Initial document
2.0	22FEB2022	Updated	Updates according to protocol Amendments 1-5.
3.0	2MARCH2022	Updated	Updated the preliminary analysis set for safety and efficacy and added details of the interim analysis plan
4.0	26JULY2022	Update primary efficacy model and LOCF approach	Account dapagliflozin add-on in Week 12-24
5.0	12AUG2022	Cancel update on primary efficacy model, update the hyperlinks in Ver. 4.0	Collinearity issue in model update
6.0	28JUN2023	Update document for final analysis	Update the secondary analysis and remove LOCF approach.

List of Abbreviations

Abbreviation or Specialized Term	Definition
ACEi	angiotensin converting enzyme inhibitors
ADA	anti-drug antibody/antibodies
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin receptor blockers
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical class
BMI	body mass index
CSP	clinical study protocol
DKD	diabetic kidney disease
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
IPD	important protocol deviations
IXRS	interactive voice/web response system
LOCF	last-observation-carried-forward
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PK	pharmacokinetics
PT	preferred term
SAE	serious adverse event
SGLT2i	sodium-glucose cotransporter-2 inhibitor(s)
SID	subject identification
SOC	system organ class
SPP	statistical programming plan
TEAE	treatment-emergent adverse event
T2DM	Type 2 diabetes mellitus
UACR	urine albumin : creatinine ratio
ULN	upper limit of reference range
WHO-DD	World Health Organization Drug Dictionary enhanced

1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D9183C00001 Amendment 5 (14FEB2022). This document details the statistical summaries and analyses relating to each study objective and describes the general conventions and definitions that will be used. In addition, a set of table templates and specifications will be included in a statistical programming plan (SPP) to complement this document.

This study, D9183C00001 (FRONTIER 1), is a Phase 2b, randomized, double-blind, placebo-controlled, multi-centre study to evaluate the efficacy, safety, PK, and immunogenicity of MEDI3506 (Tozorakimab) in adult subjects with diabetic kidney disease (DKD); defined as subjects with T2DM and an eGFR of 25-75 mL/min/1.73 m^2 with a urine albumin : creatinine ratio (UACR) in the range of 100-3000 mg/g, who meet all eligibility criteria.

The study will investigate if MEDI3506 can reduce UACR in participants on standard of care without and with dapagliflozin. The dose-response relationship, and the safety and pharmacokinetic (PK) profile of MEDI3506 will be evaluated.

The study was started in November 2019 as a Phase 2a study and it was paused due to COVID-19 pandemic by March 2020. It was resumed in July 2020, and then endured several amendments where additional doses of MEDI3506 and the add-on of Dapagliflozin in the second half of the 6-month treatment period are introduced. Therefore, the study consists of two periods, where Period 1 is without Dapagliflozin and Period 2 is with Dapagliflozin. Accordingly, several cohorts of participants can be defined upon the evolvement of the trial design as illustrated in Table 1. Cohort 1 which are divided in two groups a and b, are subjects who have started on the Phase 2a. Cohort 1a participants were discontinued and did not have the opportunity to complete 6-month treatment due to COVID-19 pandemic. Participants in Cohort 1b were enrolled after the study was re-started and had the opportunity to complete 6-month treatment. These subjects will continue on treatment with MEDI3506/placebo without dapagliflozin. About 24 participants were randomized in Cohort 1 and 19 of them were discontinued when the study was paused. Cohort 2 are subjects who have started on the Phase 2a study but have not completed 12 weeks of treatment prior to Amendment 2. They were transitioned to the Phase 2b study and given dapagliflozin starting on Day 85 (Week 12). Finally, Cohort 3 are subjects who will enrol in ongoing Phase 2b study.

Table 1: Cohort of study participant by randomization scheme and active treatment regiment

Cohort	Randomization Scheme 1 (R1)	Randomization Scheme 2 (R2)	Active Treatment Regiment	
			6-month MEDI3506 monotherapy	MEDI3506 mono in 1st 3 mons, MEDI3506 + Dapa in 2nd 3 mons.
1a*	X		X	
1b*	X		X	
2	X			X
3		X		X

R1 = Randomization scheme for MEDI3506 60 mg, 300 mg, and matching placebo; R2 = Randomization scheme for MEDI3506 30 mg, 60 mg, 120 mg, 300 mg, and matching placebo.
* Participants in Cohort 1a were discontinued and did not have the opportunity to complete 6-month treatment due to COVID-19 pandemic. Participants in Cohort 1b were enrolled after the study was re-started and had the opportunity to complete 6-month treatment.

Should be noted that the method and the analysis details described in this document will be considered for Cohort 2 and 3. Cohort 1 will be summarized separately with some descriptive summary statistics and listing.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

To evaluate the effect of MEDI3506 as measured by change from baseline in urine albumin:creatinine ratio (UACR) at Week 24, when compared to placebo.

