Clinical Trial Protocol: C1973-203

Amendment 4, 20 December 2017

Study Title:	A Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Evaluate the Safety and Efficacy of IW-1973 in Patients with Type 2 Diabetes with Albuminuria Treated with Renin-Angiotensin System Inhibitors
Study Number:	C1973-203
Study Phase:	2
Product Name:	IW-1973 Tablets
Indication:	Diabetic Nephropathy
Investigators:	Multicenter
Sponsor:	Ironwood Pharmaceuticals, Inc.
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

	Date
Original Protocol:	11 April 2017
Amendment 1	05 May 2017
Amendment 2	30 May 2017
Amendment 3	03 August 2017
Amendment 4	20 December 2017

STUDY IDENTIFICATION

A summary of key study participants is provided in Table 1. All study contact details will be provided before the Site Initiation Visit.

Table 1. Key Study Participants

Role	Contact Information
Sponsor	Ironwood Pharmaceuticals, Inc. 301 Binney Street Cambridge, MA 02142 [redacted] (main office) (main fax) www.ironwoodpharma.com
Sponsor Contact	[redacted] Ironwood Pharmaceuticals, Inc. [redacted] (mobile) (fax) [redacted]
Clinical Laboratory	Covance, Inc. Central Laboratory Services 8211 SciCor Drive Indianapolis, IN 46214-2985 [redacted] (fax)
Contract Research Organization (CRO)	Covance, Inc. 210 Carnegie Center Princeton, NJ 08540-6233 [redacted] (fax)
CRO Medical Monitor	[redacted] Covance, Inc. 210 Carnegie Center Princeton, NJ 08540-6233 [redacted] (office) (mobile) [redacted]
Sponsor Medical Monitor	[redacted] Ironwood Pharmaceuticals, Inc. [redacted] (mobile) (fax) [redacted]
Safety Officer	[redacted] Ironwood Pharmaceuticals, Inc. [redacted] (office) (fax) [redacted]
Dedicated SAE Facsimile Number and Email	[redacted] (fax) [redacted]

SYNOPSIS

Sponsor: Ironwood Pharmaceuticals, Inc.

Name of Finished Product: IW-1973 Tablets

Name of Active Ingredient: IW-1973

Study Title:

A Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Evaluate the Safety and Efficacy of IW-1973 in Patients with Type 2 Diabetes with Albuminuria Treated with Renin-Angiotensin System Inhibitors

Study Number: C1973-203

Study Phase: 2

Study Objectives

Primary

- To assess the safety and tolerability of oral IW-1973 when administered daily for approximately 12 weeks to adult patients with type 2 diabetes mellitus with albuminuria who are on a stable regimen of renin-angiotensin system inhibitors
- To evaluate the effect of oral IW-1973 on renal function when administered daily for approximately 12 weeks to adult patients with type 2 diabetes mellitus with albuminuria who are on a stable regimen of renin-angiotensin system inhibitors

Study Design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group study will evaluate 2 dose levels of IW-1973 compared with placebo.

Study Population and Planned Number of Patients

The study population will consist of adult patients with type 2 diabetes mellitus, albuminuria, and impaired renal function. Patients must have been taking antihyperglycemic medications for at least 12 weeks and with their regimen stable (ie, drug and dose) for at least 28 days before the Randomization Visit. Additionally, patients must have been on a stable regimen of an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), for at least 28 days before the Randomization Visit. For details, see Eligibility Criteria.

Approximately 150 patients (50 per arm) will be stratified by baseline estimated glomerular filtration rate (eGFR) (ie, eGFR 30 to 45, >45 to 60, and >60 to 75 mL/min/1.73 m^2) and randomized 1:1:1 to daily 20 mg IW-1973, 40 mg IW-1973, or placebo. Patients who withdraw from the study after Randomization will not be replaced.

Test Product, Dose, and Mode of Administration

- 20 mg dose: Two IW-1973 Tablets, 10 mg administered orally
- 40 mg dose: Two IW-1973 Tablets, 20 mg administered orally

Reference Therapy, Dosage, and Mode of Administration

Placebo to match IW-1973 Tablets: Two tablets administered orally

Study Periods

The study will consist of 3 periods (see Study Schematic).

Screening Period: The Screening Period will begin with the signature of the informed consent form (ICF) at the Screening Visit and may last up to 45 days. At the Screening Visit (which can occur from Day -45 to Day -15), patients will undergo preliminary screening procedures to determine their eligibility. Eligible patients will return to the clinic for the Baseline Visit (Day 7 ±3) for baseline and eligibility assessments including 24-hour ambulatory blood pressure monitoring (ABPM). The end of the Screening Period will coincide with the beginning of the Treatment Period.

Treatment Period: The Treatment Period will begin on Day 1 at Randomization (there is no Day 0) and will end after the End of Treatment Visit on Day 87 (±3). Patients will be stratified by baseline eGFR (ie, eGFR 30 to 45, >45 to 60, and >60 to 75 mL/min/1.73 m^2) and randomized in a 1:1:1 ratio to receive 20 mg IW-1973, 40 mg IW-1973, or placebo for approximately 12 weeks.

Dosing on Days 1 to 7 (±1) will be BID (twice daily), morning and evening; dosing on Day 8 (±1) onward will be QD (once daily), 2 tablets in the morning.

