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

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Amendment 1, 18Feb2020

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PROTOCOL SYNOPSIS

TITLE

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

HYPOTHESES

Primary Hypothesis: MEDI3506 will reduce albuminuria compared with placebo on top of standard of care, including angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), and dapagliflozin (FORXIGA).

Secondary Hypothesis: MEDI3506 will reduce albuminuria compared with placebo on top of standard of care, including ACEi or ARB, and will exhibit an acceptable safety, immunogenicity and pharmacokinetic (PK) profile in subjects with diabetic kidney disease (DKD). Dapagliflozin on top of MEDI3506 will further reduce albuminuria.

OBJECTIVES

Primary objective: To evaluate the effect of MEDI3506 on albuminuria in subjects with DKD

Secondary objectives:

1 To evaluate safety and tolerability of MEDI3506 with and without dapagliflozin in subjects with DKD

2 To describe the PK and immunogenicity of MEDI3506 in subjects with DKD

3 To evaluate the effect of MEDI3506 in combination with ACEi or ARB with and without dapagliflozin on albuminuria in subjects with DKD

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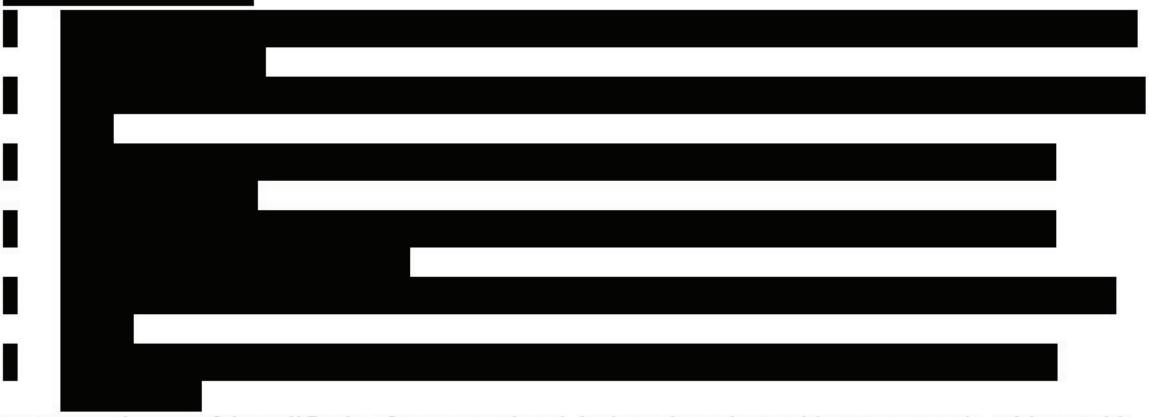

To assess the PK of dapagliflozin after repeated oral dosing when given with MEDI3506 in subjects with DKD

STUDY ENDPOINTS

Primary endpoint:

- Change from baseline to Day 169 (Week 24) in urine albumin:creatinine ratio (UACR) compared to placebo

Secondary endpoints:

- Measures of safety and tolerability including but not limited to:
  - Incidence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs)
  - Assessment of vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, respiratory rate and body temperature)
  - Electrocardiogram (ECG)

- Left ventricular ejection fraction (LVEF) as measured by echocardiogram
- B-type natriuretic peptide (BNP)
- Laboratory assessments (hematology, clinical chemistry, and urinalysis)
- For subjects testing positive for COVID-19 during the intervention and follow-up periods, the number and proportion of subjects with adverse events (AEs)/serious adverse events (SAEs), as well as the number and proportion of subjects with COVID-19 AEs/SAEs, and the proportion of asymptomatic subjects.

- MEDI3506 serum concentrations and anti-drug antibody (ADA) incidence occurring throughout the study
- Efficacy:
  - Proportion of subjects with > 30% reduction in UACR at Day 169 (Week 24)
  - Proportion of subjects with > 40% reduction in UACR at Day 169 (Week 24)
  - Proportion of subjects with > 50% reduction in UACR at Day 169 (Week 24)
  - Change from baseline to Day 85 (Week 12) in UACR
  - Change from Day 85 (Week 12) to Day 169 (Week 24) in UACR

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- CCI [redacted]

STUDY DESIGN

This is a Phase 2b, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, PK, and immunogenicity of MEDI3506 in subjects with DKD; defined as patients with type 2 diabetes mellitus (T2DM) and an estimated glomerular filtration rate (eGFR) of 25-75 mL/min/1.73 m^2 with a UACR in the range of 100-3000 mg/g, who meet all eligibility criteria. These parameters will be evaluated on top of ACEi or ARB with and without dapagliflozin. 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) CCI [redacted]. All subjects will receive 10 mg dapagliflozin by mouth daily starting on Day 85 until Day 168. 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.

TARGET SUBJECT POPULATION

Adult men or women ≥ 18 years of age with T2DM and an eGFR value of 25-75 mL/min/1.73 m^2 with a UACR of 100 - 3000 mg/g.

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- Group 1: MEDI3506 30 mg (0.2 mL), n = 95
- Group 2: MEDI3506 60 mg (0.4 mL), n = 95
- Group 3: MEDI3506 120 mg (0.8 mL), n = 95
- Group 4: MEDI3506 300 mg (2 mL), n = 140
- Group 5: Placebo (0.2 mL), n = 32
- Group 6: Placebo (0.4 mL), n = 32
- Group 7: Placebo (0.8 mL), n = 32
- Group 8: Placebo (2 mL), n = 44

All subjects will also receive 10 mg dapagliflozin by mouth daily starting on Day 85 until Day 168. Subjects already taking a sodium-glucose cotransporter-2 inhibitor (SGLT2i) will be rolled over to 10 mg dapagliflozin. Subjects who have completed 12 weeks of treatment prior to approval of Amendment 2 will continue on treatment with MEDI3506/placebo without dapagliflozin.

STATISTICAL METHODS

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 matching placebo will give approximately 85:85:85:125:125 evaluable subjects per group. 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.

Statistical analyses: The primary efficacy analysis of change from baseline to Day 169 (Week 24) in UACR compared to placebo (on treatment with dapagliflozin as standard of care) will be based on the Per Protocol Population. UACR will be log-transformed and analyzed using mixed model repeated measures (MMRM) method adjusting for fixed categorical effects of treatment, visit, and treatment-by-visit interaction, randomization stratification factors, and the continuous covariates of baseline log UACR and baseline log UACR-by-visit interaction. An unstructured covariance structure may be used to model the within-subject errors. The primary efficacy endpoint will also be analyzed using an analysis of covariance adjusting for treatment, randomization stratification factors, and baseline log UACR with last-observation-carried-forward (LOCF) imputation for missing post-baseline measurements.

The secondary efficacy analysis of change from baseline to Day 85 (Week 12) in UACR and change from Day 85 (Week 12) to Day 169 (Week 24) in UACR will be analyzed similarly to that of the primary efficacy analysis and be based on the Full Analysis Population and Per Protocol Population, respectively. For the proportions of subjects with > 30%, > 40%, and > 50% reduction in UACR, logistic regression models will be used, adjusting for treatment, randomization stratification factors, and baseline albuminuria status based on the Full Analysis Population and the Per Protocol Population.

Safety analysis will be based on the Safety Analysis Population. AE collection will begin after the subject signs the informed consent form and lasts until the end of the study. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. All TEAEs will be summarized overall and by MedDRA SOC

and PT, by severity and relationship to investigational product. All TEAEs related to dapagliflozin will also be summarized. In addition, summaries of deaths, SAEs, and treatment discontinuations due to TEAEs will be provided. Injection-site reactions will be presented.

Clinical laboratory safety tests including serum chemistry and hematology parameters will be summarized using descriptive statistics at each time point by treatment group. Change from baseline to each post baseline time point in these data will also be summarized, where appropriate. A shift table will be provided for these clinical laboratory parameters as well, where possible.

Vital signs, echocardiogram, ECGs, and BNP will be summarized using descriptive statistics at each time point by treatment group.

The incidence rate of positive antibodies to MEDI3506 and ADA titer will be reported by treatment group. Samples confirmed positive for ADA will be tested and analyzed for neutralizing antibodies (nAbs) and summarized similarly.

MEDI3506 serum concentration time profiles will be summarized for MEDI3506-treated subjects by dose cohort. Dapagliflozin concentration time profiles will also be summarized for dapagliflozin-treated subjects.

Exploratory endpoints will be summarized by treatment group.

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Safety monitoring: An independent Data and Safety Monitoring Board has been formed to evaluate safety data.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ACEi	angiotensin converting enzyme inhibitors
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-HBc	antibody to hepatitis B core antigen
ARB	angiotensin receptor blockers
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
CCI	[redacted]
BP	blood pressure
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed concentration
COPD	chronic obstructive pulmonary disease
CSP	clinical study protocol
CSR	clinical study report
CYP450	cytochrome P450
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
DKD	diabetic kidney disease
DM	diabetes mellitus
DSMB	Data and Safety Monitoring Board
DUS	disease under study
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	end of study

Abbreviation or Specialized Term	Definition
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HCP	Healthcare Professional
HIV	human immunodeficiency virus
HL	Hy's Law
CCI	[redacted]
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IRB	Institutional Review Board
IV	intravenous
IXRS	interactive voice/web response system
LSLV	last subject last visit
LV	left ventricular
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
mAb	monoclonal antibody
nAb	neutralizing antibody
NOAEL	no observed adverse effect level
PD	pharmacodynamic
PEF	peak expiratory flow
PHL	Potential Hy's Law
PK	pharmacokinetic(s)

Abbreviation or Specialized Term	Definition
PT	preferred term
QW	once every week
Q2W	every 2 weeks
Q28D	every 28 days
RAASi	renin-angiotensin aldosterone system inhibitors
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGLT2	sodium-glucose cotransporter-2
SGLT2i	sodium-glucose cotransporter-2 inhibitor(s)
SID	subject identification
SOC	system organ class
SOP	standard operating procedure
CCI	[redacted]
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TB	tuberculosis
TBL	total bilirubin
TEAE(s)	treatment-emergent adverse event(s)
TESAE(s)	treatment-emergent serious adverse event(s)
CCI	[redacted]
CCI	[redacted]
TPV	third-party vendor
UACR	urine albumin:creatinine ratio
ULN	upper limit of normal
URC	unblinded review committee
USA	United States of America
WOCBP	women of childbearing potential

1 INTRODUCTION

1.1 Disease Background

Chronic kidney disease (CKD) secondary to diabetes mellitus (DM) is known as diabetic kidney disease (DKD), and is a worldwide public health problem associated with high levels of morbidity and mortality; DM is the leading cause of end-stage renal disease (Koye et al, 2018; Mills et al, 2015). In 2017, 425 million people had DM, of whom 20% to 40% have or will develop DKD (International Diabetes Federation, 2017). Between 1990 and 2010, the number of deaths due to DKD increased by 94% (Lozano-Maneiro and Puente-Garcia, 2015).

Current guidelines recommend the use of renin-angiotensin aldosterone system inhibitors (RAASi), such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), and sodium–glucose cotransporter 2 (SGLT2) inhibitors (SGLT2i) for risk management in patients with DKD (ADA, 2020). While RAASi have been the standard of care in DKD for decades, the full risk/benefit profile of SGLT2i is still emerging (Neuen et al, 2019).

However, the pathophysiology of DKD is multifactorial, with both hemodynamic effects and inflammation, which is not addressed by current standard of care, contributing to disease progression (Hickey and Martin, 2018). Inflammatory pathways in DKD are mediated through infiltrating immune cells and proinflammatory cytokines, chemokines, and adhesion molecules (Hickey and Martin, 2018). Accumulating evidence supports the hypothesis that the activation of inflammatory molecules and pathways mediates the instigation and progression of DKD (Alicic et al, 2017; Alicic et al, 2018).

Interleukin (IL)-33 is an “alarmin” cytokine that is constitutively expressed in endothelial and epithelial barrier surfaces. When released in response to stimuli such as infection, mechanical stress, or cell death, IL-33 serves to augment the innate and adaptive immune response. Released IL-33 binds to its receptor, ST2, inducing activation of downstream inflammatory pathways (Chen et al, 2017). Inappropriate persistence and skewing of the immune response has been hypothesized to induce glomerular and tubulointerstitial inflammation and fibrosis leading to progressive loss of kidney function (Alicic et al, 2018; Chen et al, 2017; Navarro-Gonzalez and Mora-Fernandez, 2008).

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1.2 MEDI3506 Background

MEDI3506 is a human immunoglobulin (Ig) G1 monoclonal antibody (mAb) that binds to human IL-33, prevents binding of IL-33 to its receptor ST2, and inhibits conversion to

disulfide-bonded IL-33. Through this dual mechanism of action, MEDI3506 has the potential to slow progression of DKD, a widespread and potentially fatal condition.

Refer to the current MEDI3506 Investigator's Brochure (IB) (Edition 5.2) for details.

1.3 Dapagliflozin Background

Dapagliflozin (FORXIGA) is a highly potent, selective, and reversible inhibitor of SGLT2 that improves glycemic control in patients with DM and provides cardio-renal benefits in patients with T2DM and without diabetes. As of October 2021, dapagliflozin is approved in more than 100 countries to treat T2DM, 100 countries for heart failure indications, and 51 countries for chronic kidney disease indications. Dapagliflozin is commercially available as 5 mg and 10 mg tablet formulations to be taken once daily. Dapagliflozin has a well-established safety profile across indications.

Refer to the current dapagliflozin IB (Edition 17) for details.

1.4 Summary of Nonclinical Experience

1.4.1 MEDI3506

Nonclinical pharmacology studies demonstrated that MEDI3506 binds human IL-33 specifically and with high affinity. In addition, in vitro and in vivo studies have demonstrated the mechanism of action of MEDI3506. Nonclinical pharmacokinetic (PK) characteristics were established in cynomolgus monkeys following single, subcutaneous (SC) administration in a non-Good Laboratory Practice (GLP) study, and following repeat SC or intravenous (IV) administration in 4- and 26-week GLP studies. In the single-dose study, MEDI3506 exhibited linear PK at the tested doses. In the repeat-dose toxicology studies, MEDI3506 mean maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) values after SC dosing generally increased in a dose proportional manner from [redacted] to [redacted] mg/kg. Slight accumulation (mean accumulation ratios were [redacted] to [redacted]) of MEDI3506 was observed after multiple SC or IV doses after [redacted] or [redacted] weeks of dosing.

The potential toxicity of MEDI3506 was evaluated in 2 repeat-dose studies. In a repeat-dose GLP toxicity study in cynomolgus monkeys following SC or IV administration every week (QW) for [redacted] weeks (5 doses in total), there were no adverse MEDI3506-related findings noted. The no observed adverse effect level (NOAEL) at the highest doses tested was [redacted] mg/kg via SC injection and [redacted] mg/kg via IV injection. At the NOAEL for the SC and IV routes, mean MEDI3506 C_{max} values were [redacted] and [redacted] µg/mL, respectively, and mean area under the concentration-time curve from 0 to [redacted] days ($AUC_{0\text{-}31d}$) values were [redacted] and [redacted] µg × day/mL, respectively. In a GLP [redacted]-week, repeat-dose toxicity study in sexually mature cynomolgus monkeys, MEDI3506 was administered QW via SC injection at [redacted] or [redacted] mg/kg for [redacted] weeks and compared with vehicle control. No MEDI3506-related adverse effects were observed. One mid-dose female was pre-terminally euthanized on Day [redacted] due to

poor and deteriorating condition, and was noted as having necrotizing, ulcerative colitis with peritonitis and bacteremia at necropsy. In the absence of similar findings in other animals treated with equal or higher doses of MEDI3506, this was considered an incidental finding. Based on the results of this study, the NOAEL was considered to be the highest dose of CCI mg/kg/week, corresponding to mean C_{max} and AUC from 0 to 7 days (AUC_{0-7d}) values of CCI µg/mL and CCI µg × day/mL, respectively, on Day CCI.

Refer to the current MEDI3506 IB (Edition 5.2) for further details.

1.4.2 Dapagliflozin

Refer to the dapagliflozin IB (Edition 17) for a summary of nonclinical experience with dapagliflozin.

1.5 Summary of Clinical Experience

1.5.1 MEDI3506

One Phase 1 clinical study of MEDI3506 (Study D9180C00001) has closed and Phase 2 studies in atopic dermatitis (Study D9182C00001), asthma (Study D9181C00001), and chronic obstructive pulmonary disease (COPD) (Study D9180C00002) are ongoing. Two Phase 3 studies in COPD have started (Studies D9180C00003 and D9180C00004).

Study D9180C00001 was a Phase 1, first-time-in-human, randomized, blinded (investigator and subject blinded; sponsor unblinded), placebo-controlled clinical study to evaluate the safety, tolerability, PK, and immunogenicity of single and repeated doses of MEDI3506. The study entailed 3 parts. Part I involved single ascending dose administration of MEDI3506, either SC or IV to healthy adult subjects with a history of mild atopy; Part II involved multiple ascending dose administration of MEDI3506 SC to adult subjects with Global Initiative for Chronic Obstructive Lung Disease (GOLD) I to II COPD; Part III involved single dose administration of MEDI3506 IV to healthy adult Japanese subjects.

In healthy subjects with a history of mild atopy in Part I of the study, a similar proportion of subjects experienced at least 1 treatment-emergent adverse event (TEAE; ie, adverse events [AEs] occurring after the first dose of investigational product [MEDI3506 or placebo]) in the MEDI3506 and placebo groups. All reported TEAEs were Grade 1 or 2 (mild or moderate) in severity. There were no TEAEs leading to discontinuation of investigational product, treatment-emergent serious adverse events (TESAEs), or deaths.

In subjects with GOLD I to II COPD in Part II of the study, a similar proportion of subjects experienced at least 1 TEAE in the MEDI3506 SC and placebo groups. A majority of reported TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. One subject experienced a TEAE leading to discontinuation of investigational product (MEDI3506 CCI), and 3 subjects experienced TESAEs. There was 1 death due to non-

small cell lung cancer (MEDI3506 [redacted]) and 1 death due to coronary artery thrombosis (MEDI3506 [redacted]), and 1 Grade 3 TESAE of ankle fracture. The TEAE leading to discontinuation of investigational product, TESAEs, and deaths were considered not related to investigational product by the investigator.

In healthy Japanese subjects in Part III of the study, a similar proportion of subjects experienced at least 1 TEAE in the [redacted] MEDI3506 and placebo groups. All reported TEAEs were Grade 1 (mild) in severity. There were no TEAEs leading to discontinuation of investigational product, TESAEs, or deaths.

The MEDI3506 serum concentration versus time profiles from healthy subjects with a history of mild atopy showed linear and time-invariance first order absorption and first order elimination for single doses of [redacted]. For multiple Q2W SC doses in subjects with GOLD I to II COPD, slight accumulation was observed, based on the trough concentration, following the first and third dose. The multiple and single dose half-lives were consistent. No relevant differences were found in C_{max} in healthy western subjects with mild atopy and healthy Japanese subjects at [redacted], but a trend towards lower AUC was observed in the Japanese subjects. These differences may be related to the small number of subjects included in the comparison (6 healthy non-Japanese subjects and 6 healthy Japanese subjects dosed with [redacted]

Treatment-emergent anti-drug antibodies (ADA) were detected in 4 out of 66 subjects in the MEDI3506 groups. No subjects in the placebo groups (n = 22) had treatment-emergent ADA. TEAEs were similar in frequency and severity for ADA-positive and ADA-negative subjects. No impact of ADA on MEDI3506 PK was observed, except in 1 subject where the onset of treatment-emergent ADA coincided with a decrease in MEDI3506 serum concentration.