2.1.2 Secondary Study Objectives

1) To evaluate the effect of MEDI3506 as measured by change from baseline in urine albumin:creatinine ratio (UACR) at Week 12, when compared to placebo.
2) To evaluate safety and tolerability of MEDI3506 between Period 1 and 2 in subjects with DKD
3) To describe the PK and immunogenicity of MEDI3506 in subjects with DKD
4) To evaluate the effect of MEDI3506 in combination with ACEi or ARB between Period 1 and 2 on albuminuria in subjects with DKD

2.1.3 Exploratory Study Objectives

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2.2 Study Design

This is a Phase 2b, randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy, safety, PK, and immunogenicity of MEDI3506 in adult subjects with DKD. Approximately 565 subjects from around 130 study sites among multiple countries will be randomized (95:95:95:140:140) to MEDI3506 30, 60, 120, or 300 mg, or volume-matched placebo dosed subcutaneously (SC) every CCI days over a 168-day (24-week) treatment period.

Assuming 10% dropout, this will allow approximately 505 evaluable subjects to complete the study. The study includes a screening period of up to 35 days (Day -37 to Day -3), a 168-day (24-week) treatment period, and a 70-day (10-week) follow-up period. The study periods are shown in Figure 1.

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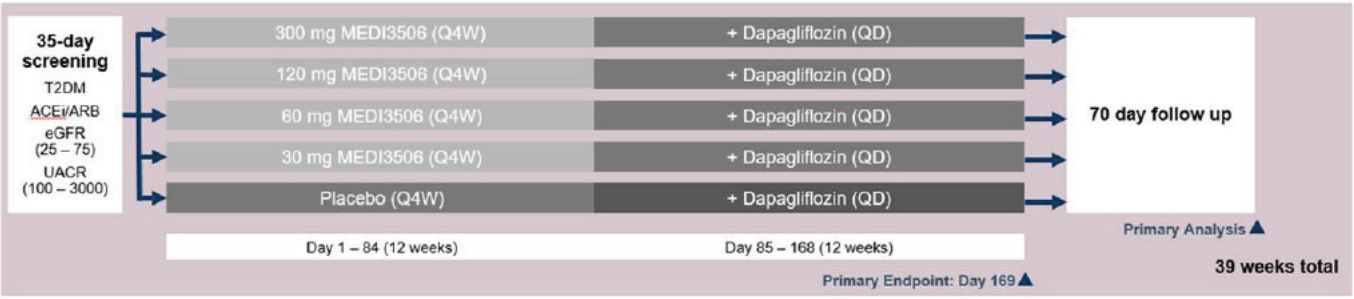
Figure 1: Study Flow Diagram



2.3 Treatment Assignment and Blinding

An IXRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be stratified at the time of randomization in order to ensure approximate balance between treatment groups within each sub-population.

- Stratum 1: Subjects without SGLT2i background outside Japan
- Stratum 2: Subjects with SGLT2i background outside Japan
- Stratum 3: Subjects without SGLT2i background in Japan
- Stratum 4: Subjects with SGLT2i background in Japan

Subjects will be randomized to receive 30, 60, 120, or 300 mg MEDI3506 (95, 95, 95, and 140 subjects, respectively) or 0.2 mL, 0.4 mL, 0.8 mL, or 2 mL placebo (32, 32, 32, and 44 subjects, respectively) by an IXRS system.

IXRS will also allocate 2 bottles of dapagliflozin (35 tablets each) at Visit 6 and 1 bottle of dapagliflozin (35 tablets) at Visit 8 to eligible subjects that will be used to cover the need of daily administration between two visits of MEDI3506/placebo administration. This will

ensure that the patient has sufficient stock of dapagliflozin if a visit is delayed. If there is any issue with one of the bottles (e.g. lost or damaged), the patient can receive a replacement at any visit (Visit 7 or Visit 8); kit replacement option is available in IXRS.

The procedure for using IXRS is as follows:

- The investigator or designee contacts the IXRS and provides the SID number and subject's baseline characteristic(s) used to verify that it is the same subject
- The correct number of kits of MEDI3506 and/or placebo will be assigned to the subject
- Confirmation of kit assignment is sent to the unblinded investigational product manager who prepares the investigational product to be dispensed to the subject per the response system and records the appropriate information in the investigational product accountability log
- Blinded study personnel will receive a notification containing a dose tracking number, that will not disclose how many kits are assigned to the subject.

Since MEDI3506 and placebo are not identical in appearance or viscosity, investigational product will be administered by site personnel who will not be directly involved in the management of study subjects. In the event that the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, AstraZeneca must be notified immediately. If the treatment allocation for a subject need to be known to treat an individual subject for an adverse event (AE), the investigator must notify AstraZeneca immediately. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of investigational product preparation and administration used to maintain the blind.

2.4 Sample Size

A sample size of 565 subjects randomized using a 95:95:95:140:140 ratio to receive either 30, 60 mg, 120 mg, or 300 mg MEDI3506 or placebo will give approximately 85:85:85:125:125 evaluable subjects per group, assuming 10% dropout. This will provide at least 85% power for the 300 mg arm and 80% power for the 30, 60, and 120 mg arms to detect a 30% reduction in change from baseline to Day 169 (Week 24) in UACR between each MEDI3506 treatment group and placebo group (or placebo/ MEDI3506 ratio of 1.429) with a one-sided alpha of 0.05 without multiplicity adjustment, assuming a coefficient of variation of 1.31 or standard deviation of 1.0 in log scale.

