CLINICAL PROTOCOL

Brief Protocol Title:	A Phase 2 Study of MZE829 in Adults with APOL1 Kidney Disease
Full Protocol Title:	An Open-Label Phase 2 Study to Evaluate the Safety, Tolerability, and Effect on Albuminuria of MZE829 in Adults with Proteinuric Chronic Kidney Disease and the *APOL1* High Risk Genotype
Protocol Number:	MZE829-201
EU CTR Number:	2024-517525-10-00
IND:	167141
Investigational Product:	MZE829 HCl Capsules
Study Phase:	2
Study Sponsor:	Maze Therapeutics 171 Oyster Point Blvd, Suite 300 South San Francisco, CA 94080
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Protocol Version Number:	1.0
Protocol Effective Date:	02 OCT 2024

Confidentiality Statement

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1. SYNOPSIS

Name of Sponsor/Company:

Maze Therapeutics

Name of Investigational Product:

MZE829 HCl capsules

Name of Active Ingredient:

MZE829 HCl salt

Brief Title of Study:

A Phase 2 Study of MZE829 in Adults with APOL1 Kidney Disease

Protocol Number: MZE829-201	**EU CTR Number: 2024-517525-10-00**

Number of Study Center(s):

Approximately 100 global sites

Phase of Development: 2

Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of MZE829 in adults with proteinuric APOL1 kidney disease	• Safety and tolerability based on incidence of adverse events (AEs), and changes in vital signs, clinical laboratory assessments, 12-lead electrocardiograms (ECGs)
Secondary	
• To evaluate the change in albuminuria after treatment with MZE829 • To characterize the plasma pharmacokinetics (PK) of MZE829	• % participants with ≥30% reduction from baseline in urine albumin to creatinine ratio (UACR) at Week 12 • Geometric mean plasma drug concentrations
Exploratory	
• To explore the change in proteinuria after treatment with MZE829 • To explore the change in proteinuria after discontinuation of MZE829 • To explore the change in estimated glomerular filtration rate (eGFR) after treatment with MZE829 • To explore the relationship between MZE829 and urine and blood biomarkers • To explore genotypes associated with kidney disease severity and response to MZE829 • To explore changes in health-related quality-of-life measurements	• Change from baseline in UACR at Week 12 • % change from baseline in UACR at Week 12 • % change from baseline UACR over time during the Treatment Period • % participants with ≥30% reduction from baseline in UACR at Week 16 • % participants with ≥30% reduction from baseline in urine protein to creatinine ratio (UPCR) at Week 12 • Change in UPCR at Week 12 • % change from baseline in UPCR at Week 12

	• % change in UPCR over time during the Treatment Period • % participants with ≥30% reduction from baseline in UPCR at Week 16 • Change from baseline in eGFR at Week 12 • % change from baseline in exploratory biomarkers • Association between exploratory biomarkers and response to MZE829 • Association between gene variants, kidney disease severity, and response to MZE829. • Change from baseline to Week 12 in Kidney Disease Quality of Life Instrument Short Form Health Survey 36 (KDQOL-36), a patient-reported outcome (PRO) measure.

Study Design

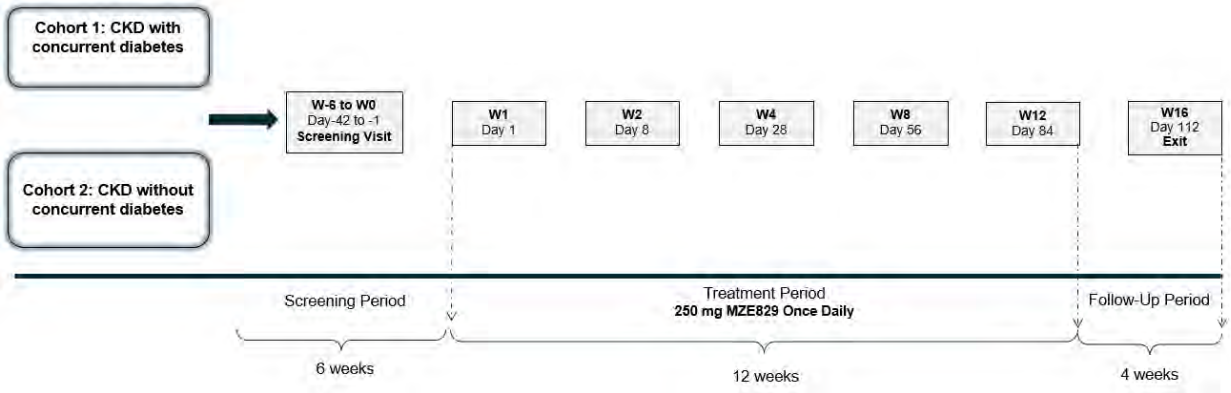
MZE829-201 is a Phase 2, open-label study of MZE829 in adults aged 18 to 65 years with proteinuric chronic kidney disease (CKD) and the *APOL1* high risk genotype, or APOL1 Kidney Disease (AKD).

The study will consist of 2 cohorts, each comprised of approximately 28-34 participants. Cohort 1 will be comprised of participants with the *APOL1* high risk genotype, proteinuric kidney disease and concurrent diabetes. Cohort 2 will be comprised of participants with the *APOL1* high risk genotype, proteinuric kidney disease and without concurrent diabetes. At least 5 participants in Cohort 2 should have focal segmental glomerulosclerosis (FSGS) confirmed by biopsy.

Cohort 1: CKD with concurrent diabetes administered MZE829 250 mg once daily
Cohort 2: CKD without concurrent diabetes administered MZE829 250 mg once daily

The study will include a Screening Period (Day -42 to -1). The Screening Period visit can be conducted over two separate visits. The first visit at minimum will include informed consent, demographics, and *APOL1* genotyping. Once genotyping results are available, participant can return to complete the remainder of the Screening visit procedures. Following Screening, participants meeting all eligibility criteria for a cohort will be enrolled and receive once-daily oral doses of MZE829 during the open-label 12-week Treatment Period. Upon completion of the treatment period, participants will return for an Exit visit at Week 16. During study visits, assessments for safety, efficacy, PK, and exploratory biomarkers will be performed as listed in the Schedule of Events (Table 1.1). A Safety Monitoring Committee (SMC) will be convened for this study to conduct safety reviews throughout the study and provide advisory support to the Sponsor on any warranted changes to study design.

Study Design Schematic



Number of Participants (planned):

Up to 68 participants are planned to be enrolled with approximately 28 to 34 participants in each cohort across approximately 100 global study centers. At least 5 participants in Cohort 2 should have focal segmental glomerulosclerosis (FSGS) confirmed by biopsy.

Participants who discontinue early from the study for non-safety related reasons may be replaced at the discretion of the Sponsor.

Eligibility Criteria:

Participants not meeting all inclusion criteria, or meeting at least one exclusion criterion, may be re-screened once if there is a reasonable possibility of eligibility. Inclusion in the study of any participant who meets all eligibility criteria on rescreening will be at the discretion of the Investigator.

Inclusion Criteria

Participants for inclusion in this study must meet **all** of the following criteria:

For All Participants (Cohort 1-2):

1) 18 to 65 years of age (inclusive) at the time of signing the informed consent
2) Body mass index (BMI) of 18 to ≤45 kg/m^2 and total body weight of ≥40 kg
3) Confirmed *APOL1* high risk genotype of G1/G1, G2/G2, or G1/G2
4) Diagnosis of chronic kidney disease with persistent high urine albuminuria
    a. Confirmed by UACR ≥300 mg/g. Based on the average of 3 consecutive first morning void samples collected during the Screening Period. Collection should be completed by Day -10 for confirmation of eligibility
5) Estimated glomerular filtration rate (eGFR) ≥25 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2 at Screening based on the Chronic Kidney Disease Epidemiology Collaboration (2021 CKD-EPI Creatinine-Cystatin C) equation
6) Stable doses of background standard of care treatment for CKD for at least 8 weeks prior to Screening, including but not limited to:
    a. Renin-angiotensin-aldosterone system (RAAS) inhibitors (required unless not tolerated or contraindicated)
    b. SGLT2 inhibitors, mineralocorticoid receptor antagonists, GLP-1 receptor agonists (permitted but not required)
    c. Anti-hypertensive treatment (if indicated)

7) Negative tests for HBcAb, HBsAg, HCV antibody, and HIV antibody at Screening
    a. Participants with positive anti-HCV antibody are allowed if HCV RNA PCR is negative
8) Women of childbearing potential must have a negative pregnancy test at Screening (serum) and at Day 1 (serum or urine)
9) Participants who are completely abstinent from sexual intercourse (if this is the participant's usual and preferred lifestyle) or in same sex relationships do not require contraception. For other participants, use of highly effective contraception is required. (See Appendix 13.4)
10) Post-menopausal female participants do not require contraception if ≥12 months without menses and follicle-stimulating hormone (FSH) documented in postmenopausal range (≥40 IU/L)

Cohort 1:

11) Diagnosis of Type 2 diabetes mellitus on a stable regimen of antidiabetic medication(s) and/or insulin for at least 8 weeks prior to Screening (See Section 6.9)
12) Participants with a concurrent diagnosis of hypertension-related CKD or focal segmental glomerulosclerosis (FSGS; with or without confirmation by biopsy and without a known cause other than APOL1) are eligible provided other selection criteria for Cohort 1 are met

Cohort 2:

13) Diagnosis of CKD attributed to any of the following:
    a. Hypertension
    b. FSGS with or without confirmation by biopsy and without a known cause other than APOL1

Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study:

For All Participants

1) Any condition that in the opinion of the Investigator would interfere with the evaluation of the investigational product or lead to increased risk of harm. This may include, but is not limited to, the following:
    a. History of cancer within past 2 years, excepted for treated non-melanoma skin cancer, stage 0 cervical cancer, or stage 1 prostate cancer
    b. Clinically significant liver disease
    c. Unstable cardiac disease, including history of unstable angina, myocardial infarction or stroke within 12 months prior to Screening
    d. Requirement for supplemental oxygen or history of intubation within 6 months prior to Screening
    e. Organ or bone marrow transplantation
    f. Clinically significant and active infection
    g. Uncontrolled hypothyroidism
    h. History of thromboembolism within 1 year prior to Screening
    i. Ongoing alcohol or substance abuse as determined by the Investigator
    j. Conditions that may alter drug absorption, e.g., history of bariatric surgery
    k. Pregnancy or currently nursing
2) Use of any potent immunosuppressants within 5 PK half-lives or 12 weeks prior to Screening, whichever is longer, including but not limited to: abatacept, adalimumab, anakinra, azathioprine, cyclophosphamide,

certolizumab, etanercept, golimumab, infliximab, rituximab, ruxolitinib, sarilumab, tofacitinib, or tocilizumab

   a. Cyclosporine, mycophenolate mofetil, and/or tacrolimus are permitted if stable regimen and dose for at least 8 weeks prior to Screening