Refer to the current MEDI3506 IB (Edition 5.2) for further details.

1.5.2 Dapagliflozin

Refer to the current dapagliflozin IB (Edition 17) for a summary of clinical experience with dapagliflozin.

1.6 Rationale for Conducting the Study

This Phase 2b study is being conducted to assess functional improvement, as defined by change in urine albumin excretion, in subjects with DKD dosed with MEDI3506. Additionally, the safety, PK, and immunogenicity profile of MEDI3506 will be evaluated across the dose range to enable future studies. The interaction of MEDI3506 with standard of care on albuminuria will be assessed by treatment of subjects with, first MEDI3506/placebo and ACEi or ARB and, second MEDI3506/placebo and ACEi or ARB together with

dapagliflozin. Several exploratory endpoints will also be determined to document target engagement, proof of mechanism, and potential treatment responders.

1.7 Benefit-risk and Ethical Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

1.7.1 MEDI3506

Safety data from the Phase 1 clinical study for MEDI3506 (Study D9180C00001) has not identified medically important risks associated with single SC doses of CCI, and a single IV dose of CCI MEDI3506 in healthy subjects with a history of mild atopy (N = 42). In addition, no medically important risks are associated with multiple SC doses of CCI MEDI3506 in subjects with GOLD I to II COPD (N = 18), or a single IV dose of CCI MEDI3506 in healthy Japanese subjects (N = 6). Phase 1 data do not suggest any increase in frequency of TEAEs with increased dose, with the exception of injection-site reactions. Except for the TESAEs described (Section 1.5), all TEAEs were Grade 1 or 2 in severity. No new safety findings related to MEDI3506 have been identified.

The purpose of this Phase 2b clinical study is to evaluate the efficacy and safety of MEDI3506 in subjects with DKD. For subjects randomized to MEDI3506, there is a potential benefit in terms of functional improvement of their DKD disease status. However, as the efficacy of MEDI3506 in subjects with DKD is yet to be determined, subjects might not receive any individual benefit from participating in this study. Subjects will be expected to continue all their diabetes maintenance treatment throughout the study to minimize the risk of disease status worsening.

To date, there are no identified risks associated with MEDI3506. Potential risks for MEDI3506 include:

- Gastrointestinal adverse reactions. This is based on the observation of what was considered an incidental finding of ulcerative colitis in the 26-week toxicity study in cynomolgus monkeys (Section 1.4.1). The gastrointestinal effects of IL-33 blockade in humans is currently unclear. IL-33 is expressed in the gastrointestinal tract, where it has multiple downstream effects (Hodzic et al, 2017). Expression of IL-33 is elevated in patients with active ulcerative colitis.
- Serious infections (including opportunistic infections). This is based on the putative mechanism of action of MEDI3506, in particular, the role of IL-33 as an “epithelial alarmin” (Martin and Martin, 2016). Some evidence suggests that IL-33 may enhance the ability of neutrophils and macrophages to respond to bacterial invasion (Alves-Filho et al, 2010; Li et al, 2014). Therefore, blocking this pathway could potentially ameliorate

certain anti-infection response in the human immune system. In regard to SARS-CoV-2, AstraZeneca is not aware of any current evidence of a direct link between IL-33, or IL-33 suppression, and contracting SARS-CoV-2 and early stages of COVID-19 illness post infection. Moreover, it is hypothesized that IL-33 suppression might be beneficial in the later, hyperinflammatory phase of severe COVID-19 illness; MEDI3506 will be tested in patients with severe COVID-19 infections as part of the Accelerating COVID-19 Research and Development (ACCORD) study 2 (ACCORD-2; EudraCT number 2020-001736-95). To date, no opportunistic infections have been reported in the MEDI3506 program.

- Progression of heart failure. IL-33 is widely expressed in cardiovascular tissues (Moussion et al, 2008) and can be released locally upon tissue injury (Martin and Martin, 2016). The precise cardiac function of IL-33 signaling has remained unclear. Non-clinical toxicology studies conducted with MEDI3506 (Section 1.4.1) have not indicated any adverse cardiovascular outcomes in non-human primates. Likewise, there have been no cases of heart failure in the completed study of MEDI3506 conducted in healthy volunteers and patients with mild COPD (Section 1.5.1).
- Injection-site reactions. This is based on the SC route of administration and the nature of MEDI3506 as an exogenous protein substance. In the nonclinical 26-week repeat dose toxicity studies in cynomolgus monkeys (Section 1.4.1), non-adverse microscopic changes related to MEDI3506 were seen at the injection site. Overall, injection of MEDI3506 was well tolerated in Phase 1.
- Serious hypersensitivity (including Type 1 to 4 hypersensitivity reactions). As mAbs are foreign proteins, they have the potential to provoke hypersensitivity reactions.
- Reproductive toxicity. Consistent with ICH guidance on the timing of nonclinical studies, MEDI3506 has not been evaluated in embryo-fetal development toxicity studies.

The study design aims to minimize potential risks to subjects through the inclusion/exclusion criteria, screening procedures and safety monitoring with the establishment of an independent Data and Safety Monitoring Board (DSMB). This includes exclusion of subjects who are more likely to experience the potential risks, stipulating contraceptive requirements for subjects, routine clinical monitoring of subjects including monitoring for injection-site reactions, and routine blinded review of the safety data including potential anaphylactic symptoms by the medical monitor and the sponsor study team. In addition, sites should be equipped to manage anaphylaxis and serious allergic reactions until the subject can be transferred to a suitable facility. These risk mitigation strategies mean that the potential benefits should outweigh the risks supporting study conduct.

A more detailed description of each potential risk and mitigation strategy can be found in the current MEDI3506 IB (Edition 5.2).

1.7.2 Dapagliflozin

The safety profile of dapagliflozin has been evaluated in clinical development programs for T2DM, T1DM, heart failure and CKD. This includes more than 15,000 subjects treated with

dapagliflozin for T2DM, more than 1,000 subjects treated with dapagliflozin for T1DM, more than 1,400 subjects treated with dapagliflozin for DKD, and more than 2,000 subjects treated with dapagliflozin for heart failure. Overall, treatment with dapagliflozin 5 mg was similar to treatment with dapagliflozin 10 mg in both T1DM and T2DM. The safety profile of dapagliflozin was overall consistent across the studied indications.

The most commonly reported AEs associated with the use of dapagliflozin include genital infections, urinary tract infections, back pain, and polyuria. In addition, rash has been identified as an AE of unknown frequency in marketed use of dapagliflozin.

In the cardiovascular outcomes study, dapagliflozin on the Incidence of Cardiovascular Events (DECLARE), 8,574 patients received dapagliflozin 10 mg and 8,569 patients received placebo for a median exposure time of 48 months. Events of diabetic ketoacidosis (DKA) were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event.

The DAPA-CKD renal outcome study has shown 10 mg dapagliflozin to be efficacious and well tolerated in a wide range of patients with CKD (2152 patients treated with dapagliflozin; median follow-up = 2.4 years) (Heerspink et al, 2020a). In patients with an estimated glomerular filtration rate (eGFR) 25 to 75 mL/min/1.73m^2 dapagliflozin was shown to significantly reduce the combined risk of: 1) sustained decline in eGFR of at least 50%; 2) end-stage kidney disease; 3) or death from renal or cardiovascular causes (Heerspink et al, 2020a).

Taken together, SGLT2i have been shown to consistently reduce the risk of clinically important, patient-level cardiovascular outcomes and emerging data suggest that the combination of ACEi or ARB and SGLT2i should be routinely offered to patients with T2DM who have, or are at high risk of, progressive kidney disease (de Boer et al, 2020).

More detailed information about the known and expected benefits and potential risks of dapagliflozin may be found in the respective current IB (Edition 17).

1.7.3 Other Risks

Given the distinct molecular mechanisms of action of MEDI3506 and dapagliflozin, no adverse drug-drug interaction is expected when both drugs are taken together.

For details on background information, risks and mitigations plans, and impact of COVID-19 on the current study, see Appendix F.

1.7.4 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to the subjects of this study, the potential risks identified in association with MEDI3506 and MEDI3506/dapagliflozin are justified by the anticipated benefits that may be afforded to subjects with DKD.

1.8 Research Hypotheses

1.8.1 Primary Hypothesis

MEDI3506 will reduce albuminuria compared with placebo on top of standard of care, including ACEi or ARB, and dapagliflozin.

1.8.2 Secondary Hypotheses

MEDI3506 will reduce albuminuria compared with placebo on top of standard of care, including ACEi or ARB, and will exhibit an acceptable safety, immunogenicity, and PK profile in subjects with DKD. Dapagliflozin on top of MEDI3506 will further reduce albuminuria.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoint

Table 1 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
Efficacy	To evaluate the effect of MEDI3506 on albuminuria in subjects with DKD	Change from baseline to Day 169 (Week 24) in UACR compared to placebo. Central laboratory UACR results will be blinded to Investigators and Sponsor team starting from Visit 3 (Day 1) up to and including the EOS Visit.

DKD = Diabetic Kidney Disease; UACR = Urine albumin:creatinine ratio

2.2 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Safety	To evaluate safety and tolerability of MEDI3506 with and without dapagliflozin in subjects with DKD	Measures of safety and tolerability including but not limited to: • Incidence of TEAEs and TESAEs • Assessment of vital signs (SBP, DBP, heart rate, respiratory rate and body temperature) • ECG • LVEF as measured by echocardiogram

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
		• BNP • Laboratory assessments (hematology, clinical chemistry, and urinalysis) • For subjects testing positive for COVID-19 during the intervention and follow-up periods, the number and proportion of subjects with AEs/SAEs, as well as the number and proportion of subjects with COVID-19 AEs/SAEs, and the proportion of asymptomatic subjects.
PK, Immunogenicity	To describe the PK and immunogenicity of MEDI3506 in subjects with DKD	MEDI3506 serum concentrations and ADA incidence occurring throughout the study
Efficacy	To evaluate the effect of MEDI3506 in combination with ACEi or ARB with and without dapagliflozin on albuminuria in subjects with DKD	• Proportion of subjects with > 30% reduction in UACR at Day 169 (Week 24) • Proportion of subjects with > 40% reduction in UACR at Day 169 (Week 24) • Proportion of subjects with > 50% reduction in UACR at Day 169 (Week 24) • Change from baseline to Day 85 (Week 12) in UACR • Change from Day 85 (Week 12) to Day 169 (Week 24) in UACR

ACEi = angiotensin converting enzyme inhibitors; ADA = anti-drug antibody; AE(s) = adverse event(s); ARB = angiotensin receptor blockers; BNP = B-type natriuretic peptide; ECG = electrocardiogram; EOS = end of study; DBP = diastolic blood pressure; DKD = Diabetic Kidney Disease; LVEF = left ventricular ejection fraction; PK = pharmacokinetic; SAE(s) = serious adverse event(s); SBP = systolic blood pressure; TEAE(s) = treatment emergent adverse event(s); TESAE(s) = treatment emergent serious adverse event(s); UACR = urine albumin to creatinine ratio

CCI [redacted]

CCI [redacted]

CCI [redacted]

3 STUDY DESIGN

3.1 Description of the Study

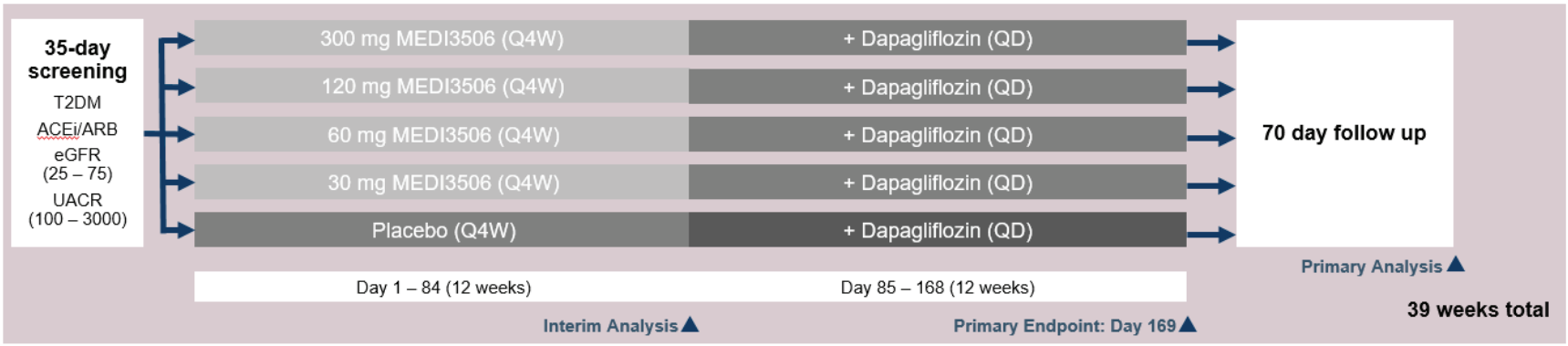
3.1.1 Overview

This is a Phase 2b, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, PK, and immunogenicity of MEDI3506 in adult subjects with 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. Furthermore, the additive effect of the SGLT2i dapagliflozin taken together with MEDI3506 on albuminuria will be assessed for 12 weeks when subjects will be treated with MEDI3506/placebo and dapagliflozin. Subjects who have started on the Phase 2a study prior to Amendment 2 will be transitioned to the Phase 2b and given dapagliflozin starting on Day 85 (Week 12). Subjects who have completed 12 weeks of treatment prior to implementation of Amendment 2 will continue on treatment with MEDI3506/placebo without dapagliflozin.

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. Note that the 19 subjects who were enrolled and discontinued prior to the study hold on 24 March 2020 due to COVID-19 are not included in the total count of 565 subjects. Subjects will be dosed subcutaneously [redacted]

Following the signing of informed consent, subjects will be assessed for study eligibility during a screening period of up to 35 days (Day -37 to Day -3) followed by a 168-day (24-week) treatment period and a 70-day (10-week) follow-up period (Figure 1).

Figure 1 Study Flow Diagram



ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate in mL/min/1.73m^2; Q4W = every 4 weeks; QD = once daily; T2DM = type 2 diabetes mellitus; UACR = urine albumin to creatinine ratio in mg/g.

3.1.2 Treatment Regimen

CCI [redacted]

- Group 1: MEDI3506 30 mg (0.2 mL), n = 95
- Group 2: MEDI3506 60 mg (0.4 mL), n = 95
- Group 3: MEDI3506 120 mg (0.8 mL), n = 95
- Group 4: MEDI3506 300 mg (2 mL), n = 140
- Group 5: Placebo (0.2 mL), n = 32
- Group 6: Placebo (0.4 mL), n = 32
- Group 7: Placebo (0.8 mL), n = 32
- Group 8: Placebo (2 mL), n = 44

All subjects will also receive daily oral tablets of 10 mg dapagliflozin starting on Day 85 until Day 168. Subjects already taking an SGLT2i will be rolled over to 10 mg dapagliflozin.

Dapagliflozin should be taken in the morning with or without food.

3.1.3 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this protocol and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study subjects become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the subject's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study subjects, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent for the mitigation procedures (note, in the case of verbal consent, informed consent form (ICF) should be signed at the subject's next contact with the study site).

- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened subjects. The investigator should confirm this with the designated Study Physician.
- Home or Remote visit (when applicable): Performed by a site qualified Healthcare Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the subjects using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix G.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

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A once daily dose of 10 mg dapagliflozin has been established as having favorable tolerability and effect on albuminuria in DKD (Heerspink et al, 2020a).

3.2.2 Rationale for Study Population

Studying subjects with DKD enables assessment of the clinical efficacy and safety of MEDI3506, as well as supporting dose selection, in a population at risk for progression to renal failure on top of standard of care, including ACEi or ARB and SGLT2i (Go et al, 2018). Subjects with DKD with eGFR 25-75 mL/min/1.73 m^2 will be recruited, as clinical studies support that the inflammatory process driving CKD progression is increased in subjects with reduced eGFR (Alicic et al, 2018; Perlman et al, 2015; Tuttle et al, 2018).

3.2.3 Rationale for Endpoints

The primary endpoint in this study is the change in UACR from baseline. The change in urine albumin excretion during the treatment period provides information about renal efficacy, and a sustained effect following investigational drug washout suggests benefit to renal structure.

The evaluation of MEDI3506/placebo taken with ACEi or ARB, or with ACEi or ARB plus dapagliflozin will clarify the interaction with standard care. The treatment duration allows a suitable assessment of safety and immunogenicity following multiple dose administration and is of sufficient length to evaluate effects on urine albumin excretion (Heerspink et al, 2019).

Standard measures of PK analysis will be used to inform understanding of MEDI3506 and dapagliflozin PK in subjects with DKD as well as help to inform the exposure-response relationship. Standard safety and immunogenicity measures will be assessed.

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4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Approximately 565 subjects are planned to be randomized in this study into 8 treatment groups (Section 3.1.2).

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Adult men or women ≥ 18 years of age at Visit 1.

2 Written informed consent and any locally required authorization (eg, data privacy) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.

3 DKD defined as
   (a) diagnosis of T2DM and
   (b) eGFR 25-75 mL/min/1.73 m^2 based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [a] and
   (c) UACR defined as 100-3000 mg albumin/g creatinine based on the mean of 3 sequential first morning void midstream urine samples at Visit 2.

4 BP ≤ 150/100 mmHg at Visit 1 and Visit 3.

5 Stable dose of ACEi or ARB for at least 6 weeks prior to Visit 1 and throughout the screening period with ACEi and ARB dosing according to local guidelines. Subjects who have been deemed unable to tolerate ACEi or ARB therapy due to allergy or complications may be enrolled. Minor dose adjustment within 2 weeks before Visit 1 is acceptable (see Section 4.7.2).

6 For subjects on any additional antihypertensive medication (including diuretic therapy), doses must be stable for at least 6 weeks prior to Visit 1 and throughout the screening period.

7 For subjects on SGLT2i treatment prior to enrollment, doses must be stable for at least 4 weeks prior to Visit 3. Existing SGLT2i treatment will be stopped and switched to 10 mg dapagliflozin on Day 85.

8 Up-to-date influenza and pneumococcal pneumonia vaccinations (subject-reported) according to local recommendations, at least 28 days prior to Visit 3 OR confirmation of off-season intent to get vaccinated. Patients screened outside of the influenza season (including those who were not vaccinated in the previous season) are eligible for randomization provided that the vaccination is planned once the influenza vaccine for the next season becomes available. For such patients, investigators are asked to confirm the patient's intent to get vaccinated for the next season. Patients who do not plan to get vaccinated against influenza should not be randomized.

9 Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

(a) Male subjects:

- For genotoxic investigational products, the male subject should use condom during treatment and until the end of relevant systemic exposure in the male subject, plus a further 90-day period (until 24 weeks after the last dose of study intervention (MEDI3506). For a non-pregnant women of childbearing potential (WOCBP) partner, contraception recommendations should also be considered.