3 STATISTICAL METHODS

3.1 General Considerations

3.1.1 Data Presentation

Data will be presented in data listings sorted by treatment group, subject number and date collected, where appropriate. Tabular summaries will be presented for each treatment with the placebo groups for volume matching combined. Categorical data will be summarized by treatment group with the number and percentage of subjects within each category. Continuous variables will be summarized by treatment group with descriptive statistics including mean, standard deviation, median, minimum, and maximum. Baseline values will be defined as the last valid assessment prior to the first administration of investigational product unless otherwise specified.

All statistical tests will be 2-sided at an alpha = 0.10 significance level unless stated otherwise. There will be no adjustment for multiplicity.

Data analyses will be performed using SAS® version 9.4 or higher (SAS Institute Inc., Cary, NC). The analytical results generated from SAS programs will follow AstraZeneca/MedImmune SAS programming standards and will be validated according to AstraZeneca/MedImmune SAS validation procedures.

3.1.2 Visit Windows

For statistical summaries and analyses by visits, the visits will be mapped based on the actual study days from the first IP dosing date according to the protocol (section 4.2 Table 5 and Table 6) and labelled as Baseline, Day 15, Day 29, Day 57, Day 85, Day 113, Day 141, Day 169, Day 200, and Day 230.
Baseline values will be defined as the last assessment prior to the first administration of study medication (Day 1).
Except the off-treatment visits of the early dropouts (any visit up to including EOT), the visit windows for post-baseline visits will be mapped based on following the table. Any out of window visit will be labelled as unscheduled visit.

Visit (nominal study day)	Visit Window (actual study day)
Baseline[a]	1
Day 15	9-21
Day 29	22-43
Day 57	44-71
Day 85	72-99
Day 113	100-127
Day 141	128-155
Day 169	156-185
Day 200/Follow up	186-215

Visit (nominal study day)	Visit Window (actual study day)
Day 230/Follow up	216-end of study

[a] Last assessment prior to first administration of study medication

- If multiple valid assessments fall within the same visit window, the following rules will be applied.
    - If there are two or more valid observations within the same visit window, then the one closest to the scheduled visit will be used in the analysis.
    - If two valid observations are equidistant from the scheduled visit, then the one with the earlier collection date will be used in the analysis.
    - If two valid post-baseline valid observations are collected on the same day, then the one with the earlier collection time will be included in the analysis.
- **For subjects who dropout treatment early,** the follow up visits (any visit after EOT) will be mapped as follows:

    - Determine the last dose visit window based on its actual study day as per the above table. If the last dose was taken up to actual study day 21, then the last dose visit window will be considered as Unscheduled.
    - Any measurement within (=<) 2 weeks post last dose will be aligned with the last dose visit window.
    - Any measurement beyond (>) 2 weeks but within (=<) 6 weeks post last dose will be aligned with the next protocol scheduled visit window after the last dose visit window. Note: if the last dose visit window is Unscheduled, then the next protocol scheduled visit window should be considered as Day 29.
    - Any measurement beyond (>) 6 weeks but within (=<) 10 weeks post last dose will be mapped as Day 200/Follow up.
    - Any measurement beyond (>) 10 weeks post last dose will be mapped as Day 230/Follow up.

3.1.3 Multiple Comparisons/Multiplicity

Multiplicity adjustment is not planned for this phase 2 study.

3.1.4 Multi-centre Studies

No per centre (where the term ‘centre’ defines each investigator site) summaries or analyses is planned.

3.2 Analysis Populations

The analysis populations are defined in Table 2.

Table 2: Analysis Populations

Population	Description
Enrolled	All subjects who sign the informed consent form.
Full Analysis Population	All subjects from cohorts 2 and 3 who are randomized and receive any study drug. Subjects are evaluated according to the treatment assigned at randomization. The Full Analysis Population will be used for all analyses of demographic baseline characteristics and efficacy data.
Per Protocol Population	A subset of the Full Analysis Population consisting of all subjects who receive the additional treatment with dapagliflozin post Week 12 and do not violate the terms of the protocol in a way that may affect the primary efficacy endpoint significantly (relevant protocol deviations (IPDs)). The relevant IPDs are reported in Section 3.3.2.
Safety Analysis Population	All subjects from cohorts 2 and 3 who are randomized and receive any study drug. Subjects are evaluated according to the actual treatment they received. The Safety Analysis set will be used for all safety analyses.
PK population	All subjects in the Full Analysis Population who have at least one detectable MEDI3506 serum concentration measurement post-treatment. The PK Analysis set will be used for all PK analyses.

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

A summary of subject eligibility and randomization (including a summary of subjects randomised but not treated with double-blind investigational product) as well as treatment administered will be provided. In addition, disposition of subjects throughout the study with respect to completion of treatment and end of study will be provided.

A summary on randomization stratification factors will be provided, i.e., SGLT2i treatment history (with SGLT2i background, without SGLT2i background) and region (Japan, Rest of World) at randomization by treatment group and overall.