3) Use of oral corticosteroids equivalent to prednisone >10 mg/day for more than 1 day within 8 weeks prior to Screening and/or use of any other systemic corticosteroid equivalent to prednisone >10 mg/day within 8 weeks prior to Screening
4) Clinically significant abnormal laboratory test results with the exception of abnormalities considered by the Investigator to be the result of underlying disease. Test results within the following ranges at Screening will exclude a patient from participation in the study:
   a. Total bilirubin ≥1.5 × upper limit of normal (ULN)
   b. Aspartate transaminase (AST) or alanine transaminase (ALT) ≥2 × ULN
   c. Serum albumin <2 g/dL
   d. TSH ≥10 mIU/L
   e. Potassium >ULN
   f. Hemoglobin <10 g/dL
   g. Absolute Neutrophil Count (ANC) <1000 cells/µL
5) Clinically significant abnormal Screening ECG, including but not limited to QTcF >450 ms or history of QT interval prolongation
6) Vital Signs outside the following ranges (assessment may be repeated at the Investigator's discretion) at the Screening visit;
   a. Systolic blood pressure 90 to 180 mg Hg, inclusive
   b. Diastolic blood pressure 40 to 100 mg Hg, inclusive
   c. Heart rate 50 to 99 bpm, inclusive
7) Medications that are strong CYP3A4 inhibitors or inducers (e.g., rifampin, carbamazepine, clarithromycin, itraconazole), including herbal supplements (e.g., St. John's wort), grapefruit, Seville-oranges, or poppy seeds within 14 days of study drug administration and throughout the study.
8) Proton pump inhibitors within 14 days of study drug administration and throughout the study.
9) Have used any investigational drug within 8 weeks or < 5 half-lives, whichever is longer, prior to the Screening visit
10) Hypersensitivity to MZE829 or its components.
11) For participants with kidney biopsy: biopsy result indicating severe or ≥50% tubulointerstitial fibrosis
12) Planned travel during the study to regions with endemic trypanosomiasis

<u>Cohort 1:</u>

12) Glycosylated hemoglobin A1c >8.0% at Screening or brittle diabetes per Investigator judgement
13) Diagnosis of Type I diabetes mellitus
14) Kidney disease attributed to other known causes including but not limited to: active infection, autoimmune disease (e.g., lupus nephritis, IgA nephropathy, membranous nephropathy, glomerular basement membrane disease), toxins, drugs (e.g., bisphosphonate, interferon), congenital abnormalities (except unilateral renal agenesis), malignancy, minimal change disease, previously diagnosed genetic kidney disease (e.g., autosomal dominant polycystic kidney disease, Alport syndrome), sickle cell disease, amyloidosis
   a. Sickle trait is permitted
   b. Solitary native kidney is permitted

Cohort 2:

15) Current treatment with an antidiabetic medication and/or insulin, glycosylated hemoglobin A1c ≥6.5% at Screening, or any of the following in the medical history:
    a. Fasting glucose ≥126 mg/dL on 2 separate days
    b. 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test
16) Kidney disease attributed to other known causes including but not limited to Type 1 or 2 diabetes mellitus, active infection, autoimmune disease (e.g., lupus nephritis, IgA nephropathy, membranous nephropathy, anti-glomerular basement membrane disease), toxins, drugs (e.g., bisphosphonate, interferon), congenital abnormalities (except unilateral renal agenesis), malignancy, minimal change disease, previously diagnosed genetic kidney disease (e.g., autosomal dominant polycystic kidney disease. Alport syndrome), sickle cell disease
    a. Sickle trait is permitted
    b. Solitary native kidney is permitted

Investigational Product, Dosage, and Mode of Administration:

MZE829 will be provided in 50 mg capsules. Participants will be instructed to take five (5) MZE829 HCl capsules (50 mg each) orally once daily for a total dose of 250 mg at approximately the same time each morning in a fasted state.

Reference Therapy, Dosage and Mode of Administration: Not Applicable

Duration of Participant Participation Including Follow-up:

Study duration for individual participants will be up to 22 weeks: up to 6 weeks in Screening, 12 weeks on study drug and 4 weeks of follow-up.

Statistical Methods:

The sample size is based on the binary endpoint of a responder. A responder is a participant with ≥30% reduction in UACR at Week 12 compared to baseline. A sample size of 28-34 provides power between 70-80% at one-sided alpha = 5% that the proportion of responders is greater than 30% assuming that the true responder rate is 50%.

Primary safety analysis:

Safety measures that are continuous will be summarized with descriptive statistics (mean, standard deviation [SD], median, maximum, minimum). Adverse events will be coded by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0. The number and percentage of participants experiencing treatment-emergent AEs along with the severity and relationship to study drug will be summarized by cohort. Further details regarding presentation and analysis of safety data will be detailed in a separate statistical analysis plan (SAP).

Analysis of secondary endpoints:

A binary endpoint (30% reduction at Week 12 compared to baseline in UACR), the proportion of responders along with 90% confidence intervals (CI) will be presented as a secondary endpoint. Data may be log-transformed as appropriate. Additional details on analysis methods will be described in the SAP.

Individual plasma drug concentrations will be listed and summarized by cohort and timepoint. These plasma drug concentrations may be assessed using population PK analysis modeling. Exploratory exposure-response analyses may be conducted. In addition, other analyses on samples may be performed to characterize MZE829 PK, biomarkers, and its variability.

Table 1.1 Schedule of Assessments

Assessment[a]	Screening Period[b]	Treatment Period					Follow-up Period	ET[c]
Week	**W -6 to 0**	**W1**	**W2[d]**	**W4**	**W8[d]**	**W12**	**W16 Exit**	
Study Day	**–42 to –1**	**1**	**8**	**28**	**56**	**84**	**112**	
Study Windows			±2 days	±2 days	±3 days	±3 days	±7 days	
Informed consent	X							
Demographics	X							
Inclusion/exclusion criteria	X	X						
Medical history	X							
APOL1 Genotyping[e]	X							
Physical examination[f]	X	X	X	X	X	X	X	X
Vital sign measurements[g]	X	X	X	X	X	X	X	X
12-Lead ECG[h]	X	X	X	X		X	X	X
Laboratory Tests[i]	X	X	X	X	X	X	X	X
Pregnancy Test[j]	X	X		X	X	X	X	X
Urine for UACR and UPCR[k]	X	X	X	X	X	X	X	X
PK blood[l]		X	X	X	X	X		
Exploratory biomarkers[m]		X		X		X	X	
KDQOL-36		X				X		
Drug Accountability[n]			X	X	X	X		X
Study Drug in-clinic administration[o]		X		X		X		
Study Drug Dispensed[p]		X	X	X	X			
Study Drug Returned[q]			X	X	X	X		X
Dosing Diary[r]		X	X	X	X	X		X
AEs[s]	←			X		→		
Prior/concomitant medications	←			X		→		

[a] When on same day/time as vital signs and PK, the order of activities: vital signs, ECGs, laboratory assessments, PK and then exploratory biomarkers.
[b] The Screening Period visit can be conducted over two separate visits. The first visit at minimum will include informed consent, demographics, and *APOL1* genotyping. Once genotyping results are available, participant can return to complete the remainder of the Screening visit procedures.

[c] In the event of an early termination from the study, participants will complete an in-clinic Early Termination (ET) visit at approximately 4 weeks after the last dose of study drug.
[d] Home health visit in lieu of in-clinic visit may be used at discretion of Investigator.
[e] *APOL1* genotyping if genotype status not previously determined by Sponsor-approved vendor. Participants will be offered an optional genetic counseling visit once the genotyping result is available.
[f] A full PE at Screening and Day 1 includes HEENT, chest, heart, abdominal, extremities, skin, and neurologic examination. Weight and height will be collected to calculate BMI at Screening, and weight only will be collected at Day 1 and all subsequent visits. An abbreviated symptom-directed PE may be conducted at the Investigator's discretion at all visits following Day 1.
[g] Oral temperature, heart rate, blood pressure, and respiratory rate will be measured in a seated position after 5 minutes. Obtain pre-dose on Day 1, Week 4 and 12 and for all other visits, at any timepoint.
[h] Single 12-lead ECG recordings after the patient has been in the supine position for at least 5 minutes. Obtain pre-dose on Day 1, Week 4 and 12 and for all other visits, at any timepoint.
[i] Blood specimens for chemistry and hematology analyses and urine specimen for urinalysis will be obtained at selected timepoints. Labs can be repeated at the discretion of the Investigator or Medical Monitor. For participants on cyclosporine or tacrolimus, see Table 13.1.
[j] All women of childbearing potential must have a negative serum pregnancy test at Screening and a negative serum or urine test at all other visits. Any positive urine pregnancy test should be confirmed with a serum pregnancy test.
[k] After the Screening visit, participants should be instructed to collect their first morning urine void at home for 3 consecutive days. Urine collection for Screening should be completed no later than Day -10. For all other visits, participants should be instructed to collect their first morning urine void at home for 3 consecutive days prior to each in-clinic or home health visit. The third day of collection should be the day of the study visit. Strenuous exertion 24 hours prior to urine collection should be avoided when possible.
[l] Blood samples for PK analysis will be collected at pre-dose (within 120 minutes prior to study drug dosing) and post-dose at lh, 2h, and 3h on Day 1; on Week 4 and Week 12, pre-dose and 2h post-dose; and for all other visits at any timepoint. See Laboratory Manual for PK collection windows.
[m] Blood and urine samples for exploratory biomarker analysis will be collected pre-dose (within 120 minutes prior to study drug dosing) at Day 1, Week 4 and 12; and at any timepoint for Exit/Week 16.
[n] Drug accountability should be performed at each in-clinic visit alongside the dosing diary. Where home health visits are used, the home health nurse should perform a check. The dosing diary and instructions will be provided to the participant on Day 1.
[o] Study drug should be administered around the same time daily during the treatment period in a fasted state. For Week 1, Week 4 and Week 12, study drug administration will occur in-clinic. The time of study drug dosing will be called "0" hour. The last dose of study drug will be taken at the Week 12 visit after the pre-dose PK sample is collected.
[p] If a Home Health visit is opted for Weeks 2 and/or 8, adequate study drug supply will be provided until the next in-clinic visit.
[q] If a Home Health visit is opted for Weeks 2 and/or 8, study drug should be returned at the next in-clinic visit.
[r] If a paper Dosing Diary will be used, it should be dispensed at every visit and returned/reviewed at the next in-clinic visit.
[s] Adverse events will be assessed from the time of signing the Informed Consent Form through Exit/ET and must be followed until they are resolved, stable, or judged by the Investigator to be not clinically significant.