(b) Female subjects:

- Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of Visit 3 without an alternative medical cause. The following age-specific requirements apply:
  - Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone levels in the postmenopausal range.
  - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female subjects of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Women of childbearing potential who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 12 weeks after last dose of study intervention (MEDI3506). Cessation of contraception after this point should be discussed with a responsible physician.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together. All WOCBP must have a negative serum pregnancy test result at Visit 1.

- Highly effective birth control methods include: sexual abstinence (periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational product [MEDI3506], and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing®. Women of childbearing potential must agree to use one highly effective methods of birth control, as defined above, from enrollment throughout the study up to the end of the follow-up period at Visit 10.

10 Able and willing to comply with the requirements of the protocol and complete the study.

[a] CKD-EPI equation: $eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black] (Levey et al, 2009). For subjects with amputation, eGFR will be adjusted based on estimated body weight loss.

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1 Concurrent enrollment in another clinical study involving an investigational treatment or drug, or received administration of an investigational drug or participation in a device trial within 3 months prior to Visit 1.

2 Previous participation in a MEDI3506 clinical trial.

3 Diagnosis of CKD other than diabetic renal disease (hypertensive nephrosclerosis superimposed on DKD is acceptable).

4 Serum potassium > 5.5 mmol/L at Visit 1 that cannot be adjusted to values ≤ 5.5 mmol/L by appropriate management (Appendix E).

5 Significant hepatic disease, including, but not limited to, acute hepatitis, chronic active hepatitis, or severe hepatic insufficiency, including subjects with ALT and/or AST > 3 × ULN and/or TBL > 2 mg/dL (> 34.2 μmol/L). Subjects with TBL > 2 mg/dL (> 34.2 μmol/L) and documented Gilbert's syndrome will be allowed to participate.

6 Hemoglobin (Hb) A1c > 10.5% measured at Visit 1.

7 B-type natriuretic peptide (BNP) level > 200 pg/mL at Visit 1.

8 History of clinically significant heart disease including but not limited to any of the following:

(a) Clinically significant congenital or acquired valvular disease, cardiomyopathy or severe pulmonary hypertension, unstable ischemic heart disease, or recent myocardial infarction < 6 months of Visit 1;

(b) Left ventricular (LV) ejection fraction < 40%, based on transthoracic echocardiogram performed during Visit 2;

(c) New York Heart Association Class 3 or 4 or history of hospitalization for heart failure within the past 12 months prior to Visit 1;

(d) History of unstable arrhythmias.

9 Any of the following concomitant conditions or diseases at Visit 1:

(a) History of treated ulcerative colitis, Crohn's disease, or microscopic colitis within the last 3 years;

(b) Anticipated dialysis or renal transplantation within 1 year;

(c) A history of alcohol and/or substance abuse (including positive drugs of abuse screen at Visit 1) that could interfere with the conduct of the trial;

(d) Prior malignancy other than:

(i) non-melanoma skin cancer (squamous or basal cell carcinoma) treated for complete cure

(ii) cervical cancer in situ treated for complete cure

(iii) any other history of malignancy treated with apparent success with curative therapy (response duration of > 5 years);

(e) History of underlying condition that predisposes the subject to infections (eg, history of splenectomy, known primary or secondary immune deficiency syndromes, cirrhosis);

(f) Infections:

(i) Significant infection (viral, bacterial, or fungal) including unexplained diarrhea within 4 weeks prior to Visit 3

(ii) History of Herpes zoster with last flare occurring within 3 months of Visit 1

(iii) Positive test for or history of treatment for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). Subjects positive for hepatitis B surface antigen (HBsAg) or antibody to hepatitis B core antigen (anti-HBc) are excluded. Those with a history of hepatitis B vaccination without a history of hepatitis B are permitted to enroll

(g) History or evidence of active tuberculosis (TB) infection at Visit 1 or one of the risk factors for tuberculosis such as but not limited or exclusive to:

(i) History of residence in a congregate setting (eg, jail or prison, homeless shelter, or chronic care facility) or healthcare workers with unprotected exposure to subjects who are at high risk of TB

(ii) Close contact (ie, share the same air space in a household or other enclosed environment for a prolonged period [days or weeks, not minutes or hours]) with a person with active pulmonary tuberculosis (TB) disease within the last 12 months;

(h) Amputation due to peripheral artery disease;

(i) Any other medical condition or clinically relevant abnormal findings in physical examination, laboratory results, or electrocardiogram (ECG) during screening that, in the opinion of the investigator, may compromise the safety of the subject in the

study, reduce the subject's ability to participate in the study, or interfere with evaluation of MEDI3506.

10 Vaccinations
   (a) Live or attenuated virus vaccination within 28 days of Visit 3 until the end of the follow-up period is not allowed.
   (b) Vaccination against COVID-19 (either first or subsequent dose) within 28 days before Visit 3; for details, see Section 4.7.4.

11 Allergic reactions
   (a) History of severe allergic reaction requiring hospitalization;
   (b) History of severe reaction to any medication including biologic agents or human gamma globulin therapy;
   (c) History of allergy or reaction to any component of MEDI3506 or dapagliflozin formulation.

12 Subjects with a known positive diagnostic nucleic acid or antigen test for SARS-CoV-2 within 6 weeks prior to randomization visit. [a]

13 Subjects with a significant COVID-19 illness within 6 months of randomization:
   (a) Subjects with a diagnosis of COVID-19 pneumonia based on radiological assessment;
   (b) Subjects with diagnosis of COVID-19 with significant findings from pulmonary imaging tests;
   (c) Subjects with a diagnosis of COVID-19 requiring hospitalization and/or oxygen supplementation therapy.

14 Receiving any of the prohibited concomitant medications (see Section 4.7.2) including:
   (a) Renin inhibitor or an aldosterone antagonist when used in combination with an ACEi or an ARB within 2 months of Visit 1;
   (b) Ongoing use of any biologic drug and/or small molecule targeting the immune system (eg, TNF blockers, anakinra, rituximab, abatacept, tocilizumab, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, or corticosteroids other than topical or inhaled);
   (c) Subjects on serum creatinine-altering drugs should be on long-term treatment at a stable dose prior to study entry. Drugs considered serum-altering include but are not limited to amphotericin, cimetidine, clofibrate, dronedarone, ketoconazole, probenecid, ranolazine, trimethoprim, aminoglycosides, or cephalosporins. Generally, any drug that has a putative ≥ 5% effect on serum creatinine is considered serum creatinine-altering. The following exclusion criteria apply:
      (i) New treatment or change of dose within 6 weeks prior to Visit 1
      (ii) Expected change of dosing regimen during the study
      (iii) Minor ACEi or ARB dose adjustment within 2 weeks of Visit 1 is acceptable, but any dose adjustments during the course of the study (ie, for control of hyperkalemia) should be discussed with the sponsor/ medical monitor
      (iv) Clinically indicated short-term use of serum creatinine-altering drugs to treat acute conditions during the study may be allowed.

15 Donation of blood or significant blood loss
   (a) All sites except Japan: Donation of blood or significant blood loss in excess of 500 mL within 3 months prior to Visit 3 (or > 1200 mL in the year prior to Visit 3).
   (b) For Japan only:
      (i) For male subjects, donation of whole blood or significant blood loss in excess of 400 mL within 3 months prior to Visit 3 or > 1200 mL in the year prior to Visit 3.
      (ii) For female subjects, donation of whole blood or significant blood loss in excess of 400 mL within 4 months prior to Visit 3 or > 800 mL in the year prior to Visit 3.
16 Plasma donation within 60 days prior to Visit 3.
17 Subjects who are institutionalized.
18 An employee, or close relative of an employee, of AstraZeneca, the contract research organization, or the study site, regardless of the employee's role.
19 Pregnancy or intention to become pregnant during the course of the study, breastfeeding, or unwillingness to use a highly effective method of contraception throughout the study in female subjects of childbearing potential.

[a] Investigators should use their best clinical judgement to decide on measures needed to minimize the risk of randomizing patients with an active SARS-CoV-2 infection. To do so, they should consider the local status of the COVID-19 pandemic, the subject's medical and vaccination history, local recommendations regarding outpatient COVID-19 screening, and testing policies.

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice/web response system [IXRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria may be rescreened any time during the recruitment period and receive a new SID number. Subjects can be rescreened up to 2 times. Prior to rescreening, subjects must be reconsented and receive a new SID number. Subjects who have been discontinued from treatment will not be rescreened.

Where subjects who do not meet the inclusion and/or exclusion criteria are randomized in error, or incorrectly started on treatment, or where subjects subsequently fail to meet the study

criteria post initiation, the investigator should inform the medical monitor immediately. The investigator and/or medical monitor may determine that the incorrectly randomized subject will not receive any further investigational product if the inclusion/exclusion criteria violation would put the subject at undue risk.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time, without prejudice to further treatment. A subject who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records). Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the investigator.

AEs will be followed up; all study materials should be returned by the subject. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

Subjects are free to discontinue study drugs at any time, without prejudice to further treatment.

- Subjects who choose to discontinue MEDI3506 prior to the dapagliflozin period (Day 85 to Day 168) will not proceed on dapagliflozin and are expected to attend their next scheduled study visit for an Early Discontinuation Visit (see Table 6) and then to complete the assessments per the follow-up visit described in Table 7. Visit 10/EOS will be conducted 60 days (± 5 days) after the last visit performed.
- Subjects who choose to discontinue MEDI3506 during the dapagliflozin period (Day 85 to Day 168) prior to the end of the treatment period are expected to attend their next scheduled study visit for an Early Discontinuation Visit (see Table 6) and then to complete the assessments per the follow-up visit described in Table 7. Visit 10/EOS will be conducted 60 days (± 5 days) after the last visit performed.
- Subjects who choose to discontinue dapagliflozin during the dapagliflozin period (Day 85 to Day 168) prior to the end of the treatment period are expected to continue in the study on remaining study therapy according to the schedule of study procedures for the remainder of the study.

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1 Withdrawal of consent from further treatment with investigational product
2 Lost to follow-up

3 An AE that, in the opinion of the investigator or the sponsor, warrants discontinuation of further dosing or meets criteria for discontinuation from investigational product (including, but not limited to, anaphylactic reaction to investigational product, new onset or progression of heart failure).
4 After initial dosing, there exists a clinically significant safety issue based on information not known or not disclosed prior to randomization
5 Subject noncompliance that, in the opinion of the investigator or sponsor, warrants treatment discontinuation for safety reasons (eg, refusal or inability to adhere to scheduled visits)
6 Pregnancy

Appendix C describes actions required in cases of increases in liver biochemistry.

Consider temporary interruption of dapagliflozin if DKA is suspected. The subject should be promptly evaluated. If DKA is confirmed, dapagliflozin should be discontinued permanently.

Subjects who have a positive SARS-CoV-2 nucleic acid test should be immediately evaluated by the investigator and sponsor. Based on investigator and sponsor judgement, subjects may be temporarily or permanently discontinued from treatment.

Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn from further study participation (Section 4.1.5), the subject is lost to follow-up, or the subject is enrolled in another clinical study.

4.1.6.1 Missed Doses of MEDI3506 or Dapagliflozin

A subject who misses a scheduled dosing visit of MEDI3506 (due to COVID-19 or other reasons) can continue study intervention if dosing is performed within 14 days of the missed visit (Table 4). If subjects cannot be rescheduled within 14 days, the dose is considered missed and study intervention should continue at the next scheduled visit per Table 6. Up to 1 dose of MEDI3506 may be missed. If the subject misses more than one dose, he/she will be considered dropped out/discontinued.

Missed/delayed doses should be captured in the eCRF. Refer to Appendix F for information on dealing with missed doses as a result of the COVID-19 pandemic.

Table 4 Guidelines for Handling Missed Doses of MEDI3506

Missed visit	Subject to be rescheduled for dosing within 14 days of missed visit. If subject is unable to be rescheduled within 14 days, skip dose (see below for missed dose).
1 missed dose	Administer next dose according to schedule
2 missed doses	Subject to be considered dropped out/discontinued

Missed doses of dapagliflozin should be handled as detailed in Section 4.7.3.

4.1.7 Replacement of Subjects

Subjects who are randomized but do not receive investigational product (MEDI3506 or placebo) may be replaced (with identical investigational product assignment, if applicable) to maintain the stipulated cohort sizes. This would include subjects who are randomized and then withdraw consent before receipt of the investigational product.

Subjects who are discontinued from further dosing or follow-up procedures or withdraw their informed consent to all follow-up prior to the end of study (EOS) visit may be replaced, if deemed necessary by the medical monitor to ensure that data are collected from a sufficient number of subjects. The medical monitor should be notified within 48 hours if a subject permanently discontinues study drug or withdraws consent to all follow-up. A determination whether to replace the subject will be made by the medical monitor.

Subject retention for dosing and for study procedures, even if dosing has been discontinued, is key to the success of this study. Sites must have a subject retention plan in place. The following approaches should be included to minimize loss of data: asking a subject for the name and contact number of a family member or friend who can be contacted to reach the subject (signed consent should be obtained); use of email contact (with care to avoid revealing confidential medical information over nonsecure email); and coverage of the cost of transportation to clinic, if needed.

For any missing visit/contact or missing data, the reason for the missing visit/contact and/or data must be recorded in the electronic data capture (EDC) system.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca. AstraZeneca will ensure the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples

are disposed of/destroyed, the action documented and the signed document returned to the study site.

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented and AstraZeneca are informed about the sample disposal.

4.2 Schedule of Study Procedures

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the proper nominal time. Randomization should only proceed if all required assessments have been performed and all inclusion/exclusion criteria as well as other protocol restrictions have been evaluated; see Section 4.1.2, Section 4.1.3, and Section 4.7.

Dosing of subjects should only be carried out if all required assessments have been performed and evaluated. Dosing is not allowed to proceed until the investigator has determined that the results are within acceptable range according to the defined stopping criteria; see Section 4.1.6. Laboratory assessment results should also be reviewed at every visit to ensure that stopping criteria have not been met.

4.2.1 Enrollment/Screening Period

Table 5 shows all procedures to be conducted at the screening visit.

Table 5 Schedule of Screening Procedures

Study Period	**Screening**		
Visit Number	**Visit 1**	**Phone Call 1 [a]**	**Visit 2**
Procedure / Study Day	**Day -37 to Day -3**		
Informed consent (main study)	X		
Informed consent (future use blood and urine [b])	X		
Informed consent (genetic [b])	X		
Verify eligibility criteria	X	X	
Safety assessments:			
Full medical history review	X		
Assessment of AEs/SAEs		X	X
Physical examination (full)	X		
Weight, height, and BMI calculation	X		
Vital signs	X		
ECG	X		

Table 5 Schedule of Screening Procedures

Study Period	Screening		
Visit Number	**Visit 1**	**Phone Call 1 [a]**	**Visit 2**
Procedure / Study Day	**Day -37 to Day -3**		
Transthoracic echocardiogram			X [c]
Concomitant medications	X	X	X
Blood collection for:			
Serum chemistry	X		
CCI [redacted]	X		
CCI [redacted]	X		
Serum beta-hCG, FSH (for women) [d]	X		
Complete blood count with differential	X		
eGFR calculation [e]	X		
Hepatitis B, C; HIV-1, HIV-2	X		
Urine collection for:			
Urinalysis	X		
Drug and alcohol screen [f]	X		
Spot urine for UACR	X		
Procedure:			
Dispense supply of containers for urine samples	X		
Reminder to collect first morning void midstream urine samples 3 days before the next visit		X	
Subjects return first morning void midstream urine collection samples for UACR analysis [g]			X

AE(s) = adverse event(s); ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CCI [redacted]; ECG = 12-lead electrocardiogram; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; CCI [redacted] hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; PTT = partial thromboplastin time; SAE(s) = serious adverse event(s); UACR = urine albumin:creatinine ratio.

NOTE: Where the values for clinical laboratory tests (Section 4.3.3) are outside the usual range for a subject during screening, based on their medical history, retesting may be undertaken on one occasion without requiring a re-screen.

NOTE: Investigator should ensure that all subjects are contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked to follow up suspected reports according to local guidelines.

[a] Phone Call 1 will occur after results from the initial screening visit are available and the subject is confirmed otherwise eligible in order to remind subjects to collect the first morning void and schedule Visit 2.

[b] Optional informed consent is required for agreement to the future use of blood and urine samples and genetic testing, if appropriate.

Table 5 Schedule of Screening Procedures

Study Period	Screening		
Visit Number	Visit 1	Phone Call 1 [a]	Visit 2
Procedure / Study Day	Day -37 to Day -3		

[c] If otherwise eligible at Screening Visit 1, a Screening Visit 2 will be scheduled to conduct the transthoracic echocardiogram, which may be performed independently of other Visit 2 procedures during the screening period.

[d] Testing for menopause will only be performed if menopausal status cannot be established from full medical history review.

[e] For subjects with amputation, eGFR will be adjusted based on estimated body weight loss.

[f] Alcohol screen breathalyzer to be performed in line with local practices. Drug screen to be performed in line with local practices and investigator discretion.

[g] Subjects collect 3 consecutive first morning void midstream urine samples (ideally day of visit and preceding 2 days [refrigerated overnight]) which are returned on the day of visit. This collection may be repeated once during the course of screening. Eligibility will be determined based on the results.

4.2.2 Randomized Treatment Period

Table 6 shows all procedures to be conducted during the treatment period.

Table 6 Schedule of Treatment Period Study Procedures

Study Period	Treatment Period							
Visit Number	V3	V4	V5	V6	V7	V8	V9	Early D/c Visit
Procedure / Study Day	Day 1	Day 29 (± 5 days)	Day 57 (± 5 days)	Day 85 (± 5 days)	Day 113 (± 5 days)	Day 141 (± 5 days)	Day 169 (± 5 days)	
Verify eligibility criteria	X							
Randomization	X							
Safety assessments:								
Physical examination (abbreviated) with weight [a]	X	X	X	X	X	X	X	X
Vital signs [b]	X	X	X	X	X	X	X	X
Transthoracic echocardiogram							X [c]	X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Blood collection for:								
Serum chemistry	X	X		X		X	X	X
CCI [redacted]	X	X		X			X	X
CCI [redacted]							X	X

Table 6 Schedule of Treatment Period Study Procedures

Study Period	Treatment Period							
Visit Number	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Procedure / Study Day	**Day 1**	**Day 29 (± 5 days)**	**Day 57 (± 5 days)**	**Day 85 (± 5 days)**	**Day 113 (± 5 days)**	**Day 141 (± 5 days)**	**Day 169 (± 5 days)**	**Early D/c Visit**
Complete blood count with differential, prothrombin time,and PTT	X			X			X	X
PK (MEDI3506) [d]		X		X			X	X
PK (dapagliflozin) [e]						X	X	
ADA (MEDI3506) [f]	X	X		X			X	X
CCI [redacted]								
CCI [redacted]								
Blood for future use [f,g]	X	X				X		X
Genetic research sample [g,h]	X							
Urine collection for:								
Urinalysis [f]	X							
Pregnancy test (females of childbearing potential) [f]	X	X	X	X	X	X	X	X
UACR [i]	X	X	X	X	X	X	X	X
CCI [redacted]								
Urine for future use [f,g]	X	X		X		X		X
Procedure:								
Site to remind patients to collect first morning void midstream urine samples 3 days before the next visit		X	X	X	X	X	X	X
IP administration (MEDI3506/placebo) [j]	X	X	X	X	X	X		
IP administration (dapagliflozin) [k]				Day 85 to Day 168 QD				

ADA = anti-drug antibody(ies); AE(s) = adverse event(s); CCI [redacted]
D/c = discontinuation; CCI [redacted]
CCI [redacted]; IP = investigational product; PK = pharmacokinetics; PTT = partial thromboplastin time; QD = once daily; SAE(s) = serious adverse event(s); CCI [redacted]; UACR = urine albumin:creatinine ratio V= Visit.