The number and percentage of participants with one or more disruptions due to COVID-19 pandemic will be presented by treatment group. A listing of all participants affected by the COVID-19 related study disruption by unique participant number identifier and by investigational site, and a description of how the individual's participation was altered, will be produced. COVID-19 related study disruptions can be:

1. Visit related (if visit is impacted by global/country situation, then contact mode will be specified);

2. Study drug related (if study drug action taken (except "Drug Withdrawn") was impacted by global/country situation; study drug administration or location was impacted by global/country situation; who performed a study drug administration);

3. Concomitant medication related (if when treatment was stopped due to any global/country related situations i.e.: epidemic/pandemic, healthcare crisis etc.);

4. Discontinuation of study drug due to COVID-19 pandemic (if study drug action taken "Drug Withdrawn" was impacted by global/country situation);

5. Withdrawal from study (if primary reason for ending study is related to global/country situation).

3.3.2 Important protocol deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or wellbeing (ICH E3 guidance). The category of IPDs for the study are:

1. Informed consent
2. Study conduct/procedures
3. Investigational product
4. Safety
5. Other reasons

The relevant IPDs are those that have the potential to affect the results of the primary efficacy endpoint. Therefore, the category of relevant IPDs for the study would be:

- Did not meet inclusion/exclusion criteria
- Did received prohibited medication before end of treatment
- Missed visit (we allow 1 missed visit. For IA any missed Visit before Day 85 would be relevant PD, but not for the Final Analysis if they attend the rest
- Did not provide UACR samples / samples were lost / samples were damaged

Details of the IPDs will be provided in the protocol deviation plan (PDP), which will be developed for the study. The method for identifying IPDs will be documented in the PDP. All blinded IPDs will be agreed prior to study unblinding by blinded study personnel. Unblinding IPDs (i.e. those that relates to study medication/dosing and which could

potentially unblind a reviewer to subject's treatment group) will be agreed by unblinded personnel.

The number and percentage of participants with at least one IPD, including and excluding COVID-19 related IPDs, will be summarised following the IPD categories for each study intervention group and overall. A listing of all identified IPDs will also be provided. All issues reported due to COVID-19 pandemic, regardless of whether the type of issue is considered a protocol deviation or not, will be listed separately.

3.3.3 Demographics and Baseline Characteristics

Demographic information related to sex, age, race, weight, height, and body mass index (BMI) will be presented by treatment group and for all subjects combined. A summary of baseline disease characteristics may include duration of diabetes, specified diabetes complications, and smoking and alcohol history.

3.3.4 Study Drug Exposure

The number of doses and total dose received will be summarized for each investigational product (MEDI3506 or placebo) by descriptive statistics and frequencies.

3.3.5 Concomitant Medications

Concomitant medications will be coded using the current WHO Drug Dictionary enhanced (WHO-DD). The number and percentage of subjects who took concomitant medications for the highest anatomical therapeutic chemical (ATC) class and preferred term will be summarized by treatment for the safety analysis population. The summary of concomitant medications will include all concomitant medications taken on or after the date of first dose of investigational product or any concomitant medication started prior to first dose of investigational product that continued beyond the date of first dose of investigational product.

3.3.6 Prohibited Concomitant Medications

If a subject receives prohibited concomitant medication, which may impact their efficacy assessments, they should discontinue investigational product. A list of prohibited concomitant medications is provided in the CSP, all use of prohibited medications will be reviewed and identified prior to unblinding by the medical monitor.

For the purpose of analyses, prohibited concomitant medications and therapies will be summarized by highest ATC class and preferred term.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy

3.4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the UACR change from baseline at Day 169 (Week 24) compared with placebo. Type of the estimate of interest is the percent change from baseline.

3.4.1.2 Primary Efficacy Analyses

The primary efficacy endpoint of change from baseline in UACR at Day 169 (Week 24) for each of the MEDI3506 treatment groups compared with the pooled placebo group will be analyzed based on the Per Protocol Population. For the intercurrent events, if a subject is lost to follow-up (EOT), discontinues treatment due to AE, or uses prohibited medication, the UACR data are treated as missing on or after the event and no imputation is performed. The primary analysis will use a mixed model repeated measures (MMRM) analysis with a restricted maximum likelihood (REML) approach without multiplicity adjustment. UACR will be log-transformed before entering the data in the MMRM analysis to alleviate the skewness of the data. The model will adjust for fixed effects of treatment, visit, and treatment-by-visit interaction, randomization stratification factors, baseline log UACR and baseline log UACR-by-visit interaction. Randomization stratification factors are with SGLT2i background or not, in Japan or rest of world.

To allow generality for the covariance structure for the repeated measures, the variance-covariance matrix will be assumed to be unstructured, i.e., purely data dependent, to model within subject errors. If the unstructured variance-covariance matrix will not fit, i.e., fail to converge, the following covariance structures will be utilized in the order of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry. The first (co)variance structure which does not have a convergence problem will be the one used for the analysis. If a structured covariance has to be used, the "sandwich" estimator of the variance covariance matrix of the fixed effects parameters will be used in order to deal with possible model misspecification of the covariance matrix. The denominator degrees of freedom will be calculated according to the Kenward-Roger method. Additionally, there will be no adjustment for multiplicity.

If none of the above models converge, the analysis will be altered to use an analysis of covariance (ANCOVA) with last observation carried forward (LOCF) imputation method implemented. Details of this analysis is provided in the Section 3.4.5 for sensitivity analysis.

Additionally, all collected values of UACR will be listed.

3.4.1.2.1 Data Convention

Central laboratory urine samples for the determination of albumin and creatinine and calculation of UACR will be collected at the timepoints described in the schedule of study procedures in the protocol.