2. INTRODUCTION

2.1. Study Rationale

The *APOL1* high risk genotype is associated with an increased risk of Chronic Kidney Disease (CKD) and disease progression to End Stage Kidney Disease (ESKD). Currently, no targeted therapies for APOL1 are available. This study will evaluate the safety, tolerability, and effect on albuminuria of MZE829, a novel APOL1 inhibitor, in individuals with APOL1 kidney disease and persistent albuminuria.

2.2. Background

Chronic kidney disease is a global health issue and is estimated to affect around 700 million people worldwide (Francis, 2024). While CKD is not limited to a particular region and affects all socioeconomic strata, individuals of African ancestry are disproportionately impacted. For example, Africa is projected to experience the greatest rise in the number of individuals needing kidney replacement therapy by 2030 (Liyanage, 2015). In the US, the burden of CKD and ESKD is considerably higher in the Black population as compared to the White population, with rates of ESKD approximately 3.8 times as high in Black vs White populations in the US (US Renal Data System, 2022). The increased risk can be partially attributed to a locus on chromosome 22—specifically 2 distinct missense variants - termed G1 and G2, in the apolipoprotein L1 gene (*APOL1*) (Genovese, 2010; Tzur, 2010).

The *APOL1* high risk genotype is associated with increased risk of a variety of distinct kidney diseases, including hypertension attributed to CKD, focal segmental glomerulosclerosis (FSGS), human immunodeficiency virus (HIV) - associated nephropathy, sickle cell nephropathy, and lupus nephritis (Ashley-Koch, 2011; Kopp, 2011; Genovese, 2010; Dummer, 2015). The *APOL1* high risk genotype has also been associated with more rapid decline in renal function in individuals with CKD, including those with diabetic kidney disease (Parsa, 2013; Chen, 2023). These data are consistent with *APOL1* risk variants increasing the risk of developing kidney disease and the risk of more rapid disease progression. *APOL1* risk variants are most prominently associated with proteinuric kidney diseases, or kidney diseases associated with significant amounts of protein excreted in the urine, suggesting that the glomerulus is the likely site of injury.

Common therapeutic options for CKD include renin-angiotensin system inhibitors, sodium glucose transporter 2 inhibitors, and mineralocorticoid receptor antagonists. However, some individuals with CKD and the *APOL1* high risk genotype are unable to tolerate or may experience inadequate responses to currently available therapeutic options, highlighting the need for medicines targeting the underlying genetic drivers of disease (Lipkowitz, 2013).

The mechanisms by which *APOL1* risk variants cause kidney disease are still unclear but are likely to be a consequence of aberrant pore formation and activity in the G1 and G2 variants. The only known biochemical activity of APOL1 is the assembly of a pH-gated cation selective pore. Recent data suggest that risk variant APOL1 associates more efficiently with membranes than non-risk APOL1, leading to greater pore formation and ion flux, which may explain the differential cytotoxicity seen with G1 and G2 variants (Bruno, 2021; Vandorpe, 2023).

A hypomorphic variant in *APOL1*, p.N264K, has recently been shown to be defective in pore activity in cellular systems (Hung, 2023). Individuals who harbor the hypomorphic p.N264K variant in the context of the *APOL1* high risk genotype are protected from APOL1 kidney disease, providing strong evidence that pore formation and ungated ion flux activity is critical to the ability of G1 and G2 APOL1 to cause kidney disease. Moreover, a 13-week open-label study found that treatment with an APOL1 ion flux blocking small molecule reduced proteinuria by an average of 47% and showed evidence of response as early as 2 weeks in participants with the *APOL1* high risk genotype and heavy proteinuria (Egbuna, 2023).

2.3 Clinical Experience

The first-in-human study MZE829-101 assessed the safety, tolerability, and pharmacokinetics of single and multiple ascending doses of MZE829 in 111 healthy adult participants. There were no severe AEs or serious adverse events (SAEs) reported during the study across all cohorts. There were no clinically significant changes in vital signs, laboratory values, ECGs, and clinical examination during the study. MZE829 was well-tolerated at single doses up to 480 mg and multiple doses up to 350 mg once-daily for 7 days. In these cohorts combined, all treatment-related adverse events (TRAEs) were reported as mild and transient. Headache was the only TRAE reported in ≥3 participants (20% vs. 4%, MZE829-treated vs. placebo) in these cohorts. Linear and dose proportional plasma PK, relatively low PK variability, low (<1%) urinary excretion, and a food effect (increase of approximately 30-50%) were observed.

Dose-related headache, nausea, and vomiting were observed at projected supratherapeutic doses. Mild TRAEs of headache, nausea, and vomiting were reported in a 480 mg split-dose cohort. In the 480 mg QD cohort, mild and moderate TRAEs of headache, vomiting, and nausea were reported. All TRAEs resolved upon discontinuation of MZE829. Due to the tolerability issues observed in multiple participants, dosing in the 480 mg QD cohort was stopped after 2 doses.

2.3. Benefit/Risk Assessment

No efficacy studies of MZE829 have been conducted to date. For further information regarding risks associated with MZE829, please refer to the Investigator's Brochure (IB).

Nonclinical GLP repeat dose studies of MZE829 in Wistar Han rats and cynomolgus monkeys through 13 weeks duration have been completed and support the Phase 2 study. Doses in male rats of up to 30 mg/kg/day and in female rats up to 300 mg/kg/day as well as in monkeys up to 100 mg/kg/day did not result in any additional MZE829-related safety findings, confirming the benefit-risk ratio has not changed since the completion of the IND-enabling studies. Cardiovascular safety pharmacology studies conducted in monkeys demonstrated MZE829 was well-tolerated and had no adverse effects on cardiovascular function, including no qualitative or quantitative MZE829-related QTc changes. Respiratory safety pharmacology evaluation indicated a lack of MZE829-related effects on parameters at the highest dose of 100 mg/kg/day.

In the completed Phase 1 study in healthy adult participants (MZE829-101), MZE829 was generally safe and well tolerated at exposures estimated to be in the efficacious range based on a mouse model of AKD. Clinical PK data support once-daily administration in individuals with renal impairment.

Since APOL1 is a component of HDL cholesterol, APOL1 inhibition could potentially affect lipoprotein homeostasis. However, in MZE829-101, serial monitoring of lipid profiles showed no clinically significant changes in total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and very low-density lipoprotein. Also, given the purported role of APOL1 in host defense against trypanosomiasis, inhibition of APOL1 may increase the risk of trypanosome infection. This was not observed in MZE829-101, albeit in the small number of domiciled, healthy adults.

In summary, the *APOL1* high-risk genotype is associated with increased risk and more rapid decline of CKD. The currently available therapeutic options are limited by suboptimal clinical responses, highlighting the significant unmet need for targeted treatments of APOL1 kidney disease. MZE829 is proposed to attenuate APOL1-induced kidney injury and kidney disease by inhibiting the APOL1 pore. Published clinical data for individuals treated with another APOL1 inhibitor (Egbuna, 2023) or lacking functional APOL1 (Johnstone, 2012) suggest APOL1 inhibition or absence is well tolerated. While the safety of MZE829 in individuals with CKD and the *APOL1* high-risk genotype has yet to be assessed, the available data in healthy participants and nonclinical data indicate an acceptable safety profile for continued clinical development. All participants in MZE829-201 will be closely monitored for safety and tolerability by repeated assessments of vital signs, ECGs, safety laboratory parameters, physical examinations, and AEs. Also, a Safety Monitoring Committee (SMC) will conduct ongoing review of available safety and PK data during the conduct of the study.

The significant unmet need, scientific rationale for APOL1 inhibition, preclinical toxicology data, and clinical data from healthy participants support a favorable benefit-risk profile and the initiation of the Phase 2 study in participants with CKD.

3. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of MZE829 in adults with proteinuric APOL1 kidney disease	• Safety and tolerability based on incidence of adverse events (AEs), and changes in vital signs, clinical laboratory assessments, 12-lead electrocardiograms (ECGs)
Secondary	
• To evaluate the change in albuminuria after treatment with MZE829 • To characterize the plasma PK of MZE829	• % participants with ≥30% reduction from baseline in urine albumin to creatinine ratio (UACR) at Week 12 • Geometric mean plasma drug concentrations
Exploratory	
• To explore the change in proteinuria after treatment with MZE829 • To explore the change in proteinuria after discontinuation of MZE829 • To explore the change in eGFR after treatment with MZE829 • To explore the relationship between MZE829 and urine and blood biomarkers • To explore genotypes associated with kidney disease severity and response to MZE829 • To explore changes in health-related quality-of-life measurements	• Change from baseline in UACR at Week 12 • % change from baseline in UACR at Week 12 • % change from baseline UACR over time during the Treatment Period • % participants with ≥30% reduction from baseline in UACR at Week 16 • % participants with ≥30% reduction from baseline in urine protein to creatinine ratio (UPCR) at Week 12 • Change in UPCR at Week 12 • % change from baseline in UPCR at Week 12 • % change in UPCR over time during the Treatment Period • % participants with ≥30% reduction from baseline in UPCR at Week 16 • Change from baseline in eGFR at Week 12 • % change from baseline in exploratory biomarkers • Association between exploratory biomarkers and response to MZE829 • Association between gene variants, kidney disease severity, and response to MZE829. • Change from baseline to Week 12 in Kidney Disease Quality of Life Instrument Short Form Health Survey 36 (KDQOL-36), a patient-reported outcome (PRO) measure.

4. STUDY DESIGN

4.1. Overall Study Design

MZE829-201 is a Phase 2, open-label study of MZE829 in adults aged 18 to 65 years with proteinuric chronic kidney disease (CKD) and the *APOL1* high risk genotype, or APOL1 Kidney Disease (AKD). Up to 68 participants will be enrolled into the study with approximately 28 to 34 participants in each cohort.