NOTE: Investigator should ensure that all subjects are contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked to follow up suspected reports according to local guidelines. Any subject with symptoms consistent with COVID-19 should be tested on an ad hoc basis.

Table 6 Schedule of Treatment Period Study Procedures

Study Period	Treatment Period							
Visit Number	V3	V4	V5	V6	V7	V8	V9	
Procedure / Study Day	Day 1	Day 29 (± 5 days)	Day 57 (± 5 days)	Day 85 (± 5 days)	Day 113 (± 5 days)	Day 141 (± 5 days)	Day 169 (± 5 days)	Early D/c Visit

[a] Including focused cardiac exam (Section 4.3.2.2).

[b] For the first 2 doses of MEDI3506 or placebo, patients are to remain at the site for ≥ 2 hours or until stable, whichever is later. In addition, vital signs will be taken before and immediately after administration of MEDI3506 or placebo, and at 30 minutes (± 5 minutes) as well as 120 minutes (± 10 minutes) thereafter or until stable, whichever is later. Following the observation period, subject discharge will be at the discretion of the investigator. For all other dosing visits, vital signs will be collected 30 minutes (± 5 minutes) after administration of MEDI3506 or placebo or when stable.

[c] May be performed independently of other Visit 9 procedures within the visit window.

[d] PK samples on MEDI3506/placebo dosing days will be collected pre-dose of MEDI3506/placebo administration.

[e] Dapagliflozin PK samples will be collected at the following time points relative to dapagliflozin administration: Day 141 (predose and 2 h postdose) and Day 169 on study visit. Patients will be reminded to take dapagliflozin on site visits during dapagliflozin administration time (Day 85 to Day 168/Visit 6 to Visit 8).

CCI [redacted]

[g] If consent obtained.

[h] After randomization. If, for any reason, the sample is not drawn pre-dose on Visit 3 (Day 1), it may be taken at any visit until the final follow-up visit/Early Discontinuation Visit.

[i] Subjects collect 3 consecutive first morning void midstream urine samples (ideally day of visit and preceding 2 days [refrigerated overnight]) which are returned on the day of visit.

[j] In the event that a dose cannot be administered within the window of the scheduled dosing date, the dose may be administered outside of the dosing window as long as it is at least 14 days prior to the next dose and recorded as a protocol deviation.

[k] Subjects enrolled that have reached the Day 85 visit prior to Amendment 2 approval should continue in the study without the addition of dapagliflozin to their dosing regimen.

4.2.3 Follow-up Period

Table 7 shows all procedures to be conducted during the follow-up period.

Follow-up of subjects who discontinue MEDI3506 or dapagliflozin is detailed in Section 4.1.6.

Subjects who wish to withdraw from the study should be asked if they are willing to have an EOS visit prior to withdrawal.

Table 7 Schedule of Follow-up Procedures

Study Period	Follow-up Period
Visit Number	**Visit 10/EOS**
Procedure / Study Day	**Day 230 (± 5 days)**
Safety assessments:	
Physical examination (full) with weight	X
Vital signs	X
ECG	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Blood collection for:	
Serum chemistry	X
CCI	X
CCI	X
Complete blood count with differential	X
PK (MEDI3506)	X
ADA (MEDI3506)	X
CCI	X
CCI	
Blood for future use [a]	X
Urine collection for:	
Urinalysis	X
UACR [b]	X
Pregnancy test (females of childbearing potential)	X
Exploratory biomarkers	X
Urine for future use [a]	X

ADA = anti-drug antibody(ies); AE(s) = adverse event(s); BNP = B-type natriuretic peptide; ECG = 12-lead electrocardiogram; EOS = end of study; CCI CCI ; PK = pharmacokinetics; SAE(s) = serious adverse event(s); CCI UACR = urine albumin:creatinine ratio.

NOTE: Investigator should ensure that all subjects are contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked to follow up suspected reports according to local guidelines.

[a] If consent obtained.

[b] Subjects collect 3 consecutive first morning void midstream urine samples (ideally day of visit and preceding 2 days [refrigerated overnight] which are returned on the day of visit.

4.3 Description of Study Procedures

4.3.1 Efficacy

The primary efficacy endpoint of change from baseline to Day 169 (Week 24) in UACR compared to placebo will be analyzed based on the Per Protocol Population. Urine will be collected for UACR analysis based on the schedule of study procedures in Table 5, Table 6, and Table 7. Containers for urine sample collection will be dispensed at Visit 1. Subjects will be reminded by phone call to bring in 3 first morning void midstream urine samples: day of visit and preceding 2 days (refrigerated overnight, which are return on the day of visit). Ideally, first morning void midstream urine samples should be collected after at least 6 hours of supine rest, even if the subject returns to sleep; if not possible/convenient, then first morning void midstream urine samples should be collected when the subject gets up for the day.

4.3.2 Medical History and Physical Examination, Electrocardiogram, Weight, Height, BMI Calculation, and Vital Signs

In addition to the medical history, physical examinations, weight, height, body mass index (BMI) calculation, vital signs, and ECG assessments described below, additional assessments may be performed at the investigator's discretion.

4.3.2.1 Medical History

Complete medical history will include history of and current medical conditions, past or present cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, psychiatric, genitourinary, menopausal status, drug and surgical history, or any other diseases or disorders. In relation to the study objectives, diagnosis date for T2DM and CKD will also be recorded.

4.3.2.2 Physical Examination, Height, Weight, and BMI calculation

Full and abbreviated physical examinations will be performed by a licensed healthcare provider (eg, physician, physician's assistant, or licensed nurse practitioner). Full physical examinations will include, but are not limited to, assessment of general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Abbreviated physical examinations will include assessment of cardiovascular, respiratory, and nervous systems. Each clinically significant abnormal finding will be recorded in the medical history, and each treatment-emergent abnormality including injection-site reactions identified by assessing SC injection sites will be recorded as a TEAE. Physical examinations, weight, height, and BMI calculation will be performed according to the schedule of study procedures where indicated (Table 5, Table 6, and Table 7).

The focused cardiac exam conducted as part of the abbreviated physical examination will include:

- precordial palpation for LV displacement and parasternal lift, and
- auscultation for S3 gallop and increased intensity of P2.

Additional findings to document any volume overload/volume expansion will include:

- auscultation of lung fields for crackles, and
- assessment for jugular venous distension and lower extremity edema (if present at baseline, any changes to be noted at study visit).

Urogenital exam may be omitted at the discretion of the Principal Investigator.

Weight should be measured in light street clothes, without shoes, after a prior visit to the bathroom.

4.3.2.3 Vital Signs

BP will be measured at each study visit along with other vital signs of temperature, pulse, and respirations. The nominal timing of vital signs, ECGs, and blood draws is described (Section 4.2). Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last.

For the first 2 doses of MEDI3506 or placebo, vital signs will be taken before and immediately after administration of investigational product, and at 30 minutes (± 5 minutes) as well as 120 minutes (± 10 minutes) thereafter or until stable, whichever is later. Following the observation period, subject discharge will be at the discretion of the investigator. For all other dosing visits, vital signs will be collected 30 minutes (± 5 minutes) after administration of MEDI3506 or placebo or when stable.

The subject should be in a seated or supine position for at least 10 minutes prior to the collection of vital signs, as follows:

- Oral, axillary, or tympanic temperature
- Diastolic BP
- Systolic BP
- Heart (pulse) rate
- Respiratory rate

For each BP measurement, the same arm and the same appropriately sized BP cuff should be used.

Vital signs are to be recorded in the EDC system. Vital signs may be repeated once after an additional 5 minutes of rest. Clinically significant abnormalities in vital signs will be recorded as AEs.

4.3.2.4 Assessment for Injection-site Reactions

Site staff will check the injection site for local reactions and assess for any systemic reactions for 30 minutes post injection of MEDI3506 or placebo on designated visit days as described in Table 6. Local and systemic reactions will be recorded as AEs according to the criteria described in Section 5.1.

4.3.2.5 Echocardiogram

A transthoracic echocardiogram will be performed during screening to document baseline characteristics and screen for clinically significant congenital or valve disease or a reduction in LV ejection fraction of < 40% as described in Section 4.1.3. A subsequent transthoracic echocardiogram will be obtained at Visit 9 to reassess LV function and other cardiac parameters after treatment. Echocardiograms will be performed as described in a separate manual.

4.3.2.6 Electrocardiogram

At the visits specified in Table 5 and Table 7, 12-lead ECGs will be obtained after 10 minutes supine rest. Triplicate ECGs will be performed (all 3 ECGs within a 10-minute time period, at least 1 minute apart).

The investigator should date and sign the ECG tracing and record the clinical significance of any abnormal result on the tracing. The ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the clinical study site. The ECGs will be stored at the study site. ECG evaluation will be recorded in the electronic case report form (eCRF).

The same recorder should be used for each subject at each time point, if possible. Date and time settings should be checked at the start of each study day and aligned with an official timekeeper for all machines used in the study.

The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

4.3.3 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed central clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal clinically significant laboratory results should be repeated at a licensed central clinical laboratory as soon as possible (preferably within 24 to 48 hours).

In the event of an urgent or unexpected situation, or emergency, licensed local laboratory assessments may be used at the discretion of the investigator. Licensed local laboratories should also be used to ensure continuous subject monitoring, if the central laboratory kit were to become unavailable. Local laboratory results should be documented in the eCRF.

The following clinical laboratory tests will be performed (see Table 5, Table 6, and Table 7 for the schedule of tests):

Serum Chemistry

Potassium	Creatinine
Sodium	Blood urea nitrogen
AST	Albumin
ALT	Total protein
ALP	Uric acid
TBL (if result is > 1.5 × ULN, indirect and direct bilirubin will be measured)	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

Note for serum chemistry: Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

Hematology

Complete blood count with differential	Platelet count
RBC count	Hemoglobin (including CCI)
Hematocrit	Prothrombin time and PTT

HbA1c = hemoglobin A1c; PTT = partial thromboplastin time; RBC = red blood cell.

Urinalysis

Color	Glucose
Appearance	Ketones
Specific gravity	Blood
pH	Bilirubin
Protein	Leukocytes
Microscopy including WBCs, RBCs, and casts	

RBC = red blood cell; WBC = white blood cell.

Pregnancy Tests (female subjects only)

Serum beta-hCG (at screening only)	Urine hCG

hCG = human chorionic gonadotropin.

Additional Tests

FSH (female subjects only; screening)	Cystatin
Hepatitis B (HBsAg, anti-HBs, and anti-HBc) and C antibodies (screening)	BNP blood samples
HIV-1 and HIV-2 antibodies (screening)	eGFR [a]
Spot urine for UACR	Serial draws urine for UACR
Urine alcohol screen	Urine drug screen

[a] CKD-EPI equation based on serum creatinine will be used for eligibility.

anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; BNP = B-type natriuretic peptide; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; EOS = end of study; FSH = Follicle-stimulating hormone; CCI [redacted]; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus, UACR = urine albumin:creatinine ratio.

4.3.4 Pharmacokinetic Evaluation and Methods

Blood will be collected to evaluate PK of MEDI3506 and dapagliflozin in serum and plasma, respectively (see Section 4.2 for collection time points). Samples for determination of MEDI3506 and dapagliflozin concentration in serum/plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Method Validation Report.

Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Samples collected for analyses of MEDI3506 and/or dapagliflozin serum/plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Samples from subjects who received placebo may be analyzed at selected time points to confirm no dosing with MEDI3506 took place.

MEDI3506 and dapagliflozin serum/plasma PK concentrations and descriptive statistics will be tabulated. Additional PK analyses may be conducted as appropriate. If the data allow, population PK analysis will be performed but will not be reported in the clinical study report (CSR).

Instructions for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to sites.

4.3.5 Immunogenicity Evaluation and Methods

Blood samples will be collected to evaluate ADA responses to MEDI3506 (see Section 4.2 for collection time points). Evaluations will be performed using a validated immunoassay. Tiered analyses will be performed to include screening, confirmatory, and titer assay components, and the positive-negative cut points will be statistically determined from drug-naïve validation samples. Samples should be stored for 2 years after marketing approval and may be utilized for further characterization of the ADA response, including possible assessment of neutralizing antibody (nAb).

4.3.6 Genetic Evaluations and Methods

Genetic evaluation is optional for this study, for details see Appendix D.

4.3.7 Biomarker Evaluation and Methods

The subject's consent to the use of donated biological samples is mandatory.

Biological samples will be collected and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity. More specifically, exploratory serum/plasma and urine biomarkers will be evaluated for the potential effects of MEDI3506 on renal inflammation. The relevant biomarkers may include, but are not limited to, CCI [redacted].

4.3.7.1 Storage, Re-use and Destruction of Biological Samples

Samples will be stored for a maximum of 15 years from the date of the last subject last visit (LSLV), after which they will be destroyed. The results of exploratory biomarker research will be included in a scientific report or publication but may or may not be reported in the CSR. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

4.3.8 Estimate of Volume of Blood to Be Collected

The estimated total volume of blood to be collected from each subject at each visit from screening through to the EOS is 196.3 mL (Table 8). If repeats of any blood tests are required, the volume of blood collection will increase accordingly. Additional blood may be collected at the discretion of the investigator in the event of abnormal laboratory findings or an AE.

Table 8 Estimate of Blood Volumes

Visit Day	Estimated Blood Volume (mL)
Screening (Day -37 to Day -3)	approximately 22.2
Randomization to follow-up (Day 1 to Day 230)	approximately 174.1
Total	approximately 196.3

4.4 Study or Study Component Suspension or Termination

AstraZeneca reserves the right to temporarily suspend or permanently terminate this study or component of the study at any time. The reasons for temporarily suspending or permanently terminating the study may include but are not limited to the following:

1 The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2 Subject enrollment is unsatisfactory
3 Non-compliance that might significantly jeopardize the validity or integrity of the study
4 Sponsor decision to terminate development of MEDI3506 for this indication
5 Sponsor decision to terminate the study based on a planned futility analysis

If AstraZeneca determines that temporary suspension or permanent termination of the study or component of the study is required, AstraZeneca will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, AstraZeneca will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study or component of the study is suspended or terminated for safety reasons, AstraZeneca will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. AstraZeneca will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study or component of the study is suspended for safety reasons and it is deemed appropriate by AstraZeneca to resume the study or component of the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Products

AstraZeneca will provide the investigators with investigational products (Table 9) using designated distribution centers.

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

4.5.1.5 Monitoring of Dose Administration

Post dose of MEDI3506 or placebo, vital signs will be periodically assessed (Section 4.3.2.3, Table 6), and SC injection sites will be assessed for injection-site reactions (Section 4.3.2.4).

As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

CCI

[redacted]

4.5.4 Treatment Compliance

MEDI3506/placebo is administered by study site personnel, who will monitor compliance. For dapagliflozin, when administered at the study site, the date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and eCRF. The dose of the study drugs and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

When the subjects self-administer dapagliflozin study drug at home, compliance with dapagliflozin will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets etc, during the study site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of dapagliflozin tablets dispensed to and taken by each subject must be maintained and reconciled with study drugs and compliance records. Study drug start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

Site personnel should support patient urine collection, and dapagliflozin compliance by:

1 Clear instructions on the exact activities (orally and written)
2 Emphasize that dapagliflozin treatment in patients with chronic kidney disease has demonstrated cardiovascular and renal benefits (ADA, 2020; DeSantis, 2020; McMurray et al, 2019; Wiviott et al, 2019)
3 Stress importance of compliance at each visit
4 Recognize patient's efforts to comply at each visit
5 Refer to the patient's spouse or other partner for support

4.5.5 Accountability

The site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to AstraZeneca.

Upon authorization by AstraZeneca, all unused investigational product should be destroyed at site, in accordance with local standard operating procedures (SOPs). Destruction can be outsourced to a third party. Certificates of destructions must be collected. Only if the site is unable to destroy unused investigational product, will it be returned to an AstraZeneca-authorized depot.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

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)CCI [redacted] 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 7 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 (eg, 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 amount 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.

Investigational product (MEDI3506 or placebo) must be administered the same day the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

4.6.2 Methods to Ensure Blinding

This is a double-blinded study in which MEDI3506 and placebo are not identical in appearance or viscosity. Neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (ICH E9) (see Section 4.6.3 for unblinding related to planned analysis).

An investigational product monitor will be designated to perform product accountability. Since MEDI3506 and placebo are not identical, investigational product will be administered

by a study team member 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 needs to be known to treat an individual subject for an 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.

To facilitate the in-stream analysis of PK and ADA samples, the randomization schedule may be provided to limited personnel who have responsibility for analyzing the samples. These unblinded sample analysts will not have any other involvement with the conduct of the study.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product (MEDI3506 or placebo) allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded. In the event there is unblinding, the investigator should promptly document and explain to AstraZeneca the reason for any premature unblinding.

AstraZeneca retains the right to unblind the treatment allocation for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

4.6.3.2 Unblinding for DSMB Purposes

If unblinding is required by the DSMB (Section 4.8.6), details of the methods for unblinding (sponsor will remain blinded) will be provided in a separate DSMB charter.

4.6.3.3 Unblinding for Interim Analysis Purposes

An interim analysis is planned for this study as described in Section 4.8.7. This will require unblinding of sponsor staff including those with clinical, medical, statistical, and programming expertise, who will form a firewalled unblinded review committee (URC) for the purpose of internal decision making on the future clinical development of MEDI3506.

Sponsor staff who are unblinded at the interim analysis will not be involved in any study activities after they are unblinded. The unblinded sponsor staff will not reveal interim analysis results or treatment codes to any sponsor staff who will continue to be involved in the conduct of the study before the final database lock. In addition, the interim analysis results will not be shared with investigators or subjects.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the final study visit. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

In general, subjects are expected to be on stable medication regimens during the study. Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the study, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Subjects may require adjustment of other glucose-lowering treatments on commencing dapagliflozin to avoid hypoglycemia. As long as it is safe, and according to the investigator's best clinical judgement, RAASi and other antihypertensive therapy, including diuretics, should be kept stable throughout the duration of the study.

4.7.2 Prohibited Concomitant Medications

Other than the medications described above, use of concomitant medications including over-the-counter medications, herbal supplements, vitamins, etc, from screening through to the Early Discontinuation Visit/EOS is discouraged. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator. While SGLT2 inhibitors are allowed if subjects have been on a stable dose for at least 4 weeks prior to Visit 3, these agents should not be initiated after enrollment in the study (see Section 4.7.3 for detailed information regarding SGLT2i use).