Participants will collect 1st morning void urine samples at home on 3 consecutive days (ideally day of visit and preceding 2 days [refrigerated overnight] which will be returned on the day of visit.

The UACR from each urine sample will be calculated as follows:

$$UACR\ (mg/mmol) = 10\ \times \frac{Urine\ Albumin\ (mg/dL)}{Urine\ Creatinine\ (mmol/L)}$$

At each visit, the geometric mean of the triplicate UACR values will be computed and used for the analysis of UACR. In case of missing values for UACR the geometric mean will be calculated considering the number of the available measurements.

As UACR is assumed to follow a log-normal distribution, it will be log transformed for statistical analysis purposes obtaining the ratio of geometric means.

Percent change from baseline in UACR at $Visit_k$, $k\ in\ \{4,\ 5,\ 6,\ 7,\ 8,\ 9\}$ will be calculated as:

$$100 \times \left(\frac{GeoMean(UACR_{Visit_k})}{GeoMean(UACR_{Baseline})} - 1 \right)$$

If the urine albumin or urine creatinine lab result is below LOD (level of detection) or LOQ (limit of quantification), impute the missing value using half of the LOD or LOQ, prior to calculating the ratio.

3.4.1.2.2 UACR Baseline

Baseline for UACR will be defined as the geometric mean of 3 consecutive days prior to the Day 1 first dose of study treatment (ideally day of Visit 3 and preceding 2 days). Only samples collected prior to the first dose of study medication will be used. For missing data see the below section on missing data handling.

3.4.1.2.3 Missing Data Handling

In general, missing data will not be imputed.

In the primary MMRM model, all subjects and all data points up to the defined timepoint will be included. No subjects will be excluded because of missing data, and no imputation will be done for missing data.

For intercurrent events, if a subject is lost to follow-up (EOT), discontinues treatment due to AE, or uses prohibited medication, the UACR data on or after intercurrent day are treated as missing.Participants are expected to provide 1st morning void urine samples at home on 3 consecutive days. In case less than 3 values of UACR are available, the geometric mean will be calculated considering the number of the available measurements.

Baseline for UACR will be defined as the geometric mean of at-least 2 measurements of Day1(Visit 3) prior to the day 1 first dose of study treatment. Only samples collected prior to

the first dose of study medication will be used. If Day 1 visit (Visit 3) has less than 2 morning void measurements, and there are 1 or more measurements at Screening (Visit 2), then geometric mean of all morning void UACR measurements from both visits will be used as baseline. If there is only 1 measurement prior to the Day 1 first dose of study treatment (either Day 1 visit (Visit 3) or Screening (Visit 2)), then that measurement will be considered as baseline.

Note: the spot urine (Screening Visit 1) values are excluded from the baseline evaluation.

3.4.1.2.4 Technical details in execution of primary analysis

The execution of the primary analysis model will involve the following four steps:

a) Log-transformation of the UACR:
   First, the UACR at baseline and the UACR at post-baseline visits (4, 5, 6, 7, 8, and 9) will be log-transformed. The log-transformed UACR at baseline will then be subtracted from the log-transformed at post-baseline visits to calculate the change of UACR in log units.
b) Execution of the model:
   The model will include the change in UACR in log units as a dependent variable and the log-transformed UACR at baseline as covariate, as well as the other independent variables described at the beginning of this section.
c) Back-transformation of the results from the model:
   The results from the execution of the model will be back transformed to the original scale after an exponentiation of the LS means to obtain the percent change from baseline of the treatments. The LS mean difference and its CI between each active treatment and placebo will also be back-transformed to yield the percent difference between two treatments with its 90% CI at Visit 10 expressed in percentage.
d) The statistics for the percent change from baseline, percent difference between treatments and percentage 90% CI will be calculated as follows:
   - percent change from baseline = (exp(estimate)-1)*100 where estimate is the LS mean
   - percent difference between treatments= (exp(estimate)-1)*100 where estimate is the LS mean difference
   - 90% CI lower and upper (%): (exp(lower)-1)*100; (exp(upper)-1)*100.

3.4.2 Secondary Efficacy

3.4.2.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- Change from baseline to Day 85 (Week 12) in UACR

3.4.2.2 Secondary Efficacy Analyses

The change from baseline to Day 85 (Week 12) in UACR will be analysed similarly to that of the primary efficacy endpoint based on the Full Analysis Population with the cutoff at Day 85.

3.4.4 Subgroup Analyses

Subgroup analyses for the primary efficacy endpoint by region (Japan versus Rest of the World) and by SGLT2i background will be presented. Descriptive summaries of the primary efficacy variable by treatment group and subgroup will also be produced.

The primary analysis model will be used for subgroup analyses, except that the corresponding randomization stratification factor will not be needed in each model. A forest plot will present the least-squares mean and 90% CI overall and for each subgroup individually.

Additional subgroup analyses may also be performed.