The study will consist of 2 cohorts comprised of approximately 28-34 participants. Cohort 1 will be comprised of participants with the *APOL1* high risk genotype, proteinuric kidney disease and concurrent diabetes. Cohort 2 will be comprised of participants with the *APOL1* high risk genotype, proteinuric kidney disease and without concurrent diabetes.

Cohort 1: CKD with concurrent diabetes administered MZE829 250 mg once daily

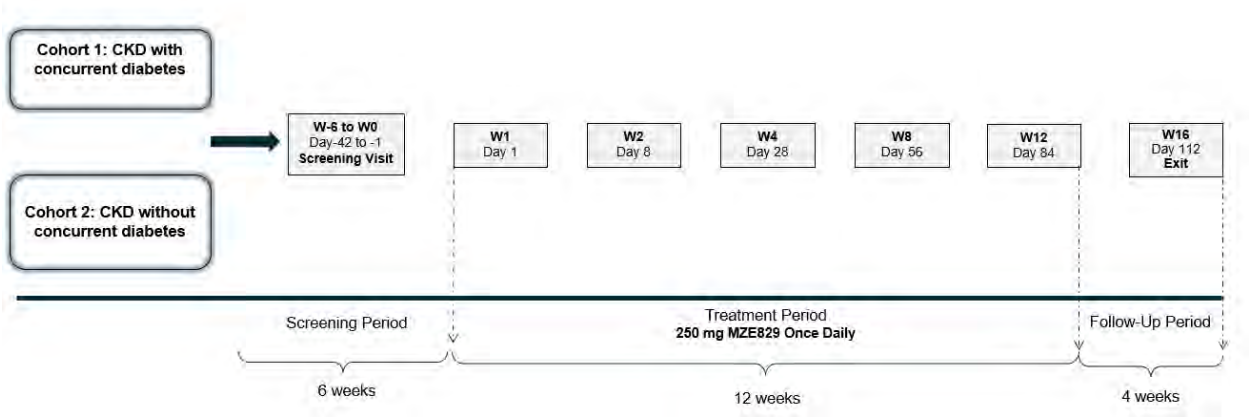
Cohort 2: CKD without concurrent diabetes administered MZE829 250 mg once daily

Cohort 2 is targeted to enroll a minimum of 5 participants with FSGS confirmed by biopsy with no evidence of severe or more than 50% tubulointerstitial fibrosis.

The study will include a Screening Period (Day -42 to -1) which can be conducted over two separate visits. The first visit at minimum will include informed consent, demographics, and *APOL1* genotyping. Once genotyping results are available, participant can return to complete the remainder of the Screening visit procedures.

Following Screening, participants meeting all eligibility criteria for a cohort will be enrolled and receive once-daily oral doses of MZE829 during the open-label 12-week treatment period. Upon completion of the treatment period, participants will return for an Exit visit at Week 16 (Figure 1). During study visits, assessments for safety, efficacy, PK, and exploratory biomarkers will be performed as listed in the Schedule of Events (Table 1.1).

Figure 1 Study Design



4.2. Number of Participants and Number of Study Centers

Up to 68 participants are planned to be enrolled with approximately 28 to 34 participants in each cohort across approximately 100 global study centers. At least 5 participants in Cohort 2 should have FSGS confirmed by biopsy.

4.3. Study Duration

The study duration for individual participants will be up to 22 weeks which includes up to 6 weeks in Screening, 12 weeks on study drug, and 4 weeks of follow-up.

4.4. Justification for Dose

A dose of MZE829 250 mg once daily was selected based on the clinical safety, tolerability, and PK data from the Phase 1 study MZE829-101 conducted in healthy adults, toxicology data, and preclinical pharmacodynamic data. Pharmacokinetic modeling was used to project plasma PK exposure for the selected dose to be assessed in this study. The expected exposure for the selected 250 mg dose was well tolerated in MZE829-101 and expected to be efficacious based on plasma PK exposure and %UACR reduction relationship established in the BAC transgenic mouse model of APOL1 kidney disease. Human plasma exposures after 250 mg dose correspond to a predicted effective concentration of 90% to 95% (~EC_{90-95}). Additional information about MZE829-101 and nonclinical data are available in the Investigator's Brochure.

4.5. End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study, including the Exit visit at Week 16. The end of the study is defined as the date of the last visit of the last participant in the study.

4.6. Criteria for Study Termination

The Sponsor may terminate the study or terminate the study at a specific site. The Sponsor may issue a protocol amendment or discontinue the study entirely, based on regulatory authority or Institutional Review Board (IRB)/Independent Ethics Committee (IEC) recommendations, drug safety or availability concerns, discontinuation of the development program for MZE829, or at the Sponsor's discretion. The Investigator reserves the right to terminate the study at the site according to the study contract.

5. STUDY POPULATION

Participants not meeting all inclusion criteria, or meeting at least one exclusion criterion, may be re-screened once if there is a reasonable possibility of eligibility. Inclusion in the study of any participant who meets all eligibility criteria on rescreening will be at the discretion of the Investigator.

5.1. Inclusion Criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

For All Participants (Cohort 1-2):

1) 18 to 65 years of age (inclusive) at the time of signing the informed consent
2) Body mass index (BMI) of 18 to ≤45 kg/m^2 and total body weight of ≥40 kg
3) Confirmed *APOL1* high risk genotype of G1/G1, G2/G2, or G1/G2
4) Diagnosis of chronic kidney disease with persistent high urine albuminuria
   a. Confirmed by UACR ≥300 mg/g. Based on the average of 3 consecutive first morning void samples collected during the Screening Period. Collection should be completed by Day -10 for confirmation of eligibility
5) Estimated glomerular filtration rate (eGFR) ≥25 mL/min/1.73 m^2 to <90 mL/min/1.73 m^2 at Screening based on the Chronic Kidney Disease Epidemiology Collaboration (2021 CKD-EPI Creatinine-Cystatin C) equation
6) Stable doses of background standard-of-care treatment for CKD for at least 8 weeks prior to Screening, including but not limited to:
   a. Renin-angiotensin-aldosterone system (RAAS) inhibitors (required unless not tolerated or contraindicated)
   b. SGLT2 inhibitors, mineralocorticoid receptor antagonists, GLP-1 receptor agonists (permitted but not required)
   c. Anti-hypertensive treatment (if indicated)
7) Negative tests for HBcAb, HBsAg, HCV antibody, and HIV antibody at Screening.
   a. Participants with positive anti-HCV antibody are allowed if HCV RNA PCR is negative
8) Women of childbearing potential must have a negative pregnancy test at Screening (serum) and at Day 1 (serum or urine)
9) Participants who are completely abstinent from sexual intercourse (if this is the participant's usual and preferred lifestyle) or in same sex relationships do not require contraception. For other participants, use of highly effective contraception is required. (See Appendix 13.4)

10) Post-menopausal female participants do not require contraception if ≥12 months without menses and follicle-stimulating hormone (FSH) documented in post-menopausal range (≥40 IU/L)

Cohort 1:

11) Diagnosis of Type 2 diabetes mellitus on a stable regimen of antidiabetic medication(s) and/or insulin for at least 8 weeks prior to Screening (See Section 6.9)
12) Participants with a concurrent diagnosis of hypertension-related CKD or focal segmental glomerulosclerosis (FSGS; with or without confirmation by biopsy and without a known cause other than APOL1) are eligible provided other selection criteria for Cohort 1 are met

Cohort 2:

13) Diagnosis of CKD attributed to any of the following:
    a. Hypertension
    b. FSGS with or without confirmation by biopsy and without a known cause other than APOL1

5.2. Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study:

For All Participants

1) Any condition that in the opinion of the Investigator would interfere with the evaluation of the investigational product or lead to increased risk of harm. This may include, but is not limited to, the following:
    a. History of cancer within past 2 years, excepted for treated non-melanoma skin cancer, stage 0 cervical cancer, or stage 1 prostate cancer
    b. Clinically significant liver disease
    c. Unstable cardiac disease, including history of unstable angina, myocardial infarction or stroke within 12 months prior to Screening
    d. Requirement for supplemental oxygen or history of intubation within 6 months prior to Screening
    e. Organ or bone marrow transplantation
    f. Clinically significant and active infection
    g. Uncontrolled hypothyroidism
    h. History of thromboembolism within 1 year prior to Screening
    i. Ongoing alcohol or substance abuse as determined by the Investigator
    j. Conditions that may alter drug absorption, e.g., history of bariatric surgery

k. Pregnancy or currently nursing

2) Use of any potent immunosuppressants within 5 PK half-lives or 12 weeks prior to Screening, whichever is longer, including but not limited to: abatacept, adalimumab, anakinra, azathioprine, cyclophosphamide, certolizumab, etanercept, golimumab, infliximab, rituximab, ruxolitinib, sarilumab, tofacitinib, or tocilizumab
   a. Cyclosporine, mycophenolate mofetil, and/or tacrolimus are permitted if stable regimen and dose for at least 8 weeks prior to Screening
3) Use of oral corticosteroids equivalent to prednisone >10 mg/day for more than 1 day within 8 weeks prior to Screening and/or use of any other systemic corticosteroid equivalent to prednisone >10 mg/day within 8 weeks prior to Screening
4) Clinically significant abnormal laboratory test results with the exception of abnormalities considered by the Investigator to be the result of underlying disease. Test results within the following ranges at Screening will exclude a patient from participation in the study:
   a. Total bilirubin ≥1.5 × upper limit of normal (ULN)
   b. Aspartate transaminase (AST) or alanine transaminase (ALT) ≥2 × ULN
   c. Serum albumin <2 g/dL
   d. TSH ≥10 mIU/L
   e. Potassium >ULN.
   f. Hemoglobin <10 g/dL
   g. Absolute Neutrophil Count (ANC) <1000 cells/µL
5) Clinically significant abnormal Screening ECG, including but not limited to QTcF >450 ms or history of QT interval prolongation
6) Vital Signs outside the following ranges (assessment may be repeated at the Investigator's discretion) at the Screening visit;
   a. Systolic blood pressure 90 to 180 mg Hg, inclusive
   b. Diastolic blood pressure 40 to 100 mg Hg, inclusive
   c. Heart rate 50 to 99 bpm, inclusive
7) Medications that are strong CYP3A4 inhibitors or inducers (e.g., rifampin, carbamazepine, clarithromycin, itraconazole), including herbal supplements (e.g., St. John's wort), grapefruit, Seville-oranges, or poppy seeds within 14 days of study drug administration and throughout the study
8) Proton pump inhibitors within 14 days of study drug administration and throughout the study
9) Have used any investigational drug within 8 weeks or <5 half-lives, whichever is longer, prior to the Screening visit
10) Hypersensitivity to MZE829 or its components.