Subjects are not permitted to receive any of the following during the study:

- Systemic (oral or injectable) corticosteroids within 28 days of Visit 1 until the end of the follow-up period.
- Any other immunosuppressive therapy within 3 months of randomization until the end of the follow-up period.
- Any immunotherapy within 3 months of randomization, except for stable maintenance dose allergen-specific immunotherapy started 28 days prior to Visit 1 until the end of follow-up period.

- Interferon gamma within 3 months of randomization until the end of the follow-up period.
- Investigational products other than the investigational products (MEDI3506, placebo, or dapagliflozin) administered in this study within 4 months or 5 half-lives of randomization until the end of the follow-up period.
- Ig or blood products within 28 days of Visit 1 until the end of the follow-up period.
- Live or attenuated vaccines within 28 days of Visit 3 until the end of the follow-up period.
- Renin inhibitor or an aldosterone antagonist in combination with an ACEi or an ARB within 2 months of Visit 1 until the end of the follow-up period.
- Ongoing use of any biologic drug targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab, cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil, or corticosteroids other than topical or inhaled).
- Patients on serum creatinine-altering drugs should be on long-term treatment at a stable dose prior to study entry. Drugs considered serum-altering include but are not limited to amphotericin, cimetidine, clofibrate, dronedarone, ketoconazole, probenecid, ranolazine, trimethoprim, aminoglycosides, or cephalosporins. Generally, any drug that has a putative ≥ 5% effect on serum creatinine is considered serum creatinine-altering. The following exclusion criteria apply:
  - New treatment or change of dose within 6 weeks prior to Visit 1
  - Expected change of dosing regimen during the study.
  - Minor ACEi or ARB dose adjustment within 2 weeks of Visit 1 is acceptable, but any dose adjustments during the course of the study (ie, for control of hyperkalemia) should be discussed with the sponsor/ medical monitor.
  - Clinically indicated short-term use of serum creatinine-altering drugs to treat acute conditions during the study may be allowed.

The activity of cytochrome P450 (CYP450) enzymes can be altered by increased levels of certain cytokines (eg, IL-1, IL-6, IL-10, tumor necrosis factor alpha, interferon) during chronic inflammation (Huang et al, 2010). Thus, MEDI3506, through its downstream mechanism of action, has the potential to normalize the formation of CYP450 enzymes indirectly, through the alteration of local and systemic cytokine levels. However, a role for IL-33 in the regulation of CYP450 enzymes has not been reported. As a precaution, upon initiation or discontinuation of MEDI3506, in patients who are receiving concomitant drugs that have a narrow therapeutic index and are CYP450 substrates (eg, warfarin), the investigator should consider whether (increased) monitoring is indicated.

4.7.3 Considerations for SGLT2i and RAASi

If a subject is on SGLT2i treatment prior to enrollment into this study, they must have been on a stable dose for at least 4 weeks prior to the randomization visit. Starting additional SGLT2i therapy during the study, before Day 169/Early Discontinuation Visit, is not permitted. Any existing SGLT2i treatment will be discontinued on Day 85. All subjects will receive 10 mg

dapagliflozin by mouth daily starting on Day 85 until Day 168. Starting additional SGLT2i therapy at or after Day 169/Early Discontinuation Visit is permitted.

In general, any dose changes of SGLT2i treatment should be avoided during the study unless due to medical necessity. If the subject needs to interrupt SGLT2i treatment for any reason, they should be allowed to re-start it again once the respective medical condition gets resolved.

Subjects who have started on the Phase 2a study prior to Amendment 2 will be transitioned to the Phase 2b and given 10 mg dapagliflozin starting on Day 85 (Week 12). Any existing SGLT2i treatment will be discontinued. Subjects who have completed 12 weeks of treatment prior to approval of Amendment 2 will continue on treatment with MEDI3506/placebo without dapagliflozin.

For patients with T2DM and albuminuria, clinical guidelines recommend treatment with ACEi or ARB and SGLT2i (dapagliflozin in this study) (de Boer et al, 2020). The recommendation of treating patients with T2DM, CKD, and an eGFR > 30 ml/min per 1.73 m^2 with an SGLT2i and RAASi is based on the highest level of evidence (1A) that these therapies are safe and efficient in reducing adverse kidney events.

Once daily 10 mg dapagliflozin has been studied in large cardiovascular and renal outcomes studies on top of standard of care, including ACEi or ARB (DAPA-HF and DAPA-CKD studies) (Heerspink et al, 2020b; McMurray et al, 2019). Among patients with CKD and T2DM, the risk of a composite of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. Hence, discontinuation of ACEi or ARB or dapagliflozin should be avoided. Permanent discontinuation should be regarded as a last resort.

In the event of treatment interruption of any duration, resuming administration of ACEi or ARB and dapagliflozin should be considered as early as possible. Careful consideration should be given to the individual risk/benefit profile and the subject's needs.

Dapagliflozin may decrease blood pressure. Adjust other antihypertensive therapies after the start of the study if needed.

Dapagliflozin is a mild diuretic. Adjust other diuretic therapies after the start of the study if needed.

Starting dapagliflozin may require a gradual dose reduction of insulin and/or insulin secretagogues (sulfonylureas, meglitinides) to avoid hypoglycemia (Garber et al, 2020).

Treatment with dapagliflozin should be stopped immediately if diabetic ketoacidosis is suspected or confirmed, and treatment should not be re-started unless another clear precipitating factor for the condition is identified and resolved (AstraZeneca, 2020).

For more details, refer to the dapagliflozin drug label.

Modest hyperkalemia should generally be managed, if possible, without reducing or discontinuing ACEi or ARB, unless there is another reason to do so (Kidney Disease: Improving Global Outcomes Diabetes Work, 2020).

4.7.4 Vaccination Against COVID-19

There are no clinical data available to assess the interaction (if any) of MEDI3506 with any COVID-19 vaccine.

The sponsor accepts that vaccination against COVID-19, when and where it is available, and when subjects are eligible according to the applicable guidelines, is in the subject's best interest. Consequently, vaccination during the study is, in general, permitted and any delays in receiving the vaccination due to study participation should be minimized.

To help ensure the interpretability of the safety data, receipt of the COVID-19 vaccine (either the first or subsequent dose) is prohibited within 28 days before randomization or within 7 days before or after any dose of MEDI3506/placebo. Receipt of, at least, the first dose of a COVID-19 vaccine more than 28 days before randomization, without significantly delaying enrollment, is preferred but may not be possible, eg, not locally available at the time, subject not eligible at the time, express subject decision not to be vaccinated. Otherwise, vaccination may be performed at any time outside the prohibited 7-day window before or after any dose of MEDI3506/placebo. If the (approximate) date of a subsequent dose of COVID-19 vaccination is known, then enrollment of the subject should be timed so that the dose is not within 28 days before the scheduled randomization. If this date is not known, then enrollment into the study should not be delayed. If an enrolled subject does (unexpectedly) receive the COVID-19 vaccine within 28 days before the scheduled randomization, the site should contact the AstraZeneca Study Physician for advice on how the situation should be managed.

If and when a subject receives a COVID-19 vaccination, the following information will be recorded in the eCRF as a concomitant medication: the date, dose, brand name, site of administration, and lot number (if known) of each vaccine dose (eg, 10 Feb 2021; first dose; Pfizer-BioNTech COVID-19 Vaccine; left Deltoid; Lot xxx).

Any AEs suspected to be due to the vaccination should be captured in the AE form including the causality assessment related to COVID-19 vaccine.

4.8 Statistical Evaluation

4.8.1 General Considerations

Tabular summaries will be presented by treatment group, with the 4 volume-matched placebo groups combined. Categorical data will be summarized by the number and percentage of

subjects in each category. Continuous variables will be summarized by descriptive statistics. Study populations are described in Table 11. Additional details of statistical analyses will be described in the statistical analysis plan (SAP).

Table 11 Study Populations

Population	Description
Enrolled	All subjects who sign the informed consent form.
Full Analysis Population	All subjects 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. All decisions to exclude subjects from the per protocol analysis set will be made and documented prior to the unblinding of the study.
Safety Analysis Population	All subjects 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 posttreatment. The PK Analysis set will be used for all PK analyses.

PK = pharmacokinetic(s).

4.8.2 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. 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.

4.8.3 Efficacy

4.8.3.1 Primary Efficacy Analysis

The primary efficacy endpoint for this study is change from baseline to Day 169 (Week 24) in UACR compared to placebo and will be analyzed based on the Per Protocol Population. For the intercurrent events, if a subject is lost to follow-up, discontinues treatment due to AE or lack of efficacy, or uses prohibited medication, the UACR data are treated as missing after the event and no imputation is performed. As UACR is assumed to follow a log-normal

distribution, it will be log-transformed for statistical analysis purposes. The primary analysis will use a mixed model repeated measures (MMRM) analysis of change from baseline in UACR without multiplicity adjustment. The model will adjust for fixed categorical effects of treatment, visit, and treatment-by-visit interaction, randomization stratification factors, and the continuous covariates of baseline log UACR and baseline log UACR-by-visit interaction. UACR will be log-transformed before entering the data in the MMRM analysis to alleviate the skewness of the data. 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 ie, purely data dependent. If the unstructured variance-covariance matrix will not fit, then suitable alternatives will be considered with details provided in the SAP. In this MMRM model, all subjects and all data points will be included. No subjects will be excluded because of missing data, and no imputation will be done for missing data. Additionally, there will be no adjustment for multiplicity.

Additionally, the primary efficacy endpoint will also be analyzed using an analysis of covariance adjusting for treatment, randomization stratification factors, and baseline log UACR with last-observation-carried-forward (LOCF) imputation for missing postbaseline measurements.

4.8.3.2 Secondary Efficacy Analysis

The change from baseline to Day 85 (Week 12) in UACR will be analyzed similarly to that of the primary efficacy endpoint based on the Full Analysis Population. Change from Day 85 (Week 12) to Day 169 (Week 24) in UACR will be analyzed similarly to that of the primary efficacy endpoint based on the Per Protocol Population. For the proportions of patients with > 30%, > 40%, and > 50% reduction in UACR, logistic regression models will be used adjusting for treatment, randomization stratification factors, and baseline albuminuria status based on the Full Analysis Population and the Per Protocol Population.

4.8.3.3 Exploratory Analyses

Exploratory endpoints will be summarized by treatment group based on the Full Analysis Population and/or the Per Protocol Population.

Additional details of the exploratory endpoint analyses will be described in the SAP.

4.8.3.4 Subgroup Analyses

Subgroup analyses may be performed and will be described in the SAP as required.

4.8.3.5 Sensitivity Analysis

Sensitivity analyses will be performed to assess the potential impact on study endpoints due to COVID-19. Other sensitivity analyses may also be performed. Details will be described in the SAP.

4.8.4 Safety

4.8.4.1 Analysis of Adverse Events

Safety analysis will be based on the Safety Analysis Population. AE collection will begin after the subject signs the ICF and lasts until the end of the study. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. All TEAEs will be summarized overall and by MedDRA SOC and PT, by severity and relationship to investigational product. All TEAEs related to dapagliflozin will also be summarized. In addition, summaries of deaths, SAEs and treatment discontinuations due to AEs will be provided. Injection-site reactions will be presented. For subjects testing positive for COVID-19, the number and proportion of subjects with COVID-19 AEs and SAEs and the proportion asymptomatic subjects will be summarized. Number of subjects seropositive for SARS-CoV-2 at end of study who were seronegative at randomization visit will also be summarized.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Clinical laboratory safety tests including serum chemistry and hematology parameters will be summarized using descriptive statistics at each time point by treatment group. Change from baseline to each post baseline time point in these data will also be summarized, where appropriate. A shift table will be provided for these clinical laboratory parameters as well, where possible.

4.8.4.3 Analysis of Vital Signs and ECGs

Vital sign results and ECGs will be summarized using descriptive statistics at each time point by treatment group.

4.8.4.4 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.

4.8.5 Analysis of Immunogenicity/Pharmacokinetics

The incidence rate of positive antibodies to MEDI3506 and ADA titer will be reported by treatment group. Samples may be utilized for further characterization of the ADA response,

including possible assessment of nAbs. If there is a high incidence of ADAs, the association of ADA with MEDI3506 concentration will be assessed. In addition, the relationship between ADA and PD, efficacy, and safety parameters may be evaluated.

MEDI3506 serum PK concentrations and descriptive statistics will be tabulated per dose group. Additional PK analyses may be conducted as appropriate. If the data allow, population PK analysis will be performed but will not be reported in the CSR.

As an exploratory analysis, dapagliflozin plasma concentrations will be summarized by descriptive statistics for each visit and each sample point for dapagliflozin-treated subjects by dose cohort. Further details of this will be provided in the SAP. Additional PK analyses may be conducted as appropriate. If the data allow, population PK analysis will be performed, but will not be reported in the CSR.

4.8.6 Data and Safety Monitoring Board

An independent DSMB will be formed to evaluate safety data from concurrently conducted MEDI3506 Phase 2 clinical studies in other indications. Unblinded review of safety data will be required for indications where the potential risks of MEDI3506 are high due to the disease under study (DUS) and the common comorbidities of particular subject populations. Safety data from this study will be provided to the DSMB in order to perform the oversight of all safety data.

The DSMB will be responsible for safeguarding the interests of the subjects in the study by assessing the safety of the intervention during the trial and for reviewing the overall conduct of the study. The DSMB will be composed of independent experts and will conduct safety reviews on a scheduled and, if needed, ad hoc basis. 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.

CCI [redacted]

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

5.3 Definition of Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of MEDI3506 and may require close monitoring and rapid communication by the investigator to AstraZeneca. An AESI may be serious or non-serious. The rapid reporting

of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

The following AESIs will be particularly monitored in this study (see the Safety Handling Plan for instructions and timing on completing any additional information required for specific types of events related to the categories noted below):

- Serious hypersensitivity (including Type 1 to 4 hypersensitivity reactions), for example anaphylaxis (see also Appendix B) and severe allergic reactions, and immune complex disease.
- Injection-site reactions.
- Heart failure.
- Serious infections (including opportunistic infections and viral reactivations), for example varicella zoster/herpes simplex virus, Epstein Barr virus/cytomegalovirus, and TB.
- Gastrointestinal adverse events.

5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca (see Section 5.5). See Section 5.2 for the definition of SAEs and Appendix A for guidelines for assessment of severity and relationship.

If an AE evolves into a condition that meets the regulatory definition of “serious”, it will be reported on the SAE Report Form.

5.4.1 Time Period for Collection of Adverse Events

AEs will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period at Visit 10 or to date of last contact.

All SAEs will be recorded from the time of informed consent.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject’s last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.4.3 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as follows:

- Death clearly the result of disease progression should be reported and documented in the eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to disease progression, the AE causing the death must be reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.

Deaths with an unknown cause should always be reported as an SAE. A post-mortem (autopsy) may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca representative(s) within the usual timeframes (refer to Section 5.5 for additional information).

5.4.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

5.4.5 Adverse Events Based on Examination and Tests

The results from the protocol-mandated laboratory tests and vital signs will be summarized in the CSR. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

5.4.6 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of HL.

5.4.7 Disease Progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. Death clearly resulting from disease progression should not be reported as an SAE (see reporting guidelines in Section 5.4.3).

The term disease progression should not be reported as an AE or SAE, however, medically significant individual events and/or laboratory abnormalities associated with disease progression (see definition of disease progression below) that fulfill the AE or SAE definition should be reported.

5.4.8 Disease under Study

Symptoms of DUS are those which might be expected to occur as a direct result of DKD. Events which are unequivocally due to DUS should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the investigational product.

5.5 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel must inform the appropriate sponsor representative(s) within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated study representative works with the investigator to ensure that all the necessary information is provided to the sponsor's patient safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform sponsor

representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours after becoming aware of the event.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to inform the designated sponsor representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports an SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

For all studies except those using medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB or and will notify the IRB/IEC, if appropriate according to local requirements.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

For MEDI3506, an overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the IB (Edition 5.2), unless otherwise specified in this protocol.

Dapagliflozin has been well tolerated at doses up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and in patients with T2DM. Only suspected single intake of more than 500 mg dapagliflozin or repeated intake of more than 100 mg dapagliflozin should be reported on the eCRF overdose module. If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca investigational product occurs during the course of the study, then the investigator or other site personnel should inform appropriate sponsor representatives immediately, but no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.5. For other overdoses (ie, those not associated with an AE or SAE), reporting must occur within 30 days.

5.6.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor except for if the pregnancy is discovered before the study subject has received any study drug.

5.6.2.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs during the course of the study, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 day, ie, immediately but **no later than 24 hours** after becoming aware of the event.

The designated study representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

5.6.2.2 Paternal Exposure

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until the end of the follow-up period (Visit 10) or date of last contact should, if possible, be followed up and documented.

5.6.3 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human- or process-related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion (ie, instead of receiving the investigational product, the subject received a drug that has a similar-sounding name)
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong subject received the medication (excluding IXRS errors)
- Wrong drug administered to subject (excluding IXRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IXRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s), eg, forgot to take medication

- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 5.5) and within 30 days for all other medication errors. Medication errors should be reported using a Medication Error Report Form.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to the study team staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

6.2 Monitoring of the Study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this protocol and the Clinical Study Agreement, the terms of protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through their last protocol-specified visit/assessment (including telephone contact) regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Sections 4.1.5 and 4.1.6).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

6.4 Data Management

Data management will be performed by AstraZeneca Data Management staff or other party according to the Data Management Plan.

An electronic data capture system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or healthcare provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the Principal Investigator is not available, the treating physician or healthcare provider can contact a medical monitor through this system, which is managed by a third-party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the trial, eg, demographic information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc. will only be collected with the subject's informed consent. The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation.

Extra precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

7.2 Ethics and Regulatory Review

The IRB/IEC responsible for each site must review and approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The IRB/IEC must also approve all advertising used to recruit subjects for the study. The investigator is responsible for submitting these documents to the applicable IRB/IEC, and distributing them to the study site staff.

The opinion of the IRB/IEC must be given in writing. The investigator must provide a copy of the written approval to AstraZeneca before enrollment of any subject into the study.

AstraZeneca should approve any substantive modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IRB/IEC annually.

Before the study is initiated, AstraZeneca will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required. AstraZeneca will provide safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions where relevant, to regulatory authorities, IRB/IEC, and Principal Investigators.

Each Principal Investigator is responsible for providing reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product to the IRB/IEC. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

7.3 Informed Consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by ICH/GCP. AstraZeneca will develop a core informed consent form for use by all investigators in the clinical study. AstraZeneca must approve any modifications to the informed consent form that are needed to meet local requirements. Subjects should be adequately educated during the informed consent process about the continued scientific relevance of their data even if they discontinue treatment, as well as the effect that missing data has on trial integrity and credibility.

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

7.4 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. Any changes must be documented in a study protocol amendment.

For a substantial change to the protocol, AstraZeneca will distribute amended versions of the protocol to the Principal Investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (see Section 7.2) and reviewed as per local regulatory authority requirements. The IRB/IEC must also approve revisions to the ICF, advertising, and any other written information and/or materials resulting from the change to the protocol.