3.4.5 Sensitivity Analyses

The primary endpoint of UACR at Day 169 post baseline time point in Per Protocol Population will be analyzed, as sensitivity analysis, using an analysis of covariance (ANCOVA) adjusting for treatment, baseline log UACR, and randomization stratification factors with last-observation-carried-forward (LOCF) imputation for missing post-baseline measurements. In case the LOCF analysis is needed, some data handling needs to be considered as follows.
Due to two treatment periods, different imputation rules need to be considered for data cut-off at day 85 and all data available beyond day 85,

- If the data at week 12 is missing, the latest respond before week 12 will be carried forward

- If the data at week 24 is missing, the latest respond after week 12 will be carried forward

Should be noted that if subject does not have any data after week 12, then that subject will be excluded from the analysis in week 12-24. The data from unscheduled visits will be included together with other available data for endpoint imputation purpose.

Other sensitivity analyses may also be performed.

3.4.6 Japan Specific Analysis

A subset of the planned outputs will be repeated for participants from Japan, as required for interaction with the Japanese Regulatory Agency. The outputs will be identified in the SPP.

3.5 Pharmacodynamic Analyses

3.5.1 Pharmacodynamic Endpoint(s)

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[redacted]

3.5.2 Analysis of Pharmacodynamic Endpoint(s)

Percent change from baseline to Day 85, and Day 169 will be analysed in both per protocol population and full analysis population.
The MMRM model will be used adjusting for treatment, baseline, and randomization stratification factors.

3.6 Safety Analyses

The analyses of the safety endpoints will be performed using the Safety Analysis Population for data cut-off at day 85 and all data available beyond day 85. The evaluations will be descriptive in nature, and observed differences will be evaluated for medical relevance. No formal statistical comparisons will be performed for the safety summaries.

3.6.1 Adverse Events and Serious Adverse Events

Adverse events will be coded with MedDRA version 22.0 or later. Analysis of adverse events will include the type, incidence, severity and relationship to study investigational product summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT), by treatment group as well as MEDI3506 overall. Treatment emergent adverse event is defined as any AE reported after the first IP up to the wash-out of MEDI3506 (5 half-lives: 90 days after the last dose of IP). If an AE is reported the day of the first IP (ie. Day 1) with a missing time, this AE will be considered as treatment emergent. The AEs summaries will include only treatment-emergent AEs (TEAE), i.e., those starting after the first administration of double-blind investigational product. Subjects will be counted once for specific PT or MedDRA SOC when calculating incidence rates. If the same AE Preferred Term occurs multiple times within a subject, the highest severity and level of relationship observed will be reported. Non-treatment-emergent AEs/serious adverse events (SAEs), i.e., those AEs with onset after screening but before the start of double-blind treatment will be presented in the listings. All TEAEs related to dapagliflozin will also be summarized. For subjects testing positive for COVID-19, overall summary of AEs, AEs by PT and SOC, summary of SAEs, AESI and the proportion of asymptomatic subjects will be provided.

3.6.2 Adverse Events of Special Interest

The following AESIs have been defined in the study protocol and will be particularly monitored in this study:

- Serious hypersensitivity, including Type 1 to 4 hypersensitivity reactions, for example, anaphylaxis and severe allergic reactions, and immune complex disease.
- Injection-site reactions.
- Progression of heart failure.
- Serious infections, including opportunistic infections.
- Gastrointestinal adverse reactions.

In addition, Malignancy and COVID-19 disease may also be of interests.

All Treatment-emergent AESIs will be summarized by Special Interest Group and Preferred Term. Programmatic MedDRA search will be done in addition to AESI collected by CRF to ensure a thorough review.

3.6.3 Potential Hy's Law Cases

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of aspartate transaminase (AST) or alanine transaminase (ALT) $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. The cases of potential Hy's Law cases will be summarized overall, as well as categorized by MedDRA system organ class and preferred term by treatment group.

3.6.4 Deaths and Treatment Discontinuations due to Adverse Events

Death and AEs resulting in permanent discontinuation from the study drug will be summarized by treatment group. The summary includes overall, categorized by MedDRA system organ class, and preferred term.

3.6.5 Clinical Laboratory Evaluation

Haematology, serum chemistry, and urinalysis laboratory evaluations will be performed during the study. The haematology and serum chemistry parameters as well as their changes from baseline and percent changes from baseline will be summarized with descriptive statistics by treatment group. The haematology and serum chemistry results will also be classified as low (below lower limit of reference range), normal (within reference range), or high (above upper limit of reference range). The urinalysis results will be classified as normal or abnormal. The shift from baseline haematology, serum chemistry, and urinalysis results will be summarized by treatment group at each evaluation time.

3.6.6 Other Safety Evaluations

3.6.6.1 Vital Signs

Vital signs including heart (pulse) rate (beats/min), systolic and diastolic blood pressure (mm Hg), temperature (^{o}C), and respiratory rate (breaths/min), as well as the change from baseline for each of those parameters, will be descriptively summarized by treatment group at each time point.

3.6.6.2 Electrocardiogram

Electrocardiogram parameters will be assessed using standard 12-lead electrocardiography. The following electrocardiogram (ECG) parameters as well as the change from baseline for each of those parameters will be reported and descriptively summarized by treatment group at each of the specified time points: Heart rate (beats/min), RR (msec), PR (msec), QRS (msec), and QT (msec) intervals and the QT corrected interval.

The normality/abnormality of the ECG evaluation will be summarized using frequency tables of the number of subjects with a normal/abnormal ECG evaluation at each scheduled visit.

3.6.6.3 Physical Exam

Endpoints of Physical exam, including cardiac exam, will be listed.