11) For participants with kidney biopsy: biopsy result indicating severe or ≥50% tubulointerstitial fibrosis
12) Planned travel during the study to regions with endemic trypanosomiasis

Cohort 1:

13) Glycosylated hemoglobin A1c >8.0% at Screening or brittle diabetes per Investigator judgement
14) Diagnosis of Type I diabetes mellitus
15) Kidney disease attributed to other known causes including but not limited to: active infection, autoimmune disease (e.g., lupus nephritis, IgA nephropathy, membranous nephropathy, glomerular basement membrane disease), toxins, drugs (e.g., bisphosphonate, interferon), congenital abnormalities (except unilateral renal agenesis), malignancy, minimal change disease, previously diagnosed genetic kidney disease (e.g., autosomal dominant polycystic kidney disease, Alport syndrome), sickle cell disease, amyloidosis
    a. Sickle trait is permitted
    b. Solitary native kidney is permitted

Cohort 2:

16) Current treatment with an antidiabetic medication and/or insulin, glycosylated hemoglobin A1c ≥6.5% at Screening, or any of the following in the medical history:
    a. Fasting glucose ≥126 mg/dL on 2 separate days
    b. 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test
17) Kidney disease attributed to other known causes including but not limited to Type 1 or 2 diabetes mellitus, active infection, autoimmune disease (e.g., lupus nephritis, IgA nephropathy, membranous nephropathy, anti-glomerular basement membrane disease), toxins, drugs (e.g., bisphosphonate, interferon), congenital abnormalities (except unilateral renal agenesis), malignancy, minimal change disease, previously diagnosed genetic kidney disease (e.g., autosomal dominant polycystic kidney disease. Alport syndrome), sickle cell disease
    a. Sickle trait is permitted
    b. Solitary native kidney is permitted

5.3. Rescreening

Any participant who initially fails eligibility criteria may be rescreened once at the discretion of the Investigator. Sponsor to be consulted to determine which screening procedures need to be repeated.

5.4. Replacement of Participants

Participants who discontinue early from the study for non-safety related reasons may be replaced at the discretion of the Sponsor.

5.5. Lifestyle Considerations

Participants should be advised to maintain their usual diet (including typical protein consumption) and activity levels throughout the study. Strenuous exertion 24 hours prior to urine collection should be avoided when possible.

6. STUDY DRUG ADMINISTRATION AND MANAGEMENT

6.1. Study Drug Administered

The investigational product for this study is MZE829 supplied as 50 mg capsules in bottles.

A tabulated summary of MZE829 characteristics is shown in Table 6.1.

Table 6.1 Study Drug Characteristics

Name of IMP:	MZE829 HCl capsules
Active substance(s):	MZE829 HCl salt
Inactive substance(s):	Microcrystalline Cellulose, Mannitol, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, and Hypromellose Capsule
Appearance:	White, Opaque Hard-Shell Capsule
Strength:	50 mg (MZE829 free base equivalent)
Route of Administration:	Oral
Packaging and Labelling:	35 MZE829 HCl capsules inside 60 cc HDPE bottle with induction film seal and a desiccant pack.

6.2. Dosing and Administration

During the study, participants will be instructed to take five (5) MZE829 HCl capsules (50 mg each) orally once daily for a total dose of 250 mg at approximately the same time each morning in a fasted state. Water is permitted as desired along with study drug administration.

Study dosing will start in the clinic on Day 1 and the last dose of study drug will be in the clinic on Day 84. During in-clinic visits as specified in the SOA (Table 1.1), study drug administration will occur at the clinic. Study participants will complete a daily dosing diary to record date, time, and amount for daily dose administration.

6.3. Packaging and Labelling

Study drug will be supplied in high density polyethylene (HDPE) bottles with child-resistant caps. The bottles will be labeled as required per country requirements. Full details regarding packaging and labelling are described in the Pharmacy Manual.

6.4. Study Drug Handling, Storage, and Return

Full details regarding storage, dispensation, and return of study drug are described in the Pharmacy Manual.

6.5. Study Drug Compliance

The Investigator or designee will maintain records of study drug delivered to the study site, the inventory at the study site, the distribution to and use by each participant, and return of study drug for storage or disposal. These records should include date and times of each dose administered, quantities, dosing, expiration dates as applicable, in-clinic temperature logs, and corresponding participant identification number.

Participants will be instructed on how to return their study drug (empty/unused/partially used bottles). Participants will be counseled on the importance of adherence with their study regimen and recording study drug use in the dosing diary (e-diary or paper).

Participants who are repeatedly noncompliant will be counseled on the importance of compliance and Sponsor will be notified immediately. Discontinuation for noncompliance is at the discretion of the Investigator and Sponsor and is to be noted on the CRF.

6.6. Study Drug Accountability

Study drug will not be destroyed or returned to the Sponsor until accountability has been fully monitored. Study drug accountability will be performed and assessed by the study site personnel and the Clinical Research Monitor or designee to ensure compliance. Refer to the Pharmacy Manual for additional information.

In addition to the above, the interactive response technology (IRT) will be used to record information pertaining to study drug shipment, storage, dispensation, return/destruction, accountability, and reconciliation.

During in-clinic visits participants will receive study drug directly from the Investigator or designee. The date and time of each dose administered at the clinic site will be recorded in the source documents. The dose of study drug and study participant identification will be confirmed at the time of dosing.

A record of the quantity of study drug dispensed and administered to each participant must be maintained and reconciled with study drug compliance records.

6.7. Prior and Concomitant Therapy

Therapy considered necessary for the participant’s welfare may be given at the discretion of the Investigator. When possible, concomitant medications should be maintained at a consistent dose and dosing regimen as medically appropriate throughout the course of the study. An effort should be made to avoid initiation of any new medications, vaccines, or other interventions including procedures unless medically necessary. If the permissibility of a specific medication/treatment is in question, please contact the Sponsor or designee.

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant receives within 60 days of Screening or receives during the study must be recorded on the electronic case report form (eCRF) along with:

- Indication for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- Any changes to dosage information while in the study

The Sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

6.8. Prohibited Treatments

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Sponsor or designee should be notified before the prohibited medication/treatment is applied.

The following medications are prohibited:

- Use of medications that are strong CYP3A4 inhibitors or inducers (e.g., rifampin, carbamazepine, clarithromycin, itraconazole, etc.), including herbal supplements (e.g., St. John's wort), grapefruit, Seville-oranges, or poppy seeds are prohibited within 14 days of study drug administration and throughout the study.
- Use of proton pump inhibitors within 14 days of study drug administration and throughout the study. Participants on proton pump inhibitors at the Screening visit should be switched to shorter-acting anti-reflux medications (i.e., H_2-blockers or antacids) at least 14 days prior to the Day 1 visit if medically appropriate.
- Use of oral corticosteroids equivalent to prednisone >10 mg/day for more than 1 day within 8 weeks prior to Screening. Use of any other systemic corticosteroid equivalent to prednisone >10 mg/day within 8 weeks prior to Screening will be prohibited.
- Use of any potent immunosuppressants within 5 PK half-lives or 12 weeks prior to Screening, whichever is longer, including but not limited to: abatacept, adalimumab, anakinra, azathioprine, cyclophosphamide, certolizumab, etanercept, golimumab, infliximab, rituximab, ruxolitinib, sarilumab, tofacitinib, or tocilizumab.

- Use of any other investigational drugs are not allowed at any point during this study. In cases where an investigational drug has been used prior to the study, 5 PK half-lives or 8 weeks, whichever is longer, must have passed prior to Screening.

6.9. Permitted Treatments

Treatment consistent with local standard of care for CKD and/or diabetes is permitted provided the medication regimen and dosing have been stable for at least 8 weeks prior to Screening. Effort should be made to maintain a stable regimen as medically appropriate for the duration of the study.

Permitted treatments may include one or more of the following, but not limited to:

- Sodium-glucose co-transporter 2 (SGLT2) inhibitors
- Mineralocorticoid receptor antagonist (MRA)
- Renin-angiotensin-aldosterone system (RAAS) inhibitors (required unless not tolerated or contraindicated)
- Glucagon-like peptide-1 (GLP-1) receptor agonists

Other permitted treatments include the following immunosuppressants if the regimen and dose have been stable for at least 8 weeks prior to Screening:

- Cyclosporine, mycophenolate mofetil, and/or tacrolimus
- Corticosteroids (≤10 mg per day of prednisone or equivalent)

Permitted treatments for gastroesophageal reflux include H_2-blockers and antacids. These medications should be administered as follows:

- H_2-blockers should be administered at least 10 hours before study drug administration and/or no sooner than 2 hours after study drug administration
- Antacids should be administered at least 2 hours before study drug administration and/or no sooner than 2 hours after study drug administration

Questions regarding the permissibility of specific medications not listed here should be discussed with the Sponsor or designee**.**

7. DOSE INTERRUPTION/MODIFICATION/DISCONTINUATION/WITHDRAWAL CRITERIA

7.1. Dose Interruption and Modification

If a participant experiences a clinically significant laboratory result or medical assessment, MZE829 dosing may be paused at the discretion of the Investigator, and the Sponsor or designee should be notified immediately. Modification or continuation of dose may be permitted after consultation with the Sponsor or designee.

7.2. Discontinuation of Study Drug

In the event it is decided for a participant to permanently discontinue study drug, the participant will remain in the study to be evaluated at approximately 4 weeks after last dose administered and complete an ET visit (Table 1.1).

7.3. Withdrawal of a Participant from the Study

Subjects may be withdrawn from the study due to:

- An adverse event (AE) that cannot be improved by appropriate medical intervention or that, in the opinion of the Medical Monitor or Investigator, would lead to undue risk if the subject were to continue receiving Study Treatment
- Pregnancy or initiation of breastfeeding
- Non-compliance with protocol requirements and restrictions
- Withdrawal of consent
- Investigator’s discretion
- Death

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator. At the time of discontinuing from the study, if possible, an early termination visit should be conducted as shown in the SoA (Table 1.1). The participant will be permanently discontinued from the study drug and the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.4. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Medical History

A complete medical history will be collected from the participant and medical records and should include clinically relevant medical conditions, surgeries, review of systems, allergies, medications, and relevant family history.

8.2. *APOL1* Genotyping

A peripheral blood sample will be obtained at Screening to genotype participants for *APOL1* risk alleles (G1, G2) using qPCR, sequencing, or other standard genotyping methods if the participant's genotype status has not been previously determined by a Sponsor approved vendor.

Participants will be offered an optional genetic counseling visit once the genotyping results are available.

*The Screening Period can be conducted over two separate visits. The first visit at minimum will include informed consent, demographics, and *APOL1* genotyping. Once genotyping results are available, participant can return to complete the remainder of the Screening visit procedures.

8.3. Clinical Safety Laboratory Tests

Blood and urine specimens will be obtained at selected timepoints per the SoA (Table 1.1). Refer to Appendix 13.5 for a list of laboratory tests that will be evaluated.

8.4. Pregnancy Test

All women of childbearing potential must have a negative serum pregnancy test at Screening and a negative serum or urine test at all other visits. In the event of a positive urine pregnancy test, further administration of study drug should be held and the result confirmed by a serum pregnancy test. If serum pregnancy testing positive, study drug should be discontinued permanently (See Section 7.2).

8.5. Urine for UACR and UPCR

After the Screening visit, participants should be instructed to collect their first morning urine void at home for 3 consecutive days within the 10 days prior to the Day 1 visit. For all other visits, participants should be instructed to collect their first morning urine void at home for 3 consecutive days prior to each in-clinic or home health visit. The third day of collection should be the day of the study visit.

Participants should be reminded to abstain from strenuous activity (e.g., more than 20 minutes per day of running, swimming, weightlifting or other physical activities exceeding their usual

level of daily exertion) where possible 24 hours prior to urine collection. Refer to the Laboratory Manual for instructions on urine sample collection.

8.6. Physical Examination

A full physical examination (PE) at Screening and Day 1 includes HEENT, chest, heart, abdominal, extremities, skin, and neurologic. Weight and height will be collected to calculate BMI at Screening, and weight only will be collected at each physical examination at Day 1 and all subsequent visits. An abbreviated symptom-directed PE may be conducted at the Investigator's discretion at all visits following Day 1. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF.

8.7. Vital Signs

Oral temperature, heart rate, blood pressure, and respiratory rate will be measured in a seated position after the participant is seated for at least 5 minutes. Vital signs will be obtained prior to other scheduled study procedures at all study visits and may be repeated at the discretion of the Investigator to obtain a clinically reliable result.

8.8. Electrocardiogram

Single 12-lead ECGs will be recorded per the SoA (Table 1.1) after the participant has been in a supine position for at least 5 minutes. ECGs may be repeated to obtain a technically valid result at the discretion of the Investigator.

8.9. Pharmacokinetic (PK) Samples

Blood samples for PK analysis will be collected at timepoints specified in the SOA (Table 1.1). The time of each blood draw and the time of study drug dosing on the day of the PK blood draws will be noted on the respective eCRF page. The time of the previous dose of study drug (i.e., the day before) will also be collected on the eCRF page. Any remaining samples will be stored by the Sponsor and may be used for future analyses (i.e., additional exploratory biomarker analysis that are believed to be associated with treatment efficacy or safety).

Instructions for collection, preparation, handling, and shipping PK specimens are provided in the Laboratory Manual.

8.10. Exploratory Biomarker Analysis

Blood and urine samples will be collected at specified timepoints as noted in the SoA (Table 1.1). These samples will be used for exploratory endpoints, which may include the evaluation of various markers of renal health, immune status, and optional additional genetic

testing. Details regarding all blood and urine sample collections for exploratory biomarker analysis, including volumes, processing, and storage, are provided in the Laboratory Manual.

8.11. Kidney Disease Quality of Life Questionnaire (KDQOL-36)

KDQOL-36 is a validated survey that measures the impact of kidney disease on patients' health-related quality of life and will be administered at Week 1 and Week 12. It includes the SF-12 as a generic core and three kidney disease-specific scales: burden, symptoms, and effects (Hays, 1997).

8.12. Unscheduled Visits

Unscheduled visits may be performed at the discretion of the Investigator and/or for ad-hoc or repeat assessments including, but not limited to, AE assessment, concomitant therapy updates, and laboratory sample collections. eCRFs will be completed for each unscheduled visit.

9. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND SAFETY REPORTING

9.1. Definition of Adverse Event

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug or other protocol-imposed intervention, whether or not considered related to the study drug.

Events meeting the AE definition include the following:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events **not** meeting the AE definition include the following:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

9.2. Definition of Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose, meets 1 or more of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (i.e., the AE, in the view of the Investigator, places the participant at immediate risk of death at the time of the event; it does not refer to an event which might hypothetically have caused death if more severe)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the participant's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Is considered a significant medical event by the Investigator (i.e., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as nonserious AEs. Elective hospitalizations for conditions that existed before administration of the study drug are not to be considered SAEs. However, pre-study conditions that worsen during the course of the study and meet the SAE criteria above would be considered SAEs.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on participant or event outcome or action criteria usually associated with events that pose a threat to a participant's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs.

9.3. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be assessed from the time of signing the Informed Consent Form through Exit/ET and must be followed until they are resolved, stable, or judged by the Investigator to be

not clinically significant. Any medical event occurring during Screening prior to dosing should be added to medical history.

All SAEs and overdose will be recorded and reported to the Sponsor or designee immediately within 24 hours. The Investigator will submit any updated SAE and overdose data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

9.4. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. Additionally, AEs may be identified from laboratory reports, imaging or ECG reports, and other records.

Investigators will seek information on AEs at each participant contact. All AEs, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the AE eCRF.

A consistent, nondirective questioning methodology should be adopted for eliciting AE information at all participant evaluation time points. Examples of nondirective questions include the following:

- "How have you felt since your last study visit?"
- "Have you had any new or changed health problems since you were last here?"

9.5. Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate**: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- **Severe**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

9.6. Assessment of Causality

The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. The guideline below should be used to consider relatedness:

- **Related**: After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship with study drug.
- **Not Related**: After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship with study drug.

The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.7. Recording of AE and/or SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

9.8. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts and submit any updated SAE data to the Sponsor/designee within 24 hours of receipt of the information. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (see Section 7.4).

9.9. Reporting Requirements for SAEs

- Prompt notification (within 24 hours) by the Investigator to the Sponsor/designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participant and the safety of a study drug 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 drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it in the Investigator Site File (ISF) along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- 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. Sponsor or designee will be responsible for SUSAR reporting for the investigational product in accordance with global and local requirements, including reporting to Eudravigilance database in accordance with EU Clinical Trial Regulation.
- SAEs, including Pregnancy reports, should be reported to Sponsor’s designee:

  Attn: Syneos Health Safety & Pharmacovigilance
  Email: safetyreporting@syneoshealth.com
  Fax: +1-877-464-7787

9.10. Pregnancy Reporting

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study drug and for at least 4 weeks after the last dose of investigational product.

- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to the Sponsor as described in Section 9.9. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

9.11. Death Events

When recording a death on an eCRF or safety event report form, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept whenever possible. When reporting SAEs, “death” should not be reported as an SAE term, but rather as the outcome of a specific SAE unless the event preceding the death in unknown. If an autopsy was performed, the autopsy report should be provided to the Sponsor.

10. STATISTICAL CONSIDERATIONS

There are 2 cohorts defined for this study (Cohort 1 and Cohort 2). Each of the cohorts will be analyzed independently.

Since there is no control group, no formal statistical testing procedures will be performed on variables that do not involve a change (or percent change) from baseline. Change and percent change from baseline will be analyzed using either a paired t-test or appropriate non-parametric test (for example, Wilcoxon rank-sum test).

The statistical analysis plan (SAP) will include a detailed description of the statistical analyses described in this protocol. Where there are differences, the SAP will supersede the protocol. This section is a summary of the analyses foreseen at the time of planning the study.

10.1. Analysis Sets

The primary estimand is the on-treatment estimand. The population includes all patients who have completed the study and received treatment for 12 weeks. The safety analysis set will include all participants who receive at least one dose of study drug. The UACR and UPCR endpoints will include the safety analysis set participants who provide endpoint data on post-treatment visits.

The PK analysis set will be used for PK analyses and will include all safety analysis set participants who have at least one evaluable PK sample taken.

10.2. Sample Size Determination

The sample size is based on the binary endpoint of a responder. A responder is a participant with ≥30% reduction in UACR at Week 12 compared to baseline. A sample size of 28-34 provides power between 70-80% at one-sided alpha = 5% that the proportion of responders is greater than 30% assuming that the true responder rate is 50%.

10.3. General Considerations for Statistical Methods

Baseline is defined as data at Day 1 prior to the start of study drug administration.

Binary data summaries will include the overall number of subjects, and number and percent of subjects for each possible value (i.e., responder and non-responder). Summaries of efficacy binary data will include 90% confidence intervals.

Non-binary categorical data summaries will include the overall number of subjects, and number and percent of subjects for each possible value. Summaries of efficacy non-binary categorical data that are collected at multiple visits will include a statistical test to determine whether the distribution changed from baseline (i.e., Cochran-Mantel-Haenszel Row Mean Score).

Continuous variables summaries will include the number of subjects, mean, standard deviation, median, maximum, and minimum. Summaries of efficacy continuous variables will include a statistical test to determine whether the change from baseline and percent change from baseline (when appropriate) are statistically significant and 90% confidence intervals on the observed value, the change from baseline value and the percent change from baseline value (when appropriate).

Pharmacokinetic concentration summaries will include the number of subjects, mean, standard deviation, the number of subjects with non-zero values, geometric mean (excluding subjects that have a value of 0), median, maximum and minimum.

10.4. Disposition, Demographics, and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the safety analysis set. Reasons for discontinuation from study treatment and discontinuation from study will be summarized.

10.5. Treatment Adherence

Treatment adherence will be monitored by counting the amount of study drug dispensed and returned at each study visit.

Treatment adherence will be assessed by the proportion of subjects receiving at least one dose, and the proportion of capsules taken of the originally scheduled number. If the last dispensed bottle was not returned by the date of the last assessment assigned it will be assumed that the patient has taken the drug per protocol.

10.6. Endpoint Analyses

10.6.1. Safety Analyses

Safety measures that are continuous will be summarized as indicated in Section 10.1.

Adverse events will be coded by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA version 27.0). Treatment-emergent AEs (TEAEs) will be defined as AEs that start at or after study drug dosing. The number and percentage of participants experiencing TEAEs along with the severity and relationship to study drug will be summarized by cohort.

Further details regarding presentation and analysis of safety data will be detailed in a separate statistical analysis plan.

10.6.2. Efficacy Endpoints

A binary endpoint (30% reduction at Week 12 compared to baseline in UACR), the proportion of responders along with 90% confidence intervals (CI) will be presented as a secondary endpoint. Continuous endpoints, mean changes from baseline and 90% CI will be presented as exploratory endpoints. Similar analyses will be conducted based on UPCR as additional exploratory endpoints. Data may be log-transformed as appropriate. Additional details on analysis methods will be described in the SAP.

Individual plasma drug concentrations will be listed and summarized by cohort and timepoint. These plasma drug concentrations may be assessed using population PK analysis modeling. Exploratory exposure-response analyses may be conducted. In addition, other analyses on samples may be performed to characterize MZE829 PK, biomarkers, and its variability.

10.7. Safety Monitoring Committee (SMC)

Participant safety and study conduct will be monitored by the SMC. Standing members of the SMC include the Maze clinical study lead or designee, Medical Monitor, clinical pharmacologist, and external advisor(s) with nephrology expertise not participating in the study as an Investigator. Other attendees may be included in SMC meetings and consulted at the discretion of the Sponsor and may include other functional areas representatives (e.g., pharmacovigilance, biostatistics, etc.) and external consultants. The SMC will meet on a regular schedule and on an ad hoc basis to review study progress and available safety, efficacy, and PK data. Details of the SMC membership, meeting processes, and scope are detailed in a separate charter document.

10.8. Handling of Missing Data

Imputations will not be performed unless otherwise noted in the SAP.

10.9. Interim Analysis

No formal interim analysis is planned for this study.

11. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

11.1. Compliance Statement

This study will be conducted in accordance with the protocol and with ICH Good Clinical Practice (GCP) guidelines, US Food and Drug Administration (FDA), and Declaration of Helsinki, and any applicable local health authority and IRB/IEC requirements.

To the extent applicable, all references to ICH, GCP, FDA, the Federal Food, Drug, and Cosmetic Act, Code of Federal Regulations (CFR), and the like shall be interpreted as also referring to any corresponding requirements of local regulatory agencies, regulations, and laws. If there is any discrepancy between ICH, FDA and local requirements, the most stringent standard shall apply.

11.2. CTR compliant - Data Protection in the European Economic Area

Maze, as Data Controller, ensures that all processing activities involving personal data performed in the scope of this Study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016) and Data Protection Act 2018, its subsequent amendments and any additional national laws on Data Protection, recommendations and guidelines as applicable.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration or loss of information and processed personal data, Maze will ensure implementation and maintenance of the following measures:

- Maze ensures that only authorized personnel have physical and virtual access to data and personal information. This access will be based on function and need to access information.
- The ability to ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services;
- Network, application, data security to prevent unauthorized deletion, blocking, copying of information, disabling security measures and response to such attacks;
- Procedures that cover reporting, analysis, monitoring and resolution of security incidents;
- Ensuring that information systems, computers and software involved in the performance of the services provided in the Study are adequately backed up;
- A process for regularly testing, assessing and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing;

- Procedures to capture within reasonable time-manner any personal data breach that occurs;
- Business continuity procedures ensuring that Maze can continue to provide services through operational interruption;
- All locations, personnel and information systems that are used to perform services for the Study will be covered;

Maze will ensure technical and organizational security measures described above, are regularly reviewed and updated to consider any evolution on technological developments. Maze may apply additional specific statutory requirements, where applicable in the national laws, and will implement the necessary security measures even if they are not expressly listed above.

Besides the already above-mentioned technical and organizational measures, Maze, by means of internal measures and imposed contractual clauses to the selected sub-contractors, ensures the confidentiality of records and personal data of subjects.

With exception of the activities in the scope of the on-site monitoring, the name of the patient will neither be asked for, nor recorded by Maze. An identification number will be allocated to each patient registered in the study. This number will identify the patient and will be included on all case report forms and corresponding material and data associated with the patient.

Monitors acting on behalf of Maze will have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for the source data verification mandatory under relevant legal framework, including the ICH-GCP obligations applicable to the conduct of the study. Staff involved in the performance of this task is bound by any additional stricter confidentiality clauses imposed upon them, as compared to other staff members.

Maze has put in place a functional process of reporting of any data breach occurring at Maze's or its sub-contractor's facilities and premises. In case of the occurrence of any data breach, Maze will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, considering its source, underlying intentions, possibilities of recovery etc. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to Maze within 24 hours to ensure appropriate reporting to the relevant supervisory data protection authority within 72 hours. In addition, in case of occurrence of a high-risk breach, affected participants will be informed by Maze (via clinical Study site).

11.3. Principal Investigator Responsibilities

As required by ICH guidelines for GCP and FDA regulation (21 CFR Part 56), the Principal Investigator at each study site must obtain IRB/IEC review and approval of the study protocol,

ICFs, participant recruitment materials, and any other pertinent documents before any study related activities involving participants are performed.

As required in the ICH guidelines for GCP and 21 CFR Part 50, the Principal Investigator or designee must comply with the informed consent process, and ensure that each participant enrolled in this clinical study understands the information presented in the IRB/IEC approved ICF and agrees voluntarily to participate in the clinical study.

The Principal Investigator or designee must submit to the IRB/IEC any written safety report or update (e.g., amended IB or safety amendments and updates) provided by the Sponsor or representative, according to the IEC specific reporting requirements.

The Principal Investigator must inform the IRB/IEC of the progress of the clinical study and report any non-administrative changes made to the protocol; in any case, the Investigator must provide an update to the IRB/IEC at least once a year or in accordance with IRB/IEC continuing approval requirements.

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs or other reporting forms will be included on a Delegation of Authority form.

The clinical study report will be signed by the Sponsor.

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.4. Institutional Review Board/Independent Ethics Committee Review

A copy of the protocol, proposed ICF, other written participant information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by the Sponsor before recruitment of participants into the study and shipment of investigational product.

The Principal Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The Principal Investigator is to notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site and other AE reports received from the Sponsor, in accordance with local procedures.

The Principal Investigator is responsible for obtaining annual IRB/IEC approval/renewal as applicable throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to the Sponsor.

11.5. Informed Consent and Human Participant Protection

A study informed consent form (ICF) will be provided for the Principal Investigator to prepare the informed consent documents to be used at their site. Updates to the template are to be communicated formally in writing from the Sponsor to the Investigator. The written informed consent document is to be prepared in the language(s) of the potential participant population. The ICF should meet regulatory, Sponsor's, institutional, and other applicable requirements, be approved by the IRB/IEC prior to use for consenting prospective participants, and be in the language understandable by the study participant or participant's legally acceptable representative (LAR).

Before a participant's participation in the study, the Investigator will obtain written informed consent from the participant or participant's LAR. A LAR is an individual or entity authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The use of a LAR will be limited to regions where it is allowed by local regulations.

The participant should not undergo any study-related procedures or assessments before participant's written informed consent has been obtained.

During the informed consent process, the Investigator/authorized designee will explain to the participant/LAR the nature of the study, including the potential risks and benefits, allow the participant/LAR sufficient time to ask any questions regarding the study, and answer all the questions. The participant/LAR will then sign and personally date the ICF. The authorized person obtaining the informed consent must also sign the ICF. A copy of the ICF must be provided to the participant/LAR. The original signed ICF will be retained in accordance with institutional policy and other applicable requirements, and a copy of the signed ICF will be provided to the participant/LAR. Study participants must be reconsented to the most current version of the ICF during their participation in the study.

The Investigator/designee will ask the participant/LAR if the participant has a primary care physician and if the participant agrees to have their primary care physician informed of the participant's participation in the clinical study. If the participant/LAR agrees to such notification, the Investigator/designee will inform the participant's primary care physician of the participant's participation in the clinical study. If the participant does not have a primary care physician and the Investigator will be acting in that capacity, it will be documented in the participant's medical record/source documents. The acquisition of informed consent and the participant's/LAR's

agreement or refusal of their notification of the primary care physician should be documented in the participant's medical records/source documents.

If a potential participant is illiterate or visually impaired and does not have a LAR, an impartial witness should be present during the entire informed consent process to read the ICF to the participant. Thereafter, both the participant and the witness must sign the ICF to attest that the participant understood the nature of the study, asked questions and received answers, and the informed consent was freely given.

11.6. Confidentiality

The Investigator must ensure that the participant's confidentiality is maintained for documents submitted to the Sponsor, including the following:

- Participants are to be identified by a unique participant identification number.
- The year of birth is to be documented in accordance with local laws and regulations.
- On the eCRF demographics page, in addition to the unique participant identification number, the participant's age at time of enrollment is to be included.
- For SAEs reported to the Sponsor, any source documentation provided (e.g., medical records, laboratory results) must have any participant identifier (e.g., participant name, initials, medical records number) fully redacted (i.e., blacked out) prior to transmission.

Documents that are not submitted to the Sponsor (e.g., signed ICFs) are to be kept in confidence by the Investigator, except as described below.

In compliance with the ICH GCP/CFR Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the participant's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the participant to permit such individuals to have access to their study-related records, including personal information.

11.7. Data Quality Assurance

- All participant data relating to the study will be recorded on an eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct, and will need to confirm that the blinding procedures have or have not been maintained for each participant by physically or electronically signing the eCRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered into the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations (CROs)).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

11.8. Study Monitoring

The Sponsor’s representative(s) are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., eCRFs and other pertinent data) provided that participant confidentiality is respected.

The Sponsor’s representative(s) are responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Sponsor’s representative(s) are to have access to participant medical records and other study-related records needed to verify the entries on the eCRFs.

The Investigator agrees to cooperate with the Sponsor's representative(s) to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

11.9. Audits and Inspections

As stipulated by ICH guidelines for GCP and 21 CFR §312.58, a representative of the Sponsor, the FDA, or other regulatory agencies may conduct periodic site audits or inspections. The Investigator or designee will provide these representatives with access to all requested materials, including eCRFs and supporting source documents. In addition, the Investigator or other qualified study site personnel are to be available to answer questions, hold interviews, and provide facility tours, if requested.

11.10. Data Collection and Handling

The Investigator is responsible for complying with the requirements for all assessments and data collection (including participants not receiving protocol-required therapies), as stipulated in the protocol for each participant in the study. For participants who withdraw prior to completion of all protocol-required visits and procedures, the Investigator may search publicly available records (where permitted) to ascertain survival status. This ensures that the data sets produced as an outcome of the study are as comprehensive as possible.

The Investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. Data collection will involve the use of an electronic data capture system, to which only authorized personnel will have access. The Investigator agrees to maintain accurate eCRFs or paper case report forms and source documentation as part of the case histories. The Sponsor will supply the eCRF, which is to be completed in English.

The Investigator or designee must enter all results collected during the clinical study into eCRFs. Guidelines for completion of eCRFs will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. Detailed instructions may be found in the other study specific documents.

All entries made on the eCRF must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated according to regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure participant confidentiality in accordance with the legal and

regulatory requirements applying to protected health information. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data must be retained for the time period dictated by the applicable regulatory requirements or by the Sponsor, whichever period is longer. No records may be destroyed without the written approval from the Sponsor.

11.11. Maintenance of Source Documents and Recordkeeping Requirements

As stipulated by ICH E6 GCP Consolidated Guidance Section 8 and 21 CFR §312.57, the Investigator or designee will maintain source documentation for this clinical study that documents the treatment and study course of participants.

Source documents are original documents, data, and records from which the participant's eCRF data are obtained. These include, but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities.

The Investigator must retain all essential documents for this clinical study until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. However, the Investigator may need to retain these documents for a longer period, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor representative will be responsible for informing the Investigator and study site regarding when they no longer need to retain these documents. No records may be destroyed without the written approval from the Sponsor.

11.12. Long-term Retention of Samples for Additional Future Research

Blood and urine specimens will be collected and stored for additional analyses. These samples will be retained for long-term storage by the Sponsor and described in the informed consent.

Any blood or urine sample collected according to the SoA (Table 1.1) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study participants. This includes testing to ensure that analytical methods produce reliable and valid data throughout the course of the study. It may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results will be stored in a secure database to ensure data integrity and control.

If permitted by local law and if informed consent is provided by the participant, the Sponsor may do additional testing on remaining samples (i.e., residual and back up) to investigate and better understand the disease and the dose response and/or prediction of response to the study drug. Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples may be retained for up to 20 years.

Since the evaluations are not expected to benefit the participant directly or to alter the participant's treatment course, the results of these exploratory studies are not placed in the participant's medical record and are not to be made available to the participant, members of the participant's family, the participant's personal physician, or other third parties, except as specified in the ICF.

The participant retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the participant, the Investigator is to provide the Sponsor with the required study and participant number so that any remaining blood samples and any other components from the samples can be located and destroyed.

Information collected from samples prior to the request for destruction will be retained by the Sponsor. The Sponsor is the exclusive owner of any data, discoveries, and derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the participant through the Investigator, at the end of the storage period or as appropriate (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the Sponsor owns the commercial product. The participant has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

11.13. Publication Policy

Institution and Investigator shall comply with any publication policy of Sponsor. The institution and Investigator agree not to publish or make any public disclosure of the results of this study or any study activities without the prior written consent of the Sponsor. As used herein, the term 'publish' shall include oral presentations, written abstracts, written poster presentations, and written manuscripts or reviews, etc. Should Institution or Investigator wish to publicly disclose the results of the study or otherwise disseminate information pertaining to the activities conducted pursuant to the study, Institution and Investigator shall provide Sponsor with an opportunity to review at least sixty (60) days prior to any proposed publication or other type of

disclosure before it is submitted or otherwise disclosed. The Institution and/or Investigator agrees to delete confidential information prior to submitting any manuscript and/or abstract for publication or presentation, or to defer publication or presentation of such manuscript and/or abstract at the request of Sponsor, to permit the filing of any desired patent applications by Sponsor. As part of a multi-center Study, Institution and Investigator agree that the first publication is to be a joint publication involving all the Study sites.

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13. APPENDICES

13.1. List of Abbreviations and Definition of Terms

The following abbreviations and terms are used in this study protocol.

Abbreviation/Term	Definition
ADL	Activities of daily living
AE	adverse event
AKD	APOL1 Kidney Disease
ALT	alanine transaminase
APOL1	apolipoprotein L1 gene
APOL1	apolipoprotein L1 protein
AST	aspartate transaminase
BMI	body mass index
bpm	beats per minute
CFR	Code of Federal Regulations
CI	confidence intervals
CKD	chronic kidney disease
CRF	Case Report Form
CTR	Clinical Trials Regulation
CYP3A4	Cytochrome P450 3A4
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESKD	End-stage kidney disease
ET	Early Termination
EU	European Union
FDA	Food and Drug Administration
FSGS	focal segmental glomerulosclerosis
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
HbA_{1C}	glycosylated hemoglobin
HbcAb	Hepatitis B core antibodies
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDPE	High-density polyethylene
HEENT	Head, eyes, ears, nose, and throat
Hg	mercury
HIV	human immunodeficiency virus
HRT	Hormone replacement therapy
IB	Investigator’s Brochure

Abbreviation/Term	Definition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive response technology
KDQOL-36	Kidney Disease Quality of Life Instrument Short Form Health Survey 36
LAR	legal authorized representative
LDL	Low-density lipoprotein
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Mineralocorticoid receptor antagonist
PCR	Polymerase chain reaction
PE	Physical examination
PK	pharmacokinetics
popPK	population pharmacokinetics
PRO	Patient reported outcome
QT	QT interval
QTcF	Corrected QT interval Fridericia
RAAS	Renin-angiotensin-aldosterone system
RNA	Ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGLT2	Sodium-glucose co-transporter 2
SMC	Safety Monitoring Committee
SOA	Schedule of Assessments
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TSH	Thyroid stimulating hormone
UACR	Urine albumin-creatinine ratio
ULN	upper limit of normal
UPCR	urine protein creatinine ratio
WOCBP	women of childbearing potential

13.2. Investigator's Agreement

Study Number: MZE829-201

Study Title:
An Open-Label Phase 2 Study to Evaluate the Safety, Tolerability, and Effect on Albuminuria of MZE829 in Adults with Proteinuric Chronic Kidney Disease and the *APOL1* High Risk Genotype

Protocol Version: 1.0

Protocol Version Date:

I have read the protocol and agree to conduct the study in accordance with the protocol and all applicable laws, regulations and guidelines, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the United States Code of Federal Regulations, the Directives of the European Union, the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

The study will not commence without the prior written approval of a properly constituted institutional review board (IRB) or independent ethics committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to participants.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____ _____

Signature Date

_____

Printed Name of Principal Investigator

13.3. SPONSOR'S SIGNATURE

Study Number: MZE829-201

Study Title:
An Open-Label Phase 2 Study to Evaluate the Safety, Tolerability, and Effect on Albuminuria of MZE829 in Adults with Proteinuric Chronic Kidney Disease and the *APOL1* High Risk Genotype

Protocol Version: 1.0

Protocol Version Date: 02 October 2024

The protocol has been reviewed and approved by me and is acceptable in its present form.

Signed by:
Neda Naderi
Signer Name: Neda Naderi
Signing Reason: I approve this document
Signing Time: 02-Oct-2024 | 09:41 PDT
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02-Oct-2024 | 09:41 PDT

Reviewed & Approved By Date

13.4. Contraceptive and Barrier Guidance

13.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman of childbearing potential is one who is ovulating, premenopausal, and not surgically sterile. A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

13.4.2. Contraception Guidance

Investigators should counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise these participants on the use of acceptable methods of contraception and will check for adherence during study visits. Participants must agree to use acceptable contraception during the study and for 30 days after the last dose of study drug.

Acceptable methods include:

- Complete abstinence from sexual intercourse if this is the participant's usual and preferred lifestyle.
- Dual method of contraception either: Condom with spermicide in conjunction with use of an intrauterine device (nonhormonal or hormonal), other long-acting reversible contraception (i.e., contraceptive implant or injection) or diaphragm
- Female partners of male participants should use a dual method of contraception which may include hormonal contraception as long as it is part of the dual method.

- Post-menopausal female participants do not require contraception if ≥12 months without menses and follicle-stimulating hormone (FSH) documented in post-menopausal range (≥40 IU/L).

All male participants with sexual partners of childbearing potential must use highly effective methods of birth control (i.e., condom or complete abstinence if this is part of the participants usual lifestyle) during their participation in the study, and subsequently for 90 days after the last administration of study drug.

Participants must agree to abstain from egg or sperm donation through 90 days after administration of the last dose of study drug.

13.5. Clinical Laboratory Tests

Clinical laboratory tests will be conducted by a central laboratory according to the time points specified in Table 1.1. Instructions for collection, windows for collection, preparation, handling, and shipping clinical laboratory specimens are provided in the Laboratory Manual for the study. The following analytes will be collected and may include but are not limited to those listed in Table 13.1.

Table 13.1 Clinical Laboratory Analytes

Chemistry	Hematology	Urine	Other Laboratory Measurements
Sodium Potassium Chloride Bicarbonate Magnesium Phosphate Total protein Albumin Calcium Glucose BUN Creatinine Cystatin C eGFR[1] Total bilirubin Direct bilirubin AST ALT Alkaline phosphatase CPK Amylase Lipase GGT	Hematocrit Hemoglobin RBC count WBC count Platelet count Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Mean platelet volume Red cell distribution width WBC differential [2] **Coagulation** PT aPTT INR	**Other Urine:** UACR UPCR **Urinalysis:** RBC WBC Leukocyte esterase Epithelial cells Glucose Protein Urine pH Ketones Bilirubin Nitrite Urine specific gravity	**Pregnancy Testing:** Serum or urine pregnancy test [3] FSH [4] **Other:** Fasting lipid profile[5] HbA_{1C} TSH HBs Ag, HBc Ab, HCV Ab (HCV RNA) HIV Ab[6] Cyclosporine[7] Tacrolimus[8]

[1] CKD-EPI creatinine-cystatin 2021 equation
[2] basophils, eosinophils, immature granulocytes, lymphocytes, monocytes, neutrophils [%, absolute count]
[3] for WOCBP
[4] postmenopausal women only
[5] total cholesterol, LDL, HDL, triglycerides
[6] if HCV Ab+, then check HCV RNA
[7] Only collect if participant on cyclosporine
[8] Only collect if participant on tacrolimus

13.6. Protocol Amendment Summary

Not applicable