Any non-substantial changes will be communicated to or approved by each IRB/IEC.

7.5 Audits and Inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO THE PROTOCOL

All changes described below have been incorporated into the current version of the protocol.

9.1 Protocol Amendment 5

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 5. The main rationale for this amendment is to reintroduce the opportunity for an Interim Analysis due to the release of resources amid a decrease in the burden from the COVID pandemic.

With the exception of spelling mistakes, specific changes are listed below.

1 Synopsis (Statistical analyses): Added "randomization stratification factors" to the Primary and Secondary Analyses and reintroduced mention of the Interim Analysis with changes (see item 10).

2 Section 3.1.1 (Figure 1): Reintroduced mention of the Interim Analysis.

3 Added the Edition number to every reference to MEDI3506 IB (Edition 5.2) and dapagliflozin IB (Edition 17).

4 Section 1.5.1 (MEDI3506): Introduced mention of 2 ongoing Phase 3 studies in COPD (Studies D9180C00003 and D9180C00004).

5 Section 4.2.2 (Randomized Treatment Period, Table 6, PK MEDI3506, Day 85): Reintroduced a measurement (X) that was unintentionally removed from Amendment 4.

6 Section 4.3.7.1 (Storage, Re-use and Destruction of Biological Samples): The results of exploratory biomarker research will ~~not~~ be INCLUDED ~~reported in the CSR, but~~ in a scientific report or publication BUT MAY OR MAY NOT BE REPORTED IN THE CSR.

7 Reintroduced Section 4.6.3.3 (Unblinding for Interim Analysis Purposes) with changes: Removed second paragraph ("Prior to the interim analysis…") and last line ("Additional details will be…").

8 Section 4.8.1 (General Considerations, Table 11, Safety Analysis Population row): Removed second paragraph ("If a subject received a different treatment…").

9 Sections 4.8.3.1 (Primary Efficacy Analysis) and 4.8.3.2 (Secondary Efficacy Analysis): Added "randomization stratification factors" to the Primary and Secondary Analyses in their respective sections.

10 Reintroduced Section 4.8.7 (Interim Analysis) with changes: An interim analysis is planned after ~~all~~ at least 70% of subjects have completed their Day 85 (Week 12) visit to evaluate change from baseline ~~to Day 85 (Week 12)~~ in UACR as well as ~~PK,~~ AEs, and other safety parameters. CCI [redacted]
SAFETY MONITORING: An independent Data and Safety Monitoring Board has been formed to evaluate safety data.

11 Correction of omission in Section 9.2, item 12 (list of changes to Protocol Amendment 4).

9.2 Protocol Amendment 4

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. The rationale for this amendment is to take measures to reduce the burden on the participant, hence most of the changes applied are removals of procedures.

With the exception of spelling mistakes, specific changes are listed below.

1 Throughout the document: To reflect changes in the schedule of procedures (see Tables 6 and 7), replaced all instances of Visit 12 with Visit 10 as the new EOS, previous mentions of Visit 10 with Visit 9, Visit 9 with Visit 8, Visit 8 with Visit 7, and Visit 7 with Visit 6. Deleted all mentions of Interim Analysis (Statistical Methods in the Synopsis, Figure 1, Sections 4.6.3.3, and 4.8.7).

2 Synopsis (Exploratory objectives): Removed "for 12 weeks" from assessment of PK of dapagliflozin: "To assess the PK of dapagliflozin after repeated oral dosing when given with MEDI3506 ~~for 12 weeks~~ in subjects with DKD".

3 Synopsis (Secondary endpoints): Deleted Endpoint "Number of subjects seropositive for SARS-CoV-2 at end of study who were seronegative at randomization visit".

4 Synopsis (Secondary endpoints): Changed Endpoint about subjects testing positive for COVID-19 to "For subjects testing positive for COVID-19 ~~SARS-CoV-2 (by nucleic acid or serology test)~~, during the intervention and follow-up periods, the number and proportion of subjects with ~~COVID-19~~ AEs/SAEs, as well as the number and proportion of subjects with COVID-19 AEs/SAEs, and the proportion of asymptomatic subjects."

5 Synopsis (Exploratory endpoints): Replaced "Dapagliflozin plasma concentrations from baseline to Day 141 (Week 20)" with "Dapagliflozin plasma concentrations <u>after repeated oral dosing, when given with MEDI3506, on Day 141 (Week 20) and Day 169 (Week 24)".</u>

6 Synopsis (Study design): Reduced number of study sites from 150 to 130.

7 Synopsis (Statistical Methods): Removed mention of summarizing COVID-19 related tests, AEs, and SAEs.

8 Section 1.1 (Disease Background): Deleted "In its reduced form, IL-33 signals through ST2 and co-receptor IL-1 receptor accessory protein" from last paragraph.

9 Section 1.3 (Dapagliflozin Background): Inserted mention of dapagliflozin providing benefits in patients without diabetes and being approved in 100 countries to treat T2DM, 100 countries for heart failures indications, and 51 countries for chronic kidney disease indications.

10 Section 1.5.1 (MEDI3506): Added mention to a trend towards lower AUC in Japanese subjects compared with healthy western subjects.

11 Section 1.7.1 (MEDI3506): Updated the content of "Serious infections (including opportunistic infections)", "Progression of heart failure", and Injection-site reactions" to match with the current MEDI3506 IB.

12 Section 1.7.1: Added reference Moussion et al, 2008 and added to reference list in Section 8.

13 Section 1.7.2 (Dapagliflozin): Added CKD to the list of conditions for which the safety profile of dapagliflozin has been evaluated in clinical development programs; replaced reference Neuen et al, 2019 with de Boer et al, 2020.

14 Section 2.1 (Primary Objective and Associated Endpoint, Table 1): Added mention to blinding central laboratory UACR results from Visit 3 (Day 1) up to and including the EOS Visit.

15 Section 2.2 (Secondary Objectives and Associated Endpoints, Table 2): Deleted Endpoint "Number of subjects seropositive for SARS-CoV-2 at end of study who were seronegative at randomization visit".

16 Section 2.2 (Secondary Objectives and Associated Endpoints, Table 2): Changed Endpoint about subjects testing positive for COVID-19 to "For subjects testing positive for COVID-19 ~~SARS-CoV-2 (by nucleic acid or serology test)~~, during the intervention and follow-up periods, the number and proportion of subjects with ~~COVID-19~~ AEs/SAEs, as well as the number and proportion of subjects with COVID-19 AEs/SAEs, and the proportion of asymptomatic subjects."

17 Section 2.3(Exploratory Objectives and Associated Endpoints, Table 3, PK Objective): Removed "for 12 weeks": "To assess the PK of dapagliflozin after repeated oral dosing when given with MEDI3506 ~~for 12 weeks~~ in subjects with DKD".

18 Section 2.3(Exploratory Objectives and Associated Endpoints, Table 3, PK Endpoint): Replaced "Dapagliflozin plasma concentrations from baseline to Day 141 (Week 20)" with "Dapagliflozin plasma concentrations after repeated oral dosing, when given with MEDI3506, on Day 141 (Week 20) and Day 169 (Week 24)".

19 Section 3.1.1 (Overview): Reduced number of study sites from 150 to 130.

20 Section 3.1.1. (Overview, Figure 1): Removed "Interim Analysis", added "Primary Endpoint: Day 169", and moved Primary Analysis to the end of follow up period.

21 Section 3.2.3 (Rationale for Endpoints): Removed mention to monitoring the number of SARS-COV-2-positive patients.

22 Section 4.1.2 (Inclusion Criteria, criterion 5): Included that subjects must have a stable dose of ACEi or ARB for at least 6 weeks prior to Visit 1 and throughout the screening period, and that minor dose adjustments are acceptable if performed within 2 weeks before Visit 1.

23 Section 4.1.2 (Inclusion Criteria, criterion 6): Included that subjects must have a stable dose of antihypertensive medication for at least 6 weeks prior to Visit 1 and throughout the screening period.

24 Section 4.1.2 (Inclusion Criteria, criterion 8): Added mention of confirmation of off-season intent to get vaccinated against influenza.

25 Section 4.1.2 (Inclusion Criteria, criterion 8): Reduced number of days prior to Visit 3 from CCI to have updated influenza and pneumococcal pneumonia vaccinations.

26 Section 4.1.3 (Exclusion Criteria, criterion 9e): Added "cirrhosis" to the list of underlying condition that predisposes the subject to infections.

27 Section 4.1.3 (Exclusion Criteria, criterion 12): Updated to exclude patients with a known positive diagnostic nucleic acid test for SARS-CoV-2, within 6 weeks prior to randomization visit.

28 Section 4.1.3 (Exclusion Criteria, criterion 12): Added “antigen” and footnote a: “Investigators should use their best clinical judgement to decide on measures needed to minimize the risk of randomizing patients with an active SARS-CoV-2 infection. To do so, they should consider the local status of the COVID-19 pandemic, the subject’s medical and vaccination history, local recommendations regarding outpatient COVID-19 screening, and testing policies”.

29 Section 4.1.3 (Exclusion Criteria, criterion 13): Replaced “enrollment” with “randomization”.

30 Section 4.1.3 (Exclusion Criteria, criterion 14b): Added “cyclosporine, tacrolimus” to the list of molecules targeting the immune system.

31 Section 4.1.3 (Exclusion Criteria, criteria 15 and 16): Replaced mentions to “Day 1” with “Visit 3”, for consistency.

32 Section 4.1.6 (Discontinuation of Investigational Product): Visit 10/EOS will now happen 60 days, instead of 30, after the last visit performed.

33 Section 4.1.6 (Replacement of Subjects): Removed mention to a jointly determination between the Principal Investigator and the medical monitor whether to replace a subject who permanently discontinued the study drug or withdrew consent to all follow-up . Such decision will be made only by the medical monitor.

34 Section 4.2.1 (Enrollment/Screening Period, Table 5): Removed phone call 2.

35 Section 4.2.1 (Enrollment/Screening Period, Table 5): Removed performance of nasopharyngeal swabs.

36 Section 4.2.1 (Enrollment/Screening Period, Table 5): Removed measurement of Weight, height, and BMI calculation on Visit 2. Removed footnote “Height measured at Visit 1 only”, which was linked to this visit.

37 Section 4.2.1 (Enrollment/Screening Period, Table 5): Added footnote (d) to “serum beta-hCG, FSH (for all women)” to clarify that testing for menopause will only be performed if menopausal status cannot be established from reviewing the full medical history.

38 Section 4.2.1 (Enrollment/Screening Period, Table 5): Removed measurement of antibodies to SARS-CoV-2 virus.

39 Section 4.2.1 (Enrollment/Screening Period, Table 5): Edited first NOTE to mention that retesting will be performed for clinical laboratory tests that are outside the usual range and not only for blood pressure, eGFR, ALT, AST, bilirubin, and serum potassium.

40 Section 4.2.1 (Enrollment/Screening Period, Table 5): Deleted mention of retesting serum creatinine for eGFR calculation from footnote f.

41 Section 4.2.2 (Randomized Treatment Period, Table 6): Removed Visit 4 (Day 15) from the schedule. The treatment period ends now with Visit 9 (instead of Visit 10).

42 Section 4.2.2 (Randomized Treatment Period, Table 6): Included a measurement of Cystatin BNP on Early D/c Visit.

43 Section 4.2.2 (Randomized Treatment Period, Table 6): Reduced the frequency of measurements for CCI , complete blood count with differential, prothrombin time, and PTT, PK (MEDi3506), and PK (dapagliflozin).

44 Section 4.2.2 (Randomized Treatment Period, Table 6): Removed at home weight measurements and eGFR calculation.

45 Section 4.2.2 (Randomized Treatment Period, Table 6): Included “placebo” in “IP administration (MEDI3506)”.

46 Section 4.2.2 (Randomized Treatment Period, Table 6): Footnote e: Removed Days 85 (2 h postdose) and 113. Added Day 169 and the mention that patients will be reminded to take dapagliflozin on site visits during dapagliflozin administration time (Day 85 to Day 168).

47 Section 4.2.3 (Follow-up Period, Table 7): Removed follow-up Visit 11. After removing Visit 4 from Table 6, the EOS visit corresponds now to Visit 10 (instead of Visit 12).

48 Section 4.2.3 (Follow-up Period, Table 7): Removed nasopharyngeal swabs for SARS-CoV-2 nucleic acid test, eGFR calculation, measurement of antibodies to SARS-CoV-2 virus, BMI from Physical examination (full) with weight, and Physical examination (abbreviated) with weight.

49 Section 4.3.2.1 (Medical History): Included menopausal status.

50 Section 4.3.2.2 (Physical Examination, Height, Weight, and BMI Calculation): Removed mention of additional weight assessments.

51 Section 4.3.2.3 (Vital Signs): Added “axillary” to methods of measuring the body temperature.

52 Section 4.3.3 (Clinical Laboratory Tests, Additional Tests): Removed mention of SARS-CoV-2 nucleic acid and antibodies tests.

53 Section 4.3.3 (Clinical Laboratory Tests, Additional Tests): Added distinction between Spot urine for UACR and Serial draws urine for UACR.

54 Section 4.3.7.1 (Storage, Re-use and Destruction of Biological Samples): Specified that the results of exploratory biomarker research will not be reported in the CSR, but in a scientific report or publication.

55 Section 4.5.1.4 (Treatment Administration): Added mention that during study visits, patients will be reminded to take dapagliflozin at the clinical site until Day 168.

56 Section 4.5.4 (Treatment Compliance): Removed “weight measurement” from the procedures with which the site personnel will support patients.

57 CCI [redacted].

58 Section 4.7.1 (Permitted Concomitant Medications): Added mention that in general, subjects are expected to be on stable medication regimens during the study and that RAASi and other antihypertensive therapy as concomitant medications should be kept stable throughout the study duration.

59 Section 4.7.2 (Prohibited Concomitant Medications): Added “cyclophosphamide, cyclosporine, tacrolimus, mycophenolate mofetil” to the list of drugs targeting the immune system.

60 Section 4.7.3 (Considerations for SGLT2i and RAASi): Clarified that starting SGLT2i therapy during the study, ie, before Day 169/Early Discontinuation Visit, is not permitted.

61 Section 4.7.3 (Considerations for SGLT2i and RAASi): Clarified that starting SGLT2i therapy at, or after, Day 169 or Early Discontinuation Visit, is permitted.

9.3 Protocol Amendment 3

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. The principal rationale for this amendment is to clarify the use of vaccines against COVID-19 during the study. In addition, the exclusion criterion for prior malignancy was clarified, and an exclusion criterion for the COVID-19 vaccination was added, including recommendations regarding vaccination against COVID-19 during the study. It was clarified that a local laboratory can be used for COVID-19 testing when necessary and also that local laboratory assessments may be used at the discretion of the investigator in the event of urgent unexpected medical situations, or an emergency. Guidelines for treatment with RAASi and dapagliflozin administration, including safety precautions, were added. The requirement for subjects to be fasted before blood or urine collection was removed. The visits schedule, including an Early Discontinuation Visit, to be followed after discontinuation of MEDI3506/placebo was clarified. The definition of investigational product was clarified throughout as MEDI3506, placebo, or dapagliflozin, as appropriate.

With the exception of typographical changes, specific changes are listed below.

1 Throughout protocol: when referring to “investigational product” clarified if this referred to MEDI3506, placebo, or dapagliflozin, as appropriate.
2 Synopsis (statistical methods): Clarified that all TEAEs related to dapagliflozin will also be summarized.
3 Section 1.5.1 (MEDI3506): Updated details of ongoing studies.
4 Section 1.7.2 (Dapagliflozin): Updated with details of the number of subjects treated with dapagliflozin for DKD, and added details of the DAPA-CKD study.
5 Section 4.1.2 (Inclusion Criteria, criterion 9): Clarified that male subjects should use a condom until 24 weeks after the last dose of MEDI3506, and updated the duration for which female subjects of childbearing potential must agree to use a highly effective method of birth control from “at least 16 weeks” to “at least 12 weeks” after the last dose of MEDI3506.
6 Section 4.1.3 (Exclusion Criteria, criterion 9): Clarified that exclusion of prior malignancy other than (i) ‘non-melanoma skin cancer (squamous or basal cell carcinoma)’ and (ii) ‘cervical cancer in situ’, relates to prior malignancies of this nature that have been treated for complete cure.
7 Section 4.1.3 (Exclusion Criteria, criterion 10): Added 2 exclusion criteria related to vaccination against COVID-19 (either first or subsequent dose).
8 Section 4.1.3 (Exclusion Criteria, criterion 14): Added cross-reference to Section 4.7.2.
9 Section 4.1.6 (Discontinuation of Investigational Product): Clarified which visits subjects are expected to attend after discontinuation of MEDI3506 or dapagliflozin.
10 Section 4.1.6.1 (Missed Doses of MEDI3506): Clarified that the missed doses refer to missed doses of MEDI3506. Added cross-reference to Section 4.7.3 for the handling of missed doses of dapagliflozin.

11 Section 4.2.1 (Enrollment/Screening Period, Table 5) and Section 4.2.3 (Follow-up Period): Clarified that subjects will return first morning void midstream urine collection samples for UACR analysis.

12 Section 4.2.1 (Enrollment/Screening Period, Table 5) and Section 4.2.3 (Follow-up Period): Footnote e corrected to state that the samples that may be collected for a blood-based SARS-CoV-2 nucleic acid test if nasopharyngeal swabs are not available should be serum samples, not plasma samples.

13 Section 4.2.1 (Enrollment/Screening Period, Table 5) and Section 4.2.3 (Follow-up Period): Clarified that the alcohol screen breathalyzer is to be performed in line with local practices.

14 Section 4.2.1 (Enrollment/Screening Period, Table 5): Clarified that height is measured at Visit 1 only by adding a new footnote d.

15 Section 4.2.2 (Randomized Treatment Period, Table 6): Added a new column for an Early Discontinuation Visit.

16 Section 4.2.2 (Randomized Treatment Period, Table 6): Removed the criterion for subjects to be fasted before blood or urine collection, and clarified that ADA assessments will be performed in the sponsor's laboratory in footnote g.

17 Section 4.2.2 (Randomized Treatment Period, Table 6): New footnote i added.

18 Section 4.2.3 (Follow-up Period): Text regarding the EOS visit replaced with a cross-reference to Section 4.1.6 where more details are presented.

19 Section 4.2.3 (Follow-up Period, Table 7): Changed plasma to serum for sample collection for blood-based SARS-CoV-2 nucleic acid tests.

20 Section 4.2.3 (Follow-up Period, Table 7): Removed height from physical examination assessment as height should be measured at Visit 1 only.

21 Section 4.3.2.3 (Vital Signs): Text regarding order of assessments clarified to confirm that blood draws should occur last.

22 Section 4.3.3 (Clinical Laboratory Tests): Added details of the SARS-CoV-2 nucleic acid tests.

23 Section 4.3.4 (Pharmacokinetic Evaluation and Methods): Text added to indicate that PK analysis will be performed at selected time points for subjects who received placebo to confirm that no dosing with MEDI3506 took place.