3.6.6.4 Other Safety Endpoints

Other safety endpoints, such as left ventricular ejection fraction (LVEF) as measured by echocardiogram and BNP, will be summarized using descriptive statistics at each time point by treatment group.

3.6.7 Data and Safety Monitoring Board

An independent DSMB has been formed to evaluate safety data from concurrently conducted MEDI3506 Phase 2 clinical studies in other indications. The DSMB will have access to data aggregated by treatment group and will be able to review collected study data by treatment while the study is ongoing. The DSMB will review prespecified data periodically to ensure subject safety and make recommendations to the sponsor regarding further conduct of the study. A separate charter will detail the rules, meeting frequency and scope of the responsibilities of the DSMB.

3.7 Immunogenicity

Anti-drug antibody (ADA) analysis will be based on the safety population.

The following ADA category variables will be evaluated:

- ADA prevalence: subjects who are ADA positive at any visit (including baseline)
- Subjects who are ADA positive at baseline only
- Subjects who are ADA positive at baseline and positive post baseline
- Subjects who are ADA positive post-baseline only (treatment-induced ADA)
- Subjects who are persistently positive; persistently positive is defined as at least 2 post-baseline ADA positive measurements (with >=16 weeks apart) or an ADA positive result at the last available assessment
- Proportion of subjects who are transiently positive; transiently positive is defined as at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.
- Proportion of subjects who are treatment-boosted ADA; treatment-boosted ADA is defined as baseline ADA titer that was boosted to a 4-fold or higher level following drug administration
- ADA incidence (treatment-emergent ADA), defined as the sum of treatment-induced ADA (post-baseline positive only) and treatment-boosted ADA

Summary of ADA responses during the study with number and percentage of participants in each category and ADA titres over time displaying min, Q1, median, Q3 and max, will be provided by treatment group.

If there is a high incidence of ADA, the association of ADA with MEDI3506 pharmacokinetics will be assessed. The effect of ADA on the primary endpoint will be summarized by descriptive analysis in subgroups of TE-ADA+, ADA negative, and TE-ADA-.
Summaries of adverse events will be presented for the on-treatment period by the subgroups of TE-ADA +, ADA negative, TE-ADA-. Summaries will include adverse events (AEs),

serious adverse events (SAEs), causally of AEs and SAEs as assessed by the investigator, and adverse events of special interest.

The relationship between ADA and secondary efficacy endpoints or PD biomarkers may be explored but will be reported outside the CSR.

3.8 Pharmacokinetics

Pharmacokinetic analysis will be based on the PK analysis set. Drug concentration data for MEDI3506 and Dapagliflozin for all randomized subjects will be provided.

Descriptive statistics of MEDI3506 serum concentrations by treatment group and visit overall and also by ADA category (TE-ADA negative, TE-ADA positive, ADA negative) will be reported.

Descriptive statistics of plasma concentration of Dapagliflozin by visit will also be reported.

Figures of geometric mean serum concentration of MEDI3506 versus time by dose and Dapagliflozin versus time will be provided. In addition, spaghetti plots of individual serum MEDI3506 concentrations over time by dose and by ADA category (TE-ADA negative, TE-ADA positive, ADA negative) will also be provided.

The pharmacokinetic data may be merged with those from other clinical studies for a model-based population PK analysis. If performed, these analyses will be reported outside of the CSR. Exposure-response relationships for both efficacy, safety or biomarker endpoints may be performed. Results of these analysis will be not reported in the CSR.