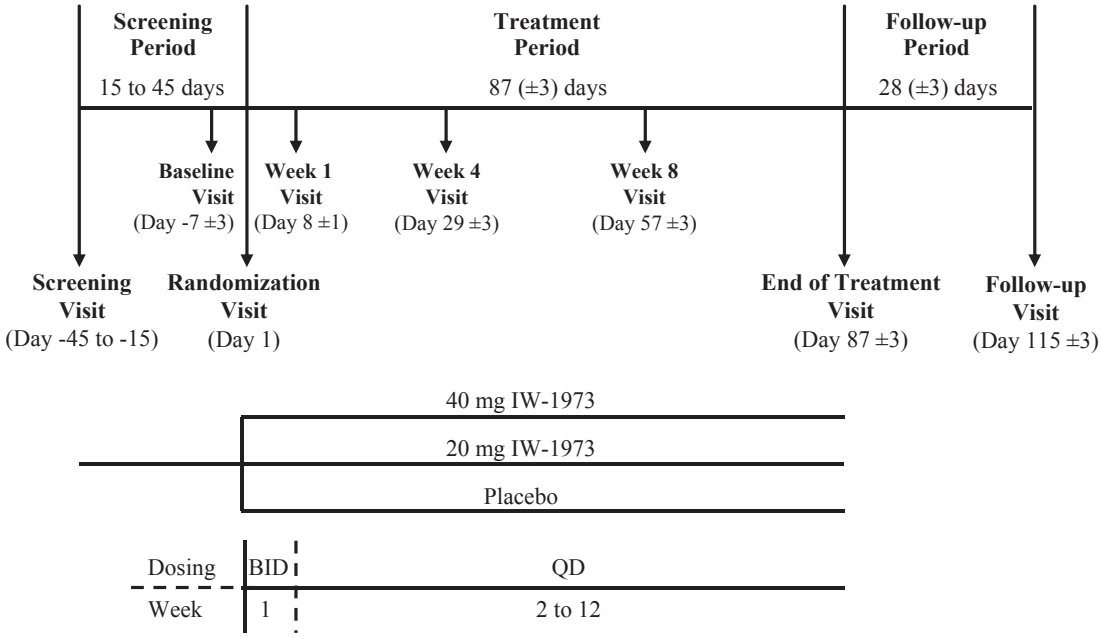
At the Randomization Visit on Day 1, patients will receive their morning dose of study drug in the clinic and will undergo safety, efficacy, and pharmacokinetic (PK) assessments, including blood and urine collections at prespecified times (Schedule of Events). Patients must stay in the clinic at least 6 hours postdose and may leave the clinic at the Investigator's discretion following all study procedures.

At the Week 1 Visit on Day 8 (±1), patients will return to the clinic and receive their first QD dose of study drug in the clinic. Patients will undergo safety, efficacy, and PK assessments, including blood and urine collections at prespecified times (see Schedule of Events). Patients must stay in the clinic at least 6 hours postdose and may leave the clinic at the Investigator's discretion following all study procedures.

At the Week 4 (Day 29 ±3), Week 8 (Day 57 ±3), and End of Treatment (Day 87 ±3) Visits, patients will return to the clinic for study drug administration; safety, efficacy, and PK assessments; and study drug supply, if applicable (see Schedule of Events).

Follow-up Period: The Follow-up Period will begin immediately after the End of Treatment Visit and will last for 28 (±3) days. At the Follow-up Visit on Day 115 (±3), patients will return to the clinic for final study assessments (see Schedule of Events).

Study Schematic



Study Drug Administration

During Week 1, patients will take study drug BID (2×/day), 1 tablet in the morning and 1 tablet approximately 12 hours later in the evening, preferably at approximately the same times each day. From the Week 1 Visit (Day 8 ±1) on, patients will take study drug QD (1×/day), 2 tablets in the morning, preferably at approximately the same time each day. Patients should take study drug with water, may take study drug with or without food, and, for QD dosing, may swallow tablets together, if desired. On study visit days, patients will receive their study drug dose in the clinic (on Randomization Day, patients will receive only their morning dose in the clinic). Study visits should be scheduled in the morning to accommodate regular dosing schedule.

Duration of Treatment

Patients will receive daily study drug for up to 90 days. Total patient participation will be 131 to 163 days, including the Screening, Treatment, and Follow-up Periods.

Dose Reduction

Per Investigator discretion, on a per-patient basis, dose may be reduced by half, ie, from 2 tablets daily to 1 tablet daily (in the morning). Each patient's dose may only be reduced once and may not be increased after reduction. Investigators should notify the Medical Monitor of all decisions to dose reduce on a per-patient basis.

Individual Stopping Criteria and Data Monitoring Committee Reviews

If any events included in the table below are reported during the study and are judged to be both study drug related and a serious adverse event (SAE; per causality and SAE definitions in the protocol), individual stopping criteria or Data Monitoring Committee (DMC) review will be triggered as described below. The inclusion of these AEs is based on the clinical experience with IW-1973, the prescribing information for riociguat, and the patient population for this study.

Treatment-emergent, Study Drug-related SAE Category	# of patients to trigger DMC review
Renal failure (eGFR <15 mL/min/1.73 m^2; dialysis or renal transplant indicated)	2
Spontaneous bleeding events (eg, hemoptysis, subarachnoid or subdural hemorrhage, hematemesis, hematochezia)	2
Symptomatic hypotension-related events (eg, syncope)	2

DMC=Data Monitoring Committee; eGFR=estimated glomerular filtration rate; SAE=serious adverse event

Individual

On an individual basis, a patient will be discontinued from study drug dosing if 1 or more SAEs from the table is reported. At the Investigator's or Sponsor's discretion, any AE(s) of concern can likewise be the basis for patient discontinuation from the trial.

Study

An independent DMC will review trial safety data. The DMC will comprise experts in cardiovascular and/or renal disease and/or diabetes and a biostatistician who have experience in clinical trials and are not involved in the conduct of this trial.

Periodic safety review meetings will be scheduled after 30 subjects have been randomized or 5 months after the first subject is randomized (whichever is earlier) and when approximately 1/3 and 2/3 of patients have completed or discontinued treatment. The committee will review accumulated AE data and recommend trial continuation, continuation with modification, or termination. For these periodic reviews, the DMC will be provided with summaries of AE and blood pressure data. If a safety/tolerability signal or concerning AE imbalance is identified at a review, the committee can request unblinding of the masked treatment groups and may request additional safety data (eg, vital signs, concomitant medications).

The DMC will also be required to perform an ad hoc review if SAEs from the same category in the above table are reported at the incidence indicated in the table shown above (eg, 2 patients with spontaneous bleeding SAEs). In this circumstance, the DMC will be provided with narrative descriptions and all relevant clinical supporting documentation related to the SAEs. Upon request, the unblinded treatment codes and dose the subjects with the SAEs received will be made available to the committee.

In addition to the periodic and ad hoc reviews, during the trial, committee members will be provided with blinded reports on all SAEs. The DMC or the Sponsor may request ad hoc meetings at any time.

Final decision-making authority regarding study conduct will rest with the Sponsor. Additional details will be provided in the DMC charter, which will be developed in collaboration with the DMC members and will be finalized before the first patient is randomized.

Study Assessments

All study assessments will be performed according to the Schedule of Events.

Clinical Laboratory Assessments

Complete blood count, serum chemistry panel, urinalysis, coagulation panel, UACR (urine albumin [mg/dL] / urine creatinine [g/dL]), estimated glomerular filtration rate (eGFR; by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation), hemoglobin A1c, Homeostatic Model Assessment to estimate insulin resistance (HOMA-IR), [redacted], urine pregnancy, and screens for hepatitis, human immunodeficiency virus, and drugs of abuse.

Hemodynamics and Vital Signs

Seated and standing BP (systolic and diastolic) and pulse measurements by automated office blood pressure (AOBP), ambulatory BP (systolic and diastolic) and pulse monitoring, respiratory rate, oral temperature. Orthostatic (standing minus seated) measurements will be calculated for BPs and pulse.

[redacted]

Other

Adverse-event recording, electrocardiograms (ECGs), physical examinations, concomitant medications.

Pharmacokinetics

Plasma IW-1973 concentrations will be measured.

[redacted]

Study Endpoints

Primary Endpoints

- Primary Safety: Incidence of TEAEs and study drug-related TEAEs
- Primary Efficacy: Change from baseline in UACR over Weeks 8 and 12

Statistical Methods

Sample Size Determination

Using an estimate of standard deviation of 0.67, a sample size of 40 patients per treatment group would provide approximately 80% power to detect a mean between-group difference of -0.376 units in change from baseline in log-transformed UACR over 12 weeks, with a one-sided significance level of 0.05 for at least 1 dose versus placebo comparison. This difference corresponds to a 31% between-group reduction of geometric mean change from baseline in UACR. Assuming a drop-out rate of 20%, approximately 150 patients will be randomly assigned in a 1:1:1 ratio (approximately 50 patients per treatment group) to 20 mg IW-1973, 40 mg IW-1973, or placebo.

Analysis Populations

Safety Population: The Safety Population will consist of all randomized patients who receive at least 1 dose of study drug. Patients in this population will be evaluated according to the treatment they actually received.

Intent-to-Treat (ITT) Population: The ITT Population will consist of all randomized patients who receive at least 1 dose of study drug. Patients in this population will be evaluated according to the treatment group they were assigned at Randomization.

PK Population: The PK Population will consist of all randomized patients who receive at least 1 dose of study drug and have at least 1 postdose PK parameter assessment.

Per-Protocol (PP) Population**:** The PP Population will consist of all ITT patients who did not have any major protocol deviations or dose reduction.

Efficacy Analyses

Corresponding with the primary efficacy objective of the trial, the primary inference for hypothesis testing is the treatment difference between the placebo group and the IW-1973 groups on the change from baseline in log UACR over Weeks 8 and 12. The primary efficacy analysis will be conducted using the ITT population using a mixed-effects model repeated measures (MMRM) analysis with change from baseline in log-transformed UACR as the response variable, treatment, site, visit, treatment-by-visit interaction, and baseline eGFR stratum as fixed effects, and baseline log UACR and baseline mean arterial pressure as covariates with unstructured as the variance-covariance structure. Treatment differences between the pooled IW-1973 dose groups and the placebo group will be estimated overall. The null hypothesis of the test will be interpreted as equality between the placebo and pooled treatment groups, and rejection of the null hypothesis as evidence that the pooled IW-1973 groups have a greater effect on lowering UACR than the placebo group. If the null hypothesis is rejected, the nature of these differences will be explored further by estimating the treatment differences between each IW-1973 dose group and the placebo group overall and at each assessment timepoint. Least square (LS) means, and LS mean differences between each

IW-1973 group and placebo, and their associated one-sided 95% confidence intervals will be calculated overall and for each assessment timepoint. The contrasts between each IW-1973 dose group and the placebo group at each assessment timepoint will be compared using a one-sided significance level of 0.05. If the treatment-by-visit interaction is significant at the 0.1 significance level, LS mean treatment differences relative to the previous visit will also be presented.

All change-from-baseline efficacy parameters will use the same MMRM model. Treatment group differences in the proportion of patients who achieved a 30% or 40% reduction in UACR from Baseline to Week 12 will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by Baseline eGFR stratum.

Summary statistics will be presented by treatment group for the biomarker parameters. Change from Baseline in these variables will also be presented, where applicable.

Safety Analyses

Adverse events (AEs) will be summarized by treatment group with preferred term (PT) under system organ class (SOC). Listings will be provided for pretreatment AEs, treatment-emergent AEs (TEAEs), severe AEs, study drug-related AEs, SAEs, and AEs leading to study discontinuation. Descriptive statistics will be provided for all safety parameters (electrocardiogram [ECG], vital signs, and clinical laboratory tests).

ECGs, vital signs, [redacted] and clinical laboratory tests will be summarized at each timepoint and listings will be provided for patients with abnormal values.

PK [redacted]

Summary statistics of IW-1973 plasma concentrations will be presented.

[redacted]

Interim Analysis

After at least one half of the subjects (N≥75) have completed the last visit, an interim analysis of unblinded efficacy data may be performed to assist with the planning of future studies. If performed, details regarding the interim analyses will be included in the SAP, along with updates to the data management plan as necessary. The independent statistician (who will not be involved in study data collection or interpretation) performing the interim analysis and Ironwood staff members, as identified in the SAP, may be unblinded. DMC reviews of safety data will be independent of this possible interim analysis of efficacy.

Final Date: 20 December 2017

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ABPM	ambulatory blood pressure monitoring
ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
ALT	alanine aminotransferase
AOBP	automated office blood pressure
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
[redacted]	[redacted]
BID	twice daily
BMI	body mass index (kg/m^2)
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
cGMP	cyclic guanosine 3', 5'-monophosphate
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	[redacted]
CMH	Cochran-Mantel-Haenszel
CYP3A	cytochrome P450 3A
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DN	diabetic nephropathy
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate ($mg/mL/1.73\ m^2$)
eNOS	endothelial nitric oxide synthase
[redacted]	[redacted]
ESRD	end-stage renal disease

Abbreviation	Term
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FPI	fasting plasma insulin
GCP	good clinical practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP	good laboratory practice
h	hour(s)
HbA1c	hemoglobin A1c (glycated hemoglobin)
HBsAG	hepatitis B surface antigen
HCV	hepatitis C virus
HDPE	high-density polyethylene
hERG	ether-à-go-go related gene
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment to quantify insulin resistance
HPF	high power field
HR	heart rate
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	intent to treat
IUD	intrauterine device
IWRS	interactive web response system
KDIGO	Kidney Disease: Improving Global Outcomes
[redacted]	[redacted]
kg	kilogram
kg/m^2	kilograms/meters squared (body mass index)
LDH	lactate dehydrogenase
L-NAME	L-nitroarginine methyl ester

Abbreviation	Term
LS	least square
m	minute
MAD	multiple ascending dose
MAP	mean arterial pressure
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEMS	Medication Event Monitoring System
mg	milligram
MI	myocardial infarction
mL	milliliter
mm Hg	millimeters of mercury
MMRM	mixed-effects model repeated measures
MPV	mean platelet volume
msec	millisecond
NO	nitric oxide
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PEG	polyethylene glycol
pd	postdose
[redacted]	[redacted]
PDE	phosphodiesterase
[redacted]	[redacted]
[redacted]	[redacted]
PID	patient identification
PK	pharmacokinetic(s)
PKG	protein kinase G
PP	per protocol
PRN	pro re nata [ie, as needed]

Abbreviation	Term
PT	preferred term
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
RAAS	renin-angiotensin-aldosterone system
SAE	serious adverse event
SBP	systolic blood pressure
Scr	serum creatinine
sGC	soluble guanylate cyclase
SOC	system organ class
tau	dosing interval
TEAE	treatment-emergent adverse event
UACR	urine albumin creatinine ratio

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

Patients must meet all of the following criteria to be eligible for enrollment in this study:

1. Patient has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Patient is an ambulatory male or female from 25 to 75 years old at the Screening Visit.
3. Patient has type 2 diabetes diagnosed by a physician or nurse practitioner ≥6 months before the Screening Visit, has been on ≥1 antihyperglycemic medication for ≥12 weeks preceding the Randomization Visit, and has been on a stable regimen (ie, same drug and same dose) of ≥1 antihyperglycemic medication for ≥28 days preceding the Randomization Visit. (Modification of short-acting insulin throughout the Screening Period will not affect eligibility.)
4. Patient has been on a stable regimen (ie, same drug and dose) of an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), for ≥28 days preceding the Randomization Visit and is expected to remain on their regimen through the Follow-up Visit. (Note: These medications may be modified during the study if medically necessary.)
5. If patient is on medications for hypertension, regimen (drug[s] and dose[s]) must be stable for ≥28 days preceding the Randomization Visit and is expected to remain stable through the Follow-up Visit. (Note: Medications for antihypertension may be modified during the study if medically necessary.)
6. Patient has the following:
   a. Estimated glomerular filtration rate (eGFR) 30 to 75 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (1) at the Screening and Baseline Visits
   b. Urine albumin creatinine ratio (UACR) >200 mg/g and <5000 mg/g at the Screening and Baseline Visits (at the Baseline Visit, the mean of the 2 first morning void tests will be used to determine eligibility)
   c. Serum albumin >3.0 g/dL at the Screening and Baseline Visits
   d. Hemoglobin A1c (HbA1c) ≤12% at the Screening and Baseline Visits
   e. Systolic blood pressure (BP) of 110 to 160 mm Hg based on the average of 3 seated automated office blood pressure (AOBP) measurements at the Screening and Baseline Visits
7. Female patient must be postmenopausal (no menses for ≥12 consecutive months); surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal sterilization [tie, clip, band, or burn]); must agree to completely abstain from heterosexual intercourse; or, if heterosexually

active, must agree to use 1 of the following methods of birth control from the date she signs the ICF until 60 days after the final dose of study drug:

   a. Progesterone implant or an intrauterine device (IUD)
   b. Combination of 2 highly effective birth control methods (eg, diaphragm with spermicide plus a condom, condom with spermicide plus a diaphragm or cervical cap, hormonal contraceptive [eg, oral and transdermal patch] plus a barrier method, partner with vasectomy [conducted ≥60 days before the Screening Visit or confirmed via sperm analysis] plus a hormone/barrier method).

8. Male patients must be surgically sterile by vasectomy (conducted ≥60 days before the Screening Visit or confirmed via sperm analysis), must agree to completely abstain from heterosexual intercourse, or, if heterosexually active, must agree to use a combination of 2 highly effective birth control methods (eg, condom with spermicide plus partner IUD, condom with spermicide plus a partner diaphragm or cervical cap, partner hormonal contraceptive [including progesterone implant] plus a barrier method, or postmenopausal partner [no menses for ≥1 year or 12 consecutive months] plus barrier method) from the Screening Visit through 60 days after the final dose of study drug.
9. Patient must agree not to make any major lifestyle (eg, diet, exercise) changes from the Screening Visit through the Follow-up Visit.

EXCLUSION CRITERIA

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Patient has a history of secondary hypertension (ie, renal artery stenosis, primary aldosteronism, or pheochromocytoma).
2. Patient has a body mass index (BMI) <20 or >45 kg/m^2 at the Screening Visit.
3. Patient has elevated (>1.5× the upper limit of normal as defined by laboratory) levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at the Screening or Baseline Visits.
4. Patient has hemoglobin level <9 g/dL at the Screening or Baseline Visit.
5. Patient has a 12-lead electrocardiogram (ECG) demonstrating severe bradycardia (heart rate <50 beats per minute) or QTcF is ≥450 msec for male patients or is ≥470 msec for female patients at the Screening or Baseline Visit. (NOTE: If on initial ECG, QTcF exceeds the limit, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the patient's eligibility at the Screening and Baseline Visits.)

6. Patient has any history of platelet dysfunction, hemophilia, von Willebrand disease, coagulation disorder, other bleeding diathesis, or significant, nontraumatic bleeding episodes, such as from a gastrointestinal (GI) source.
7. Patient has hepatic impairment defined as Child-Pugh A, B, C.
8. Patient has significant comorbidities (eg, malignancy, advanced liver disease, pulmonary hypertension, pulmonary fibrosis, lung disease requiring supplemental oxygen) or other significant conditions, including clinically significant abnormality(ies) in laboratory values, that, in the Investigator's opinion, would limit the patient's ability to complete or participate in this clinical study; has been hospitalized for cardiovascular, renal, or metabolic cause in the 3 months before the Screening Visit; or has a life expectancy of less than 1 year.
9. Patient has a history of a chronic GI disease, which in the Investigator's opinion could cause significant GI malabsorption.
10. Patient with known nondiabetic renal disease (eg, known polycystic kidney disease, focal segmental glomerulosclerosis) or nondiabetic etiology of renal function compromise. Concomitant hypertension-associated nephrosclerosis superimposed on diabetic nephropathy is acceptable.
11. Patient has had prior dialysis, renal transplant, or planned renal transplant. (Prior dialysis does not include transient, short-term dialysis indicated for an illness or during acute hospitalization. This "transient" dialysis must have occurred >3 months prior to Randomization, must have been <7 days in duration, and the current eGFR must be stable and within the eligible range [>30 mL/min/1.73 m^2].)
12. Patient has clinically active, symptomatic, or unstable coronary artery or heart disease within the 3 months before the Screening Visit, defined as 1 of the following:
    a. Hospitalization for myocardial infarction (MI), unstable angina, or heart failure
    b. New-onset angina with positive functional study or coronary angiogram revealing stenosis
    c. Coronary revascularization procedure
13. Patient has a documented history of New York Heart Association (NYHA) Class III or IV heart failure.(2) A prior brief/transient NYHA Class III or IV designation is not exclusionary provided that, at Randomization, the status is Class II or better and has been stable without deterioration into a more severe class for ≥3 months.
14. Patient has a positive hepatitis panel (hepatitis B surface antigen [HBsAg] and antihepatitis C virus [HCV]) or human immunodeficiency virus (HIV) antibody at the Screening Visit.
15. Patient has a history of viral or bacterial infection within 4 weeks of the Screening Visit.
16. Patient has had surgery with general anesthesia in the 12 weeks before the Screening Visit or has scheduled or planned surgery with general anesthesia during the study.

17. Patient has a history of active alcoholism or drug addiction during the year before the Screening Visit or, at the Screening Visit, has a positive drug screen for drugs not legally prescribed.
18. Patient is taking specific inhibitors of phosphodiesterase 5 (PDE5), nonspecific inhibitors of PDE5 (including dipyridamole and theophylline), any supplements for the treatment of erectile dysfunction, riociguat, or nitrates or nitric oxide (NO) donors in any form. These medications and supplements are prohibited from 7 days before Randomization through the duration of the study.

    Patient is taking strong cytochrome P450 3A (CYP3A) inhibitors, examples of which include azole antifungals, macrolide antibiotics, protease inhibitors, and diltiazem. These medications and excessive grapefruit intake are prohibited 14 days before Randomization through the duration of the trial.

    See Appendix 1 for a more detailed list of prohibited medications and supplements.
19. Female patient who may wish to become pregnant and/or plan to undergo egg donation or egg harvesting for current or future in vitro fertilization during the study and for at least 60 days after the final dose of study drug.
20. Male patient unwilling to refrain from sperm donation during the study and for at least 60 days after the final dose of study drug.
21. Patient has a history of clinically significant hypersensitivity or allergies to any of the inactive ingredients contained in the active or placebo drug products.
22. Patient has previously received IW-1973 in a study, or received an investigational drug during the 30 days or 5 half-lives of that investigational drug (whichever is longer) before the Screening Visit, or is planning to receive another investigational drug at any time during the study.
23. Female patient is pregnant or nursing at the Screening Visit. Nursing is not allowed from the Screening Visit through the Follow-up Visit.
24. Patient will not be able to adhere to the trial assessment schedule, or, in the clinical judgment of the Investigator, the patient is otherwise not suitable for the trial.

Note: Screening Visit assessments may take place over more than 1 day. Patients may be rescreened should they discontinue in the Screening Period due to visit window deviations or other administrative reasons. In addition, laboratory values or BPs that are outside the range specified in the protocol may be repeated to confirm eligibility during the Screening Period at the Investigator's discretion after consultation with the Medical Monitor.

SCHEDULE OF EVENTS

Visit Days → Study Procedure ↓	Screening Period		Treatment Period					Follow-up Period
	Screening Visit (Day -45 to -15)	Baseline Visit (Day -7 ±3)	Randomization Visit (Day 1)	Week 1 Visit (Day 8 ±1)	Week 4 Visit (Day 29 ±3)	Week 8 Visit (Day 57 ±3)	End of Treatment Visit (Day 87 ±3)	Follow-up Visit (Day 115 ±3)
ICF signed	X							
Demographics	X							
Medical history	X							
Prior & concomitant meds	X	X	X	X	X	X	X	X
Inclusion/exclusion evaluation/review	X	X	X					
Physical exam	X						X	
Hepatitis (HBsAg, HCV) & HIV screen	X							
Drug screen (a)	X							
Urine pregnancy test (b)	X	X	predose	predose	predose	predose	predose	X
Weight (W) & height (H)	W, H	W	W	W	W	W	W	W
12-lead ECG (c)	X	X					predose	
Respiratory rate and oral temperature	X		pre: 0 (≤30m) pd: 1h (±15m)	pre: 0 (≤30m) pd: 1h (±15m)			X	X
Seated pulse and BP (d)	X	X						
First-void urine for UACR (e)	X	preVisit	preVisit	preVisit	preVisit	preVisit	preVisit	preVisit
Issue UACR sample supplies	X	X	X	X	X	X	X	
Urinalysis sample (f)	X	X					predose	X
Serum chemistry, coagulation, hematology (f)	X	X	serum creatinine & glucose only pre: 0 (≤30m)	serum creatinine & glucose only pre: 0 (≤30m)	pre: 0 (≤30m)	serum creatinine & glucose only pre: 0 (≤30m)	pre: 0 (≤30m)	X
Hemoglobin A1c (f)	X	X		pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m)	X
Adverse event evaluations	X	X	X	X	X	X	X	X

Visit Days → Study Procedure ↓	Screening Period		Treatment Period					Follow-up Period
	Screening Visit (Day -45 to -15)	Baseline Visit (Day -7 ±3)	Randomization Visit (Day 1)	Week 1 Visit (Day 8 ±1)	Week 4 Visit (Day 29 ±3)	Week 8 Visit (Day 57 ±3)	End of Treatment Visit (Day 87 ±3)	Follow-up Visit (Day 115 ±3)
Fasting plasma glucose & insulin (f)		X		pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m)	
Urine cotinine			predose					
24- or 12-h ABPM (h)		X (24h)			X (12h)	X (12h)	X (24h)	
Return of ABPM monitor			X			X	X	X
Orthostatic (seated to standing) pulse and BP (i)			pre: 0 (≤30m) pd: 1,2,4,6h (±15m)	pre: 0 (≤30m) pd: 1,2,4,6h (±15m)	pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m)	X
Randomization			X					
MEMS instruction/review			X	X	X	X		
Study drug dispensed			X		X	X		
In-clinic study drug administration (j)			X	X	X	X	X	
Study drug return (k)				X	X	X	X	
Pharmacokinetic blood samples			pre: 0 (≤30m) pd: 1,3,6h (±15m)	pre: 0 (≤30m) pd: 1,3,6h (±15m)	pre: 0 (≤30m)	pre: 0 (≤30m)	pre: 0 (≤30m) pd: 3h (±15m)	X
Study completion								X

ABPM=ambulatory blood pressure monitoring; automated office blood pressure (AOBP); BP=blood pressure; cGMP=cyclic guanosine monophosphate; ECG=electrocardiogram; [redacted]; h=hour(s); H=height; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; KDQOL-SF=Kidney Disease Quality of Life–Short Form; m=minute(s); MEMS=Medication Event Monitoring System; pd=postdose; [redacted] pre=predose; [redacted] UACR=urine albumin creatinine ratio; W=weight

a. Urine drug screen for selected drugs of abuse
b. For female patients, a negative pregnancy test (by urine dipstick) must be documented at all study visits and confirmed negative before dosing when applicable. Female patients who are postmenopausal (no menses for ≥12 consecutive months) or surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal sterilization [tie, clip, band, or burn]) do not have to have a urine pregnancy test. Patients should be reminded of birth control requirements.
c. Patients must be supine for ≥5 m before the ECG recording (Note: If on initial ECG, QTcF is ≥450 msec for male patients or is ≥470 msec for female patients, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the patient's eligibility).
d. Seated BP will be the average of 3 measurements obtained by AOBP at 2-m intervals after the patient has been sitting quietly for ≥5 m.
e. At the Screening Visit, single urine sample, which may not be first void; thereafter, 2 first-void urine samples collected on the 2 consecutive mornings before each scheduled visit. Patients will be supplied with specimen collection supplies at the preceding study visit.
f. Except for the Screening Visit, patients must fast for ≥8 h before predose sample collection. [redacted]
g. [redacted]
h. Patients will begin using the ABPM monitor at the clinic visit before dosing, where applicable, will wear it for ≥12 or 24 h, and will return the monitor to the clinic. Baseline Visit: At least 65% patient compliance is preferred, with no more than 10 missed readings during the day (7 am – 10 pm) and/or 3 missed readings at night (10:30 pm – 6:30 am), and no more than 6 missed readings in succession. (If the ABPM assessment does not meet these criteria, the medical monitor must be contacted PRIOR to randomizing the subject.)
i. Patient must sit quietly for ≥5 m before seated BP and pulse measurements are taken by AOBP, and then assume standing position for 30 to 60 seconds before standing BP and pulse measurements are taken. At End of Treatment Visit, seated predose BP will be the average of 3 measurements. When applicable, BP and pulse measurements will be obtained before blood draws and before study drug administration.
j. Study drug will be administered in the clinic on study visit days after predose assessments (Day 1, morning dose only). Patients should take study drug with water, may take with or without food, and for QD dosing (Week 1 Visit onward), may swallow 2 tablets together.
k. At the Week 1 Visit, patients will bring the study drug bottles dispensed on Day 1 to the clinic. MEMSCaps will be read, and the subject will be administered their Day 8 (±1) study drug dose in the clinic from the Day 1 bottles. The subject will continue to dose from the Day 1 bottles until they return for the Week 4 Visit.

1. INTRODUCTION

1.1 DIABETIC NEPHROPATHY

Diabetic nephropathy (DN), also known as diabetic kidney disease, is a common and serious complication of Type 1 and Type 2 diabetes mellitus and is characterized by pathological urinary albumin excretion, glomerular lesions, hypertension, and progressive loss of renal function.(3-5) Diagnosis is based on the presence of albuminuria (urine albumin creatinine ratio [UACR] >30 mg/g) and/or reduced estimated glomerular filtration rate (eGFR <90 mL/min/1.73 m^2) in patients with diabetes.(6) The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline (7) provides a kidney disease classification system and risk-stratifies patients based on levels of albuminuria and eGFR.

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States and other industrialized countries.(8,9) Diabetic nephropathy is also a major risk factor for cardiovascular disease as well as the single strongest predictor of mortality in patients with diabetes. An estimated 20% to 40% of patients with diabetes develop DN, with higher rates seen in middle-aged African Americans, Hispanics, and American Indians.(3,9) The prevalence of DN is increasing in the United States and globally with the increasing prevalence of diabetes.(9,10) The estimated number of persons in the United States with DN has increased from 3.9 million in 1988-1994 to 6.9 million in 2005-2008.(9)

Current first-line therapy for DN includes glycemic and blood pressure (BP) control and treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors: angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs).(3,4,6) RAAS inhibitors have been shown in clinical trials to reduce albuminuria and delay progression to ESRD and renal replacement therapy. However, the current standard of care does not prevent progression to ESRD, and the prevalence of DN has not declined with increased use of RAAS inhibitors and glucose-lowering medications.(9) The burden of caring for DN patients is extremely high due to the cost of treating ESRD as well as the strong association of DN with cardiovascular disease.(3) New therapies for DN are urgently needed.

1.2 THE NO-SGC-CGMP PATHWAY

Although the pathogenesis of DN is not completely understood, nitric oxide (NO) deficiency resulting from endothelial dysfunction is believed to play an important role.(11,12) In the healthy endothelium, the enzyme endothelial nitric oxide synthase (eNOS) catalyzes the conversion of L-arginine to NO. Locally generated NO stimulates soluble guanylate cyclase (sGC) to produce cyclic guanosine 3', 5'-monophosphate (cGMP), which acts on downstream targets including cGMP-dependent protein kinases (PKG), phosphodiesterases, and ion channels. NO-sGC-cGMP signaling promotes the relaxation of vascular smooth muscles cells and blocks endothelial cell activation and cytokine-induced injury in the kidney and elsewhere.(13) Intracellular cGMP also plays a role in processes that affect vascular proliferation (14), fibrosis (15,16), and inflammation.(17)

Diabetes patients show evidence of vascular endothelial dysfunction (18,19), and endothelial dysfunction promotes the progression of DN.(18) In patients with diabetes, endothelial NO bioavailability may be reduced by several mechanisms, including the generation of advanced glycation end-products, increased uric acid levels, increased levels of the eNOS inhibitor asymmetric dimethyl arginine, and increased oxidative stress.(11,12) High levels of glucose also induce the uncoupling of endothelial eNOS, resulting in decreased production of NO and increased production of superoxide. Superoxide can react with NO to produce peroxynitrite, further reducing NO bioavailability.

Animal model data suggest that NO deficiency plays a role in the pathogenesis of DN. Animal models of diabetes generally produce only early signs of kidney disease, but models of diabetes in the context of NO deficiency, such as the diabetic eNOS-knockout mouse model, show features more consistent with human DN, including nephrotic albuminuria, systemic hypertension, glomerular hypertension, tubulointerstitial damage, and glomerular ischemia and fibrosis.(11,20) In a rat model of obstructive nephropathy, treatment with the eNOS inhibitor L-nitroarginine methyl ester (L-NAME) resulted in increased renal fibrosis and apoptosis, reduced blood flow, and reduced filtration rates.(21) In another study using a sub-total nephrectomized rat model, eNOS inhibition by L-NAME resulted in impaired autoregulation of glomerular blood flow and increased renal injury.(22) Recently, Ueda et al (23) showed that endothelial NO is required for mitochondrial integrity in cultured podocytes. They also showed

that eNOS-knockout mice exhibit morphologic evidence of podocyte damage and develop oxidative stress associated with podocyte mitochondrial abnormalities. Overall, these data indicate that NO deficiency may be involved in producing renal damage by multiple mechanisms.

1.3 RATIONALE FOR USE OF AN SGC STIMULATOR IN DIABETIC NEPHROPATHY

Pharmacologic stimulation of sGC could offer a new approach for treating DN.(24,25) By increasing intracellular cGMP levels, sGC stimulators could potentially compensate for deficient NO bioavailability and thereby improve renal endothelial function and attenuate or prevent renal inflammation and fibrosis. Both sGC stimulators (which act synergistically with NO on the native, heme-containing form of the enzyme) and sGC activators (which act independently of NO on the heme-free form of the enzyme) have shown activity in multiple animal models of DN and other kidney diseases.(24) For example, in the diabetic eNOS-knockout mouse model of DN, treatment with the sGC stimulator riociguat in combination with the ARB telmisartan reduced systemic BP, albuminuria, and renal interstitial fibrosis.(26) In another set of studies,(27) riociguat was found to reduce mortality, normalize systemic BP, and reduce renal damage in low- and high-renin models of hypertension in the rat. Furthermore, the sGC activator cinaciguat reversed impaired autoregulation of renal blood flow induced by L-NAME in rats.(28) In a recent study using the obese ZSF1 rat model of Type 2 DN, treatment with the sGC activator BI 703704 resulted in significant reductions in albuminuria, glomerulosclerosis, and interstitial fibrosis, despite only modest reductions in systemic BP. Together, these nonclinical data provide the rationale for the investigation of sGC stimulators in patients with DN.

1.4 IW-1973 BACKGROUND

For a detailed description of the properties of IW-1973 and the results of the nonclinical and clinical studies conducted thus far, please refer to the most recent Investigator's Brochure.

1.4.1 Nonclinical Studies in Support of DN

IW-1973 is a potent and selective stimulator of sGC. In vitro, IW-1973 was shown to sensitize sGC to endogenous NO, and to directly stimulate sGC independently of NO. IW-1973 also potently relaxed precontracted human subcutaneous resistance arteries ex vivo. Oral

administration of IW-1973 to normotensive and spontaneously hypertensive rats and to normotensive dogs was shown to elicit a dose-dependent decrease in systolic, diastolic, and mean arterial BP, as well as a concomitant rise in heart rate.

IW-1973 stimulated purified human recombinant sGC to produce cGMP in a concentration-responsive manner, both in the absence and in the presence of an NO donor. The EC_{50} value was 267 nM in the presence of NO; the production of cGMP was lower in the absence of NO than in the presence of NO. In vitro, IW-1973 showed anti-fibrotic and anti-inflammatory effects in human renal proximal tubular cells. In the Dahl salt-sensitive rat model of hypertension and end-organ damage, orally administered IW-1973 demonstrated a dose-dependent (1-10 mg/kg/day) reduction in BP that was sustained over a 6-week treatment period. Treatment with IW-1973 also decreased albuminuria and attenuated levels of serum biomarkers known to be involved in inflammatory and fibrotic processes. Histopathological analysis of the kidneys showed a clear reduction at all doses in glomerulosclerosis, interstitial fibrosis, vascular alterations and interstitial inflammation. Additionally, in this model, IW-1973 demonstrated significant reductions in heart hypertrophy and reduced levels of plasma N-terminal pro B-type natriuretic peptide (NT-proBNP), a marker of cardiac injury. In the ZSF1 rat model of DN, IW-1973 (10 mg/kg/day) reduced mean arterial pressure (MAP), kidney and liver weight gain, urine volume, proteinuria, and fasting glucose in comparison with untreated controls. Similar effects were observed with IW-1973 in combination with enalapril. These results support investigation of IW-1973 as a potential treatment for DN.

2. STUDY OBJECTIVES

Primary

- To assess the safety and tolerability of oral IW-1973 when administered daily for approximately 12 weeks to adult patients with type 2 diabetes mellitus with albuminuria who are on a stable regimen of renin-angiotensin system inhibitors
- To evaluate the effect of oral IW-1973 on renal function when administered daily for approximately 12 weeks to adult patients with type 2 diabetes mellitus with albuminuria who are on a stable regimen of renin-angiotensin system inhibitors

Exploratory