24 Section 4.6.1 (Methods for Assigning Treatment Groups): Requirement for approximately 113 Japanese subjects removed.

25 Section 4.6.2 (Methods to Ensure Blinding): Text to allow unblinding for PK and ADA analysis added.

26 Section 4.7.2 (Prohibited Concomitant Medications): Clarified that subjects are not permitted to receive investigational products other than the investigational products administered in this study within 4 months or 5 half-lives of randomization until the end of the follow-up period. Also corrected that subjects are not permitted to receive live or attenuated vaccines within 28 days of Visit 3 (rather than Visit 1) until the end of the follow-up period. Clarified that renin inhibitor or an aldosterone antagonist in combination with an ACEi or an ARB is not permitted within 2 months of Visit 1 until the end of the follow-up period.

27 Section 4.7.3 (Considerations for SGLT2i and RAASi): Section updated to include treatment guidelines for ACEi or ARB and SGLT2i (dapagliflozin).

28 Section 4.7.4 (Vaccination Against COVID-19) was added.

29 Section 4.8.4.1 (Analysis of Adverse Events): Clarified that all TEAEs related to dapagliflozin will also be summarized.

30 Section 4.8.5 (Analysis of Immunogenicity/Pharmacokinetics): Text amended to indicate that samples may be utilized for further characterization of ADA response, including possible assessment of nAbs.

31 Section 8 (References): New references in Section 4.7.3 added.

32 Appendix D: Corrected the timing of the collection of the blood sample for genetic research from Visit 1 to Visit 3.

33 Appendix F4: Clarified that safety clinical laboratory tests can be performed in a local licensed laboratory.

9.4 Protocol Amendment 2

The primary rationale for this amendment is to explore the efficacy of different doses of MEDI3506 on DKD on top of current standard of care in DKD (ACEi or ARB) as well as expected future standard of care (ACEi or ARB and SGLT2i). SGLT2i have been shown to consistently reduce the risk of clinically important, patient-level cardiovascular outcomes, and emerging data suggest that the combination of ACEi or ARB and SGLT2i should be routinely offered to patients with T2DM who have, or are at high risk of, progressive kidney disease. The study was therefore expanded from a Phase 2a (N = 168) to Phase 2b (N = 565). The expanded sample size is expected to facilitate decisive subgroup analysis and prevent biased patient recruitment. An additional rationale for this amendment was to add study mitigation language and language flexibility due to COVID-19 which will provide sites with measures that may be implemented if a subject is not able to visit a study site. With the exception of typographical changes, specific changes are listed below. All changes listed below were also made to the Protocol Synopsis where required.

1 Section 1.1 (Disease Background): Background text was updated to reflect the current recommendations for risk management in patients with DKD.

2 Section 1.3 (Dapagliflozin Background), Section 1.4.2 (Dapagliflozin), Section 1.5.2 (Dapagliflozin), Section 1.7.2 (Dapagliflozin), and Section 1.7.3 (Other Risks): Introductory sections added to reflect the addition of dapagliflozin to the study and to provide background information, references to nonclinical and clinical experience, and benefit-risk assessment.

3 Section 1.4.1 (MEDI3506): Added the underlined text: “Slight accumulation (mean accumulation ratios were 1.1 to 1.8) of MEDI3506 was observed after multiple SC or IV doses after CCI weeks of dosing” for additional clarity.

4 Section 1.5.1 (MEDI3506): Summary of clinical experience was updated to reflect the completion of Study D9180C00001 and summarize safety and PK observations.

5 Section 1.6 (Rationale for Conducting the Study): Text was added to reflect the addition of dapagliflozin and the interim analysis following treatment with MEDI3506/placebo on top of standard of care, without dapagliflozin.

6 Section 1.7.1 (MEDI3506): Safety-related text was updated to reflect the completion of Study D9180C00001. The following additional potential risk for MEDI3506 was added based on literature report: "Some evidence suggests that IL-33 may enhance the ability of neutrophils and macrophages to respond to bacterial invasion Alves-Filho et al 2010, Li et al 2014). Therefore, blocking this pathway could potentially ameliorate certain anti-infection response in the human immune system."

7 Section 1.7.1 (MEDI3506) and Appendix F (COVID-19 Specifics): Background information on COVID-19, risks and mitigations plans, and discussion of its impact on the current study were added.

8 Section 1.7.4 (Overall Benefit/Risk Conclusion) was added.

9 Section 1.8.2 (Secondary Hypotheses), Section 2.2 (Secondary Objectives and Associated Endpoints), Section 4.8.3.2 (Secondary Efficacy Analysis): Efficacy hypothesis, objectives, and endpoints were added to analyze albuminuria in MEDI3506 subjects compared to placebo during the first 12 weeks of treatment (without dapagliflozin) or the second 12 weeks of treatment (with dapagliflozin) and to analyze the proportion of patients achieving specific UACR reduction targets.

10 Section 2.2 (Secondary Objectives and Associated Endpoints), Section 4.8.4.1 (Analysis of Adverse Events), Section 4.8.4.4 (Other Safety Endpoints): Added safety endpoints including ECG, LVEF as measured by echocardiogram, BNP, vital signs, and laboratory assessments as well as positivity to SARS-COV-2 and related AEs. Additionally, added the corresponding statistical analysis considerations for the safety endpoints.

11 Section 2.3 (Exploratory Objective and Associated Endpoint): Added exploratory objectives and endpoints for

CCI [redacted]

(e) PK analysis of dapagliflozin concentrations.

12 CCI [redacted]

13 Section 3.1.1 (Overview), Section 3.2.2 (Rationale for Study Population), Section 4.1.2 (Inclusion Criteria, Criterion 3b): The patient population was widened from eGFR 30 – 75 mL/min/1.73m^2 to 25 – 75 mL/min/1.73m^2 to allow inclusion of a broader disease population.

14 The following study design components were modified to have a full dose range study, to explore response-to-treatment biomarkers, and to include dapagliflozin as future standard of care in DKD treatment:

(a) Section 3.1.1 (Overview), Section 3.1.2 (Treatment Regimen), Section 3.1.2 (Dose Rationale), Section 4.5.1.3 (Dose Preparation Steps), Section 4.6.1 (Methods for

Assigning Treatment Groups), Section 4.8.2 (Sample Size): Additional MEDI3506 dose levels of 30 mg and 120 mg were added;

(b) Section 3.1.1 (Overview), Section 4.1.1 (Number of Subjects), Section 4.8.2 (Sample Size): Number of study subjects was expanded to 565 total randomized subjects (505 evaluable subjects);

(c) Section 3.1.1 (Overview), Section 3.1.2 (Treatment Regimen), Section 3.2.1 (Dose Rationale), Section 4.6.1 (Methods for Assigning Treatment Groups), Section 4.8.1 (General Considerations): Two additional placebo groups were added in order to volume-match the newly added MEDI3506 dose groups and to maintain blinding;

(d) Section 3.1.1 (Overview): Number of study sites were increased to 150 among multiple countries;

(e) Section 3.1.1 (Overview), Section 3.1.2 (Treatment Regimen), Section 3.2.1 (Dose Rationale), Section 4.2.2 (Randomized Treatment Period): Dapagliflozin 10 mg daily was added to the treatment regimen for all patients from Day 85 to Day 168.

15 Section 3.1.1 (Overview), Section 4.2.2 (Randomized Treatment Period): Added a note that subjects that have reached the Day 85 visit prior to Amendment 2 approval should continue in the study without the addition of dapagliflozin to their dosing regimen.

16 Section 3.1.1 (Overview): Specified timing of the screening period for additional clarity.

17 CCI [redacted]

18 Section 3.1.3 (Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis), Appendix G (Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis): New wording was added which would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity. The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the patient maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.

19 Section 3.2.2 (Rationale for Study Population): Clarified that the study population consists of DKD patients on standard of care medication.

20 Section 3.2.3 (Rationale for Endpoints): Additional language was added to provide rationale for the endpoints.

21 Section 3.2.3 (Rationale for Endpoints), Section 4.2.2 (Randomized Treatment Period), Section 4.3.4 (Pharmacokinetic Evaluation and Methods), Section 4.8.5 (Analysis of Immunogenicity/Pharmacokinetics): Language and collection time-points regarding dapagliflozin PK were added.

22 Section 3.2.3 (Rationale for Endpoints), Section 4.3.7 (Biomarker Evaluation and Methods): For consistency with other sections of the protocol, added that plasma samples may also be used for exploratory biomarker analysis.

23 CCI [redacted].

24 Section 4.1.2 (Inclusion Criteria 3): "micro- or macro-albuminuria" changed to UACR for consistency.

25 Section 4.1.2 (Inclusion Criteria 3), Section 4.2.1 (Enrollment/Screening Period), Section 4.2.2 (Randomized Treatment Period), Section 4.2.3 (Follow-up Period), Section 4.3.1 (Efficacy): Clarified that 'midstream' urine samples should be collected UACR

26 Section 4.1.2 (Inclusion Criteria): Stable blood pressure criteria and ACEi/ARB guidelines were split into two individual criteria - 4 and 5.

27 Section 4.1.2 (Inclusion Criteria 7): Added guideline for subjects on existing SGLT2i treatment.

28 Section 4.1.2 (Inclusion Criteria, Criterion 8): Clarified that, both current influenza and pneumococcal pneumonia vaccination, are mandatory and should have taken place at least 30 days prior to randomization.

29 Section 4.1.2 (Inclusion Criteria, Criterion 9): Contraceptive use language was updated to the latest Sponsor templated text; as such, the former Appendix A was deleted and information consolidated in Inclusion Criterion 9.

30 Section 4.1.3 (Exclusion Criteria, Criterion 2), Section 4.1.4 (Subject Enrollment and Randomization): Added language to exclude patients from screening that have been previously exposed to MEDI3506/discontinued from treatment.

31 Section 4.1.3 (Exclusion Criteria, Criterion 5), Hepatic disease criterion was modified for greater specificity to avoid unnecessarily excluding patients.

32 Section 4.1.3 (Exclusion Criteria, Criterion 9): Clarified the time frame for exclusion due to 'history of treated ulcerative colitis, Crohn's disease, or microscopic colitis' of 3 years from enrollment.

33 Section 4.1.3 (Exclusion Criteria): Added criterion 12 and 13 to exclude patients with active COVID-19 infection at screening or history of significant COVID-19 illness within 6 months of enrollment.

34 Section 4.1.3 (Exclusion Criteria 14c), Section 4.7.2 (Prohibited Concomitant Medications): As many patients are on long-term treatment with fibrates or beta-blockers, criterion was updated to allow patients on study that are on long-term serum creatinine-altering drugs at a stable dose prior to study entry and to allow short-term use to treat acute conditions during the study.

35 Section 4.1.5 (Withdrawal from the Study): Modified follow-up options were added for subjects who withdraw from the study.

36 Section 4.1.6 (Discontinuation of Investigational Product): Instructions were added for potential cases of investigational product discontinuation prior to or during the dapagliflozin period.

37 Section 4.1.6 (Discontinuation of Investigational Product): Dapagliflozin administration criteria were added for suspected/confirmed cases of DKA.

38 Section 4.1.6.1 (Missed Doses): Guidelines were added in case of missed dosing in light of the COVID-19 pandemic.

39 Section 4.2.1 (Enrollment/Screening Period): To minimize burden on patients it was clarified that 'where the values for the following investigations are outside the usual range for a subject during screening, based on their medical history, retesting may be undertaken on one occasion without requiring a re-screen: Blood pressure, eGFR, ALT, AST, bilirubin, and serum potassium'.

40 Section 4.2.1 (Enrollment/Screening Period): HIV-2 screening was added to Table 5 as it was previously omitted in error.

41 Section 4.2.1 (Enrollment/Screening Period): Hepatitis A screening was removed from Table 5 as it was previously included in error.

42 Section 4.2.1 (Enrollment/Screening Period): Spot urine in footnote e was removed as spot urine for UACR calculation for eligibility was removed in a previous amendment.

43 Section 4.2.1 (Enrollment/Screening Period), Section 4.2.3 (Follow-up Period): Added blood collection for antibodies to SARS-CoV-2 virus and nasopharyngeal swabs for SARS-CoV-2 nucleic acid test as well as a footnote stating that nasopharyngeal swabs may be replaced by plasma collection if the swabs are unavailable.

44 Section 4.2.1 (Enrollment/Screening Period), Section 4.2.2 (Randomized Treatment Period), Section 4.2.3 (Follow-up Period): Added a note instructing investigators to contact patients by phone prior to scheduled visit to assess COVID-19 signs and symptoms.

45 Section 4.2.1 (Enrollment/Screening Period), Section 4.2.3 (Follow-up Period), Section 4.3.3 (Clinical Laboratory Tests): SARS-CoV-2 nucleic acid test and antibody test were added.

46 Section 4.2.2 (Randomized Treatment Period): Language in Table 6, footnote e regarding MEDI3506 PK sample collection was simplified.

47 Section 4.2.2 (Randomized Treatment Period): Note was added to specify that subject with symptoms consistent with COVID-19 should be tested on an ad hoc basis.

48 Section 4.2.2 (Randomized Treatment Period), Section 4.3.2.2 (Physical Examination, Height, Weight, and BMI calculation): Capture of at-home weight measurements was extended to the end of the treatment period to obtain data during non-visit weeks.

49 Section 4.2.2 (Randomized Treatment Period): Day 15 blood and urine sample collection time point added for exploratory biomarkers.

50 Section 4.2.2 (Randomized Treatment Period): In Table 6, footnote g, regarding samples for ADA, exploratory biomarkers, urinalysis, pregnancy test, future use, and genetic research, added: 'Subjects should be requested to be in a fasting state (except water) for at least 8 hours prior to sample collection and samples should be collected in the morning. All the assessments to be performed in central laboratories.'

51 Section 4.2.2 (Randomized Treatment Period), Section 4.2.3 (Follow-up Period): Deleted 'Japan only' following CCI and deleted the corresponding footnote to indicate that

samples should be collected from all subjects and that testing will be performed in a central laboratory.

52 Section 4.2.3 (Follow-up Period): Table 7, footnote d was modified for additional clarity as follows: ~~Bring in~~Subjects collect 3 consecutive first morning void midstream urine samples (ideally day of visit and preceding 2 days [refrigerated overnight] which are returned on the day of visit.

53 Section 4.3.1 (Efficacy), Section 4.8.3.1 (Primary Efficacy Analysis): ITT population was changed to Per Protocol Population as the basis of the primary efficacy endpoint analysis based on the updated study design.

54 Section 4.3.2.5 (Echocardiogram): Added statement that echocardiogram procedures are described in a separate manual.

55 Section 4.3.3 (Clinical Laboratory Tests): Local lab testing option for clinical laboratory safety tests including serum pregnancy tests was removed as these tests are to only be done centrally.

56 Section 4.3.3 (Clinical Laboratory Tests): CCI was removed from 'Additional Tests' table as it is already included in the Hematology panel.

57 Section 4.3.4 (Pharmacokinetic Evaluation and Methods): Added language stating that PK samples may be used to evaluate safety or efficacy aspects and that samples may be collected at additional time points if needed for safety reasons.

58 Section 4.3.8 (Estimate of Volume of Blood to Be Collected): Blood volume estimates were updated based on additional collections for dapagliflozin PK and COVID-19 testing.

59 Section 4.5.1 (Identity of Investigational Products): Dapagliflozin supplied concentration and formulation, and packaging information was added.

60 Section 4.5.1.3 (Dose Preparation Steps): Preparation information for MEDI3506 30 mg/120 mg and placebo 0.2 mL/0.8 mL doses were added.

61 Section 4.5.1.4 (Treatment Administration): Dapagliflozin treatment administration information was added.

62 Section 4.5.1.6 (Reporting Product Complaints). Email address for reporting product complaints was updated.

63 Section 4.5.3 (Storage): Dapagliflozin storage information added.

64 Section 4.5.4 (Treatment Compliance): Information regarding the monitoring of dapagliflozin treatment compliance was added. Added additional guidelines for site personnel to support compliance.

65 Section 4.6.1 (Methods for Assigning Treatment Groups): Details on stratification of randomized subjects was added in order to ensure approximate balance between treatment groups within each sub-population.

66 Section 4.7.1 (Permitted Concomitant Medications): Added language stating that adjustment of other glucose-lowering treatments on commencing dapagliflozin may be required to avoid hypoglycemia.

67 Section 4.7.2 (Prohibited Concomitant Medications): Precaution wording for CYPs was added based on previous discussions with MHRA regarding a MEDI3506 clinical study in a different indication.

68 Section 4.7.3 (SGLT2 Inhibitors): Added section containing detailed information on SGLT2i use during the study.

69 Section 4.8.1 (General Considerations): Study population categories were updated appropriately based on the updated study design.

70 Section 4.8.2 (Sample Size): Calculations of statistical power were updated based on the updated study design.

71 Section 4.8.3.1 (Primary Efficacy Analysis): Added text to clarify UACR data treatment in case of intercurrent events, and updated to reflect that analysis will be based on the Per Protocol Population

72 Section 4.8.3.1 (Primary Efficacy Analysis): Text was added to indicate that UACR will be log-transformed for statistical analysis purposes as UACR is assumed to follow a log-normal distribution.

73 Section 4.8.3.1 (Primary Efficacy Analysis): Covariates were updated to simplify models.

74 Section 4.8.3.5 (Sensitivity Analysis): Section was added to describe sensitivity analysis to assess COVID-19 impact on study endpoints.

75 Section 4.8.4.1 (Analysis of Adverse Events): Text was updated to reflect that safety analysis will be based on the Safety Analysis Population. Description of safety analysis related to COVID-19 prevalence among study patients was also added.

76 Section 4.8.7 (Interim Analysis): Change from baseline to Day 85 (Week 12) in UACR was defined as part of the interim analysis. Other changes in this section were made for clarity and descriptiveness.

77 Section 5.3 (Definition of Adverse Events of Special Interest): Replaced “Gastrointestinal adverse reactions assessed as related to study treatment” with “Gastrointestinal adverse events” as all GI events should be recorded as an AESI.

78 Section 5.6.1 (Overdose): Instructions in the event of a dapagliflozin overdose were added.

79 Appendix F (COVID-19 Specifics): Appendix F was added to describe the background information, risks and mitigations plans, and impact of COVID-19 on the current study.

9.5 Protocol Amendment 1

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. The principal reason for this amendment is to provide administrative clarification.

All changes to the protocol were considered to be non-substantial and are summarized below:

1 Title Page: Replaced Marvin Sinsakul with Alexis Hofherr as Medical Monitor

2 Protocol Synopsis: Updated to be consistent with the changes made to the body of the protocol.

3 Section 3.1.1 (Overview): Approximate number of study sites and potential number of countries was updated.

4 Section 3.1.1 (Overview) and Figure 1 (Study Flow Diagram): Treatment period was updated to 168 days as it was incorrectly listed as 169 days previously.

5 Section 4.1.2 (Inclusion Criteria [Inclusion criterion 3b]) and Table 4 (Schedule of Screening Procedures [footnote e]): Clarified that for subjects with amputation, eGFR will be adjusted based on estimated body weight loss.

6 Section 4.1.2 (Inclusion Criteria): Inclusion criterion 3c, Spot urine was removed from the inclusion criteria as it was intended to pre-select patients for first morning void UACR analysis; however, first morning void is more reliable for UACR analysis than spot urine.

7 Section 4.1.2 (Inclusion Criteria): Inclusion criterion 4b was revised from "Stable dose of ACEi or ARB for at least 6 weeks prior to Visit 1 at the maximum labelled or maximum tolerated dose" to "Stable dose of ACEi or ARB for at least 6 weeks prior to Visit 1 with ACEi and ARB dosing according to local guidelines" to allow investigator discretion based on local guidelines as to appropriate dose of ACEi or ARB therapy. Additionally, edits were made to the following (as indicated) for clarification: "Minor ~~D~~dose adjustment ~~of the next/previous titration dose~~ within 2 weeks of Visit 1 is acceptable."

8 Section 4.1.2 (Inclusion Criteria): Inclusion criterion 4c was changed to criterion 5, to clarify that subjects are not required to be on both ACEi/ARB and other hypertensive medications, but if subjects are on other hypertensive medication, they should be on stable doses for at least 6 weeks prior to Visit 1.

9 Section 4.1.2 (Inclusion Criteria): For inclusion criterion 6, up-to-date influenza and pneumococcal pneumonia vaccinations (patient reported) was clarified to be 'according to local recommendations'.

10 Section 4.1.3 (Exclusion Criteria): Exclusion criterion 3a, Replaced "Evidence of chronic liver disease at Visit 1" with exclusion criteria 4 for "History or presence of hepatic disease" to avoid ambiguity in the former sentence.

11 Section 4.1.3 (Exclusion Criteria): Exclusion criterion 8d(i-iii), Clarified that non-melanoma skin cancer, including squamous or basal cell carcinoma, or cervical cancer in situ, as well as any other history of malignancy treated with apparent success with curative therapy are not excluded.

12 Section 4.1.3 (Exclusion Criteria): Exclusion criterion 8f(ii), For history of herpes zoster, added "with last flare occurring" for clarity, and changed to "within 3 months of Visit 1" rather than Visit 3, as it should be part of screening before requesting the transthoracic echocardiogram and first morning void urine.

13 Section 4.1.3 (Exclusion Criteria): Exclusion criterion 9, "Live or attenuated virus vaccination within 28 days of Visit 1 until the end of the follow-up period is not allowed" was changed to "Live or attenuated virus vaccination within 28 days of Visit 3 until the end of the follow-up period is not allowed" to align risk mitigation strategy for potential risk of infection while on study.

14 Section 4.1.3 (Exclusion Criteria [Exclusion criterion 11c]) and Section 4.7.2 (Prohibited Concomitant Medications): Clarified that only chronic use of any serum creatinine-altering drugs within 1 month prior to Visit 1 is prohibited.

15 Section 4.1.3 (Exclusion Criteria): Exclusion criterion 12, Japan-specific exclusion criteria for blood donation and blood loss were added.

16 Section 4.2.1 (Enrollment/Screening Period), Section 4.2.2 (Randomized Treatment Period) and Section 4.2.3 (Follow-up Period): "Assessments should be performed in the order shown in the table" was deleted to allow investigator judgement and the orders of certain procedures are already listed in appropriate sections of the protocol.

17 Table 4 (Schedule of Screening Procedures): Weight, height, and BMI calculation was added for Visit 2 for an additional assessment time point.

18 Table 4 (Schedule of Screening Procedures): "protime" was corrected to "prothrombin time".

19 Table 4 (Schedule of Screening Procedures), Section 4.3.2 (Medical History and Physical Examination, Electrocardiogram, Weight, Height and Vital Signs), and Section 4.3.2.2 (Physical Examination, Height, Weight, and BMI calculation): Added BMI as an additional safety assessment.

20 Table 4 (Schedule of Screening Procedures) and Table 7 (Estimate of Blood Volumes): Screening period was updated from Day -35-Day -1 to Day -37-Day -3 to allow clinical study sites sufficient time to remind participants to collect first morning void urine samples 3 days prior to the next visit.

21 Table 4 (Schedule of Screening Procedures), Table 5 (Schedule of Treatment Period Study Procedures), and Table 6 (Schedule of Follow-up Procedures): Reminder to participants "to collect first morning void urine samples from the 3 mornings before visit" was changed to "to collect first morning void urine samples 3 days before the next visit" for clarity. A phone call reminder 3 days prior to Visit 3 was also added in Table 4.

22 Table 4 (Schedule of Screening Procedures): Footnote d, Clarified that, if otherwise eligible based on screening Visit 1, transthoracic echocardiogram may be performed independently of other Visit 2 procedures within the screening period for additional flexibility.

23 Table 4 (Schedule of Screening Procedures): Footnote e, Added clarification that serum creatinine for eGFR calculation and spot urine for UACR may be retested once during the course of screening.

24 Table 4 (Schedule of Screening Procedures): Footnote f, Clarified that drug screen is to be performed in line with local practices and investigator discretion to allow for patients who may be using tetrahydrocannabinol for medical reasons.

25 Table 5 (Schedule of Treatment Period Study Procedures): Visit windows that were previously ± 2 days were increased to ± 5 days for patient centricity to allow greater flexibility for clinical visit.

26 Table 5 (Schedule of Treatment Period Study Procedures): Rows for Physical examination and Weight were combined for brevity and consistency.

27 Table 5 (Schedule of Treatment Period Study Procedures): Added the underlined text to the 'At home weight measurements' row for clarity and consistency with footnote b: "To be completed at least weekly for the first 12 weeks to capture…".

28 Table 5 (Schedule of Treatment Period Study Procedures) and Table 6 (Schedule of Follow-up Procedures): Added monthly testing for CCI for sites in Japan.

29 Table 5 (Schedule of Treatment Period Study Procedures), Table 6 (Schedule of Follow-up Procedures), and Section 4.3.2.5 (Echocardiogram): Transthoracic

echocardiogram was moved from Visit 11 to Visit 10 in order to assess cardiac benefits during the treatment period.

30 Table 5 (Schedule of Treatment Period Study Procedures): Revised language in footnote b for the at-home weight scale and app to allow a designee of the investigator to train subjects on their usage and to state that the scale will be distributed to subjects at Visit 3 (rather than Visit 1) since the first at-home measurements will be done at Visit 3.

31 Table 5 (Schedule of Treatment Period Study Procedures) and Table 6 (Schedule of Follow-up Procedures): eGFR calculation was added to complement serum chemistry.

32 Table 5 (Schedule of Treatment Period Study Procedures): Pregnancy test was added to Visit 10 for additional monitoring.

33 Table 5 (Schedule of Treatment Period Study Procedures): Footnote c, removed vital signs measurements at 60 minutes and increased window to ± 10 minutes for the 120 minute vital sign measurement after administration of investigational product to reduce burden of unnecessary procedures and flexibility of measurement.

34 Table 5 (Schedule of Treatment Period Study Procedures): Footnote d, Clarified that transthoracic echocardiogram may be performed independently of other Visit 10 procedures within the visit window for additional flexibility.

35 Table 5 (Schedule of Treatment Period Study Procedures): Footnote f, removed Day 169 PK sample collection as there will be no investigational product administered at this time point.

36 Table 6 (Schedule of Follow-up Procedures): Height and BMI calculation were added for Visit 12 for an end of study visit assessment.

37 Section 4.3.1 (Efficacy): Added clarification as to what constitutes a ‘first morning void’ sample.

38 Section 4.3.2.2 (Physical Examination, Height, and Weight): Deleted “Weight assessment will be conducted at every study visit” to avoid redundancy with text in the same paragraph: “Physical examinations, weight, height, and BMI calculation will be performed according to the schedule of study procedures where indicated”

39 Section 4.3.2.2 (Physical Examination, Height, and Weight): Specified that weight should be measured in light street clothes, without shoes, after a prior visit to the bathroom to ensure that measurements are under similar conditions.

40 Section 4.3.2.2 (Physical Examination, Height, Weight, and BMI calculation): Added text for clarity and for consistency with Table 5 (Schedule of Treatment Period Study Procedures): 1) additional remote weight assessments will be obtained at least weekly at home using a remote digital scale for the first 12 weeks <u>after initial dose of investigational product; 2)</u> subjects will be trained on how to use the app and weight scale by investigators or designee and take the scale home at Visit 3; and 3) if needed, subjects may be provided with a smartphone in order to use the app, and that data will be available to site and sponsor in real time for review.

41 Section 4.3.2.3 (Vital Signs): Revised the order of procedures for vital signs to occur prior to 12-lead ECG for consistency with the Schedule of Study Procedures.

42 Section 4.3.2.6 (Electrocardiogram): Revised text to state that only ECG evaluation will be recorded in the eCRF and removed the specific ECG variables (RR, PR, QRS, QT intervals).

43 Section 4.3.3 (Clinical Laboratory Tests): Clarified that clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed local or licensed central clinical laboratory to avoid ambiguity.

44 Section 4.3.3 (Clinical Laboratory Tests): Added a footnote to specify that the CKD-EPI equation based on serum creatinine for eGFR calculation will be used to determine eligibility.

45 Section 4.3.3 (Clinical Laboratory Tests): Added alcohol and drug screening tests for consistency with Table 4 (Schedule of Screening Procedures).

46 Section 4.5.1.4 (Treatment Administration) and Table 5 (Schedule of Treatment Period Study Procedures [footnote j]): Added instructions for cases where dosing is not performed within the dosing window: “In the event that a dose cannot be administered within the window of the scheduled dosing date, the dose may be administered outside of the dosing window as long as it is at least 14 days prior to the next dose and recorded as a protocol deviation”.

47 Section 4.7.2 (Prohibited Concomitant Medications): Removed “cyclophosphamide” from the bullet for chronic use of any serum creatinine-altering drugs for consistency with Section 4.1.3 (Exclusion Criteria).

48 Section 4.8.3.2 (Additional Analyses of the Primary Endpoint): Replaced “each” with “Day 169” in the following, “The primary endpoint at the Day 169 post baseline time point will also be analyzed using…” for specificity.

49 Section 4.8.7 (Interim Analysis): Added UACR as a potential parameter for interim analysis.

50 Section 5.3 (Definition of Adverse Events of Special Interest): Clarified that only gastrointestinal adverse reactions that are assessed as study treatment related will be classified as an AESI.

Appendix A Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

AEs for **malignant tumors** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. However, in certain situations medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **Non-Serious** AE. For example, if the tumor is included as medical history and progression

occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1	An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2	An event of moderate intensity that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3	A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4	An event, and/or its immediate sequelae, that is associated with an imminent risk of death.
Grade 5	Death as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

A guide to Interpreting the Causality Question

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational product.

- Time Course. Exposure to suspect investigational product. Has the subject actually received the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology) or products of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related:	The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
Not protocol related:	The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

Appendix B National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   (b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3 Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   (a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   (b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

C 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational product.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

C 2 Definitions

Potential Hy's Law

AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law

AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

C 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central laboratories being used:

When a subject meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met. Where this is the case, the investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the subject meets PHL criteria (see Section C 2 within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

Local laboratories being used:

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the subject meets PHL criteria (see Section C 2 within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

C 4 Follow-up

C 4.1 Potential Hy's Law Criteria Not Met

If the subject does not meet PHL criteria, the investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

C 4.2 Potential Hy's Law Criteria Met

If the subject does meet PHL criteria, the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to clinical study protocol (CSP) process for SAE reporting.

- For subjects that met PHL criteria prior to starting investigational product, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the subject's condition

- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data

- Subsequent to this contact the investigator will:

  – Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  – Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL lab kit should be used
  – Complete the three Liver CRF Modules as information becomes available

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

C 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the investigational product, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to investigational product and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and

amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

C 6 Laboratory Tests

Table C1 Hy's Law Laboratory Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA [a] IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [b]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

[a] HCV RNA is only tested when IgG anti-HCV is positive or inconclusive

[b] Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly

Appendix D Genetic Research

Rationale and Objectives

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 4.1.8 of the protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 3 at or after randomization. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an AE, such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of LSLV, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the subject enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 7 of the protocol.

Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study site. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the

subject understands that they may freely discontinue from the genetic aspect of the study at any time.

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as Hospitals, Academic Organization or Health Insurance Companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and Determination of Sample Size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan will be prepared where appropriate.

Appendix E Patient Treatment Guidelines

Hyperkalemia

Subjects will have their serum potassium measured by a Central Laboratory. If the serum potassium is between 5.6 and 5.9 mEq/L, inclusive (5.6 to 5.9 mmol/L), application of standard clinical assessment and care for the medical circumstance at hand should be implemented. Assuming that the result represents a true case of hyperkalemia, corrective measures should be initiated to prevent further increases in serum potassium, including review of the patient's dietary intake, any use of nonsteroidal anti-inflammatory drugs (NSAIDs), use of potassium-sparing medications, and use of potassium supplements. The need for diuretics, sodium polystyrene sulphonate and/or acute therapies may need to be considered. The ACEi or ARB dose may also need to be reduced, but this should be done only after review with the medical monitor.

If the serum potassium measured by the Central Laboratory is ≥ 6.0 mEq/L (6.0 mmol/L), immediate measures must be carried out to determine the cause and corrective actions instituted. Decisions to adjust or discontinue the ACEi and ARB will be at the discretion of the Principal Investigator and the medical monitor.

If after corrective measures are taken, including temporary discontinuation of ACEi or ARB, in a patient who has a serum potassium of ≥ 6.0 mEq/L (6.0 mmol/L), and the potassium fails to decrease to ≤ 5.5 mEq/L (5.5 mmol/L), the ACEi or ARB must be discontinued permanently and the medical monitor should be notified.

Subjects who discontinue ACEi or ARB may remain on investigational drug following consultation with the medical monitor and should be followed for the full duration of the study.

Appendix F COVID-19 Specifics

F 1 Background to COVID-19

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel SARS-CoV-2 that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the World Health Organisation to declare a pandemic situation on 12 March 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect subjects, site staff, and society as a whole.

Both European Medicines Agency (EMA) and Food and Drug Administration (FDA) as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect subjects participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline.

F 2 Risk Assessment for COVID-19 Pandemic

There are 2 investigational products with different mechanisms of action that are unlikely to impact on the course of infection with SARS-CoV-2. MEDI3506 does have an anti-inflammatory mode of action with inhibition of IL-33 and prevention of binding to its receptor ST2. While this poses a theoretical risk of adversely influencing the antiviral response, this is judged to be unlikely. Dapagliflozin is an anti-glycemic agent and is believed not to cause immune suppression. Therefore, risk of the subjects exposed to SARS-CoV-2 or to suffer from COVID-19 is expected to be similar to the background population with the same co-morbidities as those in the study, in particular CKD and T2DM. The risk of exposure to infected people cannot be completely excluded as the subjects may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other subjects of the clinical study).

Measures to mitigate the additional risks caused by COVID-19 are:

- This study will resume enrolling only when the sponsor and contract research organization in collaboration deem it is safe to start the study. In addition, the study will not resume until the local confinement measures or other safety restrictions linked to the

COVID-19 pandemic imposed by the local authorities are compatible with safe conduct of the study.

- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Subjects will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat and fatigue throughout the study during the pandemic. Once clinical signs of infection are reported by subjects, the investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. The decision to continue with dosing the subject with the study drugs in the event of him/her showing symptoms of COVID-19 infection will be per investigator's discretion.
- If, for reasons related to the COVID-19 pandemic, a subject is not able to attend their scheduled visit within the visit window, they can have their visit rescheduled within 14 days of the original scheduled visit; however, visits that cannot be rescheduled within a 14-day window must be skipped and subjects should continue at the next scheduled visit.
- During the COVID-19 pandemic, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the subjects will allow collection of data for AEs, concomitant medications, adherence to the eDiary and patient-reported outcome measures to be reported and documented. The term telemedicine visit refers to remote contact with the subjects using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- The probability of virus transmission will be controlled as much as possible by:
  - Advising subjects to adhere to local requirements for reduction of the public exposure while ambulatory.
  - Assessment of potential COVID-19 infection by optional laboratory assessment based on availability (test capacity and turnaround time) of approved tests and on investigator's discretion.
  - Requesting all subjects to be contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and asking subjects to not attend the site in case of suspected reports. In addition, sites will ask subjects regarding any contact with a person who has tested positive for SARS-CoV-2. If applicable, subjects will be referred to the local healthcare system for further follow-up and treatment.
  - Applying physical distancing and person-to-person contact restrictions during site visits and in-house confinement.
  - Use of personal protective equipment by study subjects (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits)

where physical distancing is not possible if deemed appropriate by the investigators and site staff and guided by local requirements.

– Implementation of logistical improvements of the site and structural measures of the study site building to further improve physical distancing.

F 3 Restrictions Related to COVID-19

During the COVID-19 pandemic, subjects are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. If applicable, prior to Screening Visit 1, potential subjects should be called to confirm they are not experiencing any COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection. If appropriate, subjects will be referred to the local healthcare system. Physical distancing and person-to-person contact restrictions will be applied and explained to subjects while staying at the study site. Where physical distancing is not possible, study subjects will be asked to use surgical face masks and/or gloves if deemed appropriate by the investigator and site staff and guided by local requirements.

F 4 Data Quality Assurance Related to COVID-19

Monitoring visits at site will be limited to a minimum required as deemed appropriate during COVID-19 pandemic, per local regulations.

In addition, where possible, other measures for carrying out protocol-related activities, such as but not limited to home nursing and safety clinical laboratory tests performed in a local licensed laboratory, may be employed as required.

F 5 References

1. Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic, EMA, Version 3 (28/04/2020). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

2. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020, Updated on April 16, 2020 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

Appendix G Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

G 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections G 2 to G 6. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

G 2 Rescreening of Patients To Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened subjects. The investigator should confirm this with the designated Study Physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrollment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Section 4.2.1, the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Section 4.2.1. The procedures detailed in Section 4.2.1 must be undertaken to confirm eligibility using the same randomization number as for the patient.

G 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service will visit the patient's home / or other remote location as per local SOPs, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

G 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events and concomitant medication to be reported and documented. If applicable, safety procedures and blood sample collection will be performed according to the revised SoA in the Study Instructions for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis.

G 5 At-home or Remote Location Investigational Product Administration Instructions

If a site visit is not possible, at-home or remote location administration of investigational product may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance, or by the patient or his/her caregiver. The option of at-home or remote location investigational product administration ensures patients safety in cases of a pandemic where patients may be at increased risk by traveling to the site/clinic. This will also minimize interruption of investigational product administration during other study disruptions, eg, site closures due to natural disaster.

G 5.1 At-home or Remote Location Investigational Product Administration by a Qualified HCP or TPV Service

A qualified HCP from the study site or TPV service should administer the investigational product at the patient's home or other remote location according to the CSP. All necessary supplies and instructions for administration and documentation of investigational product administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

G 5.2 At-home or Remote Location Investigational Product Administration by the Patient or His/Her Caregiver

Prior to at-home or remote location investigational product administration the investigator must assess the patient or his/her caregiver to determine whether they are appropriate for at-

home or remote location administration of investigational product. Once the patient or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of investigational product administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

G 6 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home / remote visits will be captured by the qualified HCP from the study site or TPV service