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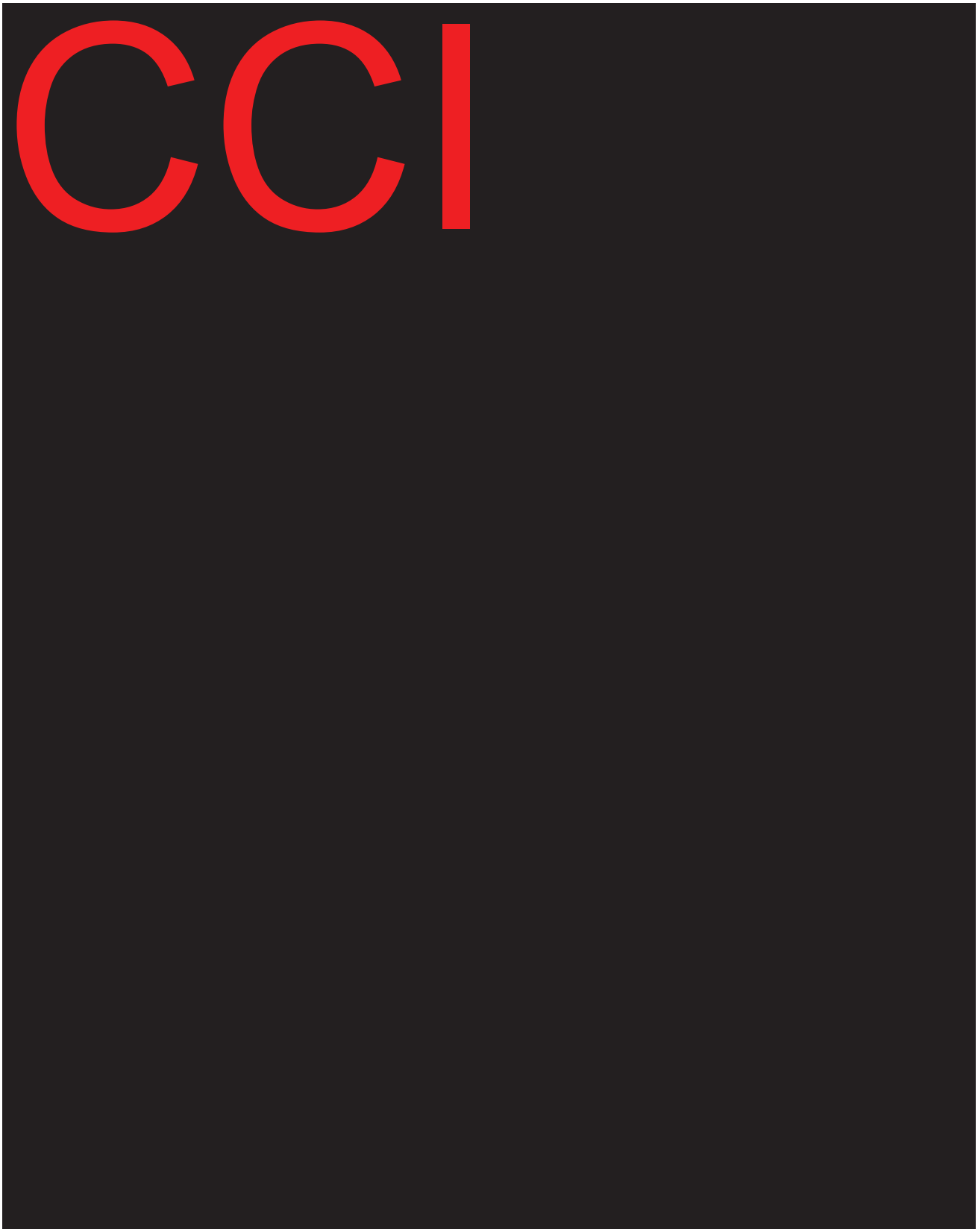
APPENDIX



A 3 Safety Analysis

Safety analysis will be based on the Interim Safety Analysis set. Selected safety outputs will be presented by treatment group and overall. The interim safety analysis will be performed

on the same subjects as the Full Analysis Population (FAP), but evaluated according to the actual treatment they received. If there is no dosing error, this is exactly the same population as the FAP.

The safety and tolerability criteria are defined and tabulated below. When either the Go or Amber criteria are met, it will be considered as acceptable.

Table 4: Safety and Tolerability Go/No Go Criteria

	GO in line with current safety profile	Amber change in safety profile with potential impact on label or development	Alert major impact on label of continued development
Overall Tolerability	Tolerability not an important barrier to adherence with < 10 % discontinuation due to AEs related to MEDI3506	Tolerability may impact adherence with ≥ 10 – 25 % discontinuation due to AEs related to MEDI3506	Tolerability has a meaningful impact on adherence with ≥ 25 % discontinuation due to AEs related to MEDI3506
Hypersensitivity	No imbalance in serious anaphylactic reactions with base case (i.e. perfunctory) contraindication statement only	Increased frequency of serious hypersensitivity reactions that results in labelling beyond base case contraindication	Occurrence of major anaphylactic-type reactions or high frequency of hypersensitivity reactions that negatively impact benefit/risk assessment
Serious infections	No clinically meaningful imbalance in infections of any type, particularly severe intensity or serious events	Clinically meaningful increased frequency of nonserious infections and/or relatively increased frequency (5 – 10 patients more than placebo)* serious infections	Dose-dependent meaningfully increased frequency of serious infections (>10 patients on highest dose relative to placebo)* and a relatively increased frequency (3 – 5 patients on highest dose relative to placebo)* of fatal infections impacting the benefit/risk ratio of MEDI3506
Progression of heart failure	No clinically meaningful imbalance in HF-related AEs	Clinically meaningful increased frequency of HF-related AEs (5 – 10 patients more than placebo)*	Dose-dependent meaningful increase of hospital admissions for HF (>10 patients on highest dose than placebo)* or a relatively increased frequency (3 – 5 patients more than placebo)* of deaths due to HF that impacts on benefit/risk evaluation of MEDI3506

* The cut-off target patient numbers presented in the criteria above should be used as an approximation and interpreted in context of the overall B/R profile of MEDI3506

The number, percentage and percentage per patient exposure year (PEY) of participants reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class. A summary of adverse events in any category will be presented by treatment. The incidence of common (⩾5% of participants in any treatment group) TEAEs, common treatment-emergent serious AEs (TESAE), and AEs leading to discontinuation of study medication will be summarized by system organ class, preferred term and treatment group, sorted in decreasing overall (across treatments) frequency. Moreover, TEAEs leading to hospitalization will also be presented.

Listings will be presented of participants with SAEs, AEs leading to discontinuation, and participants who died. A listing will be presented of participants with AEs, detailing whether these are SAEs, AEs leading to discontinuation, or result in death.

Summary statistics of laboratory data will be presented. Participants with laboratory values which are highlighted as abnormal will be listed. Summary statistics of vital signs data may be collected.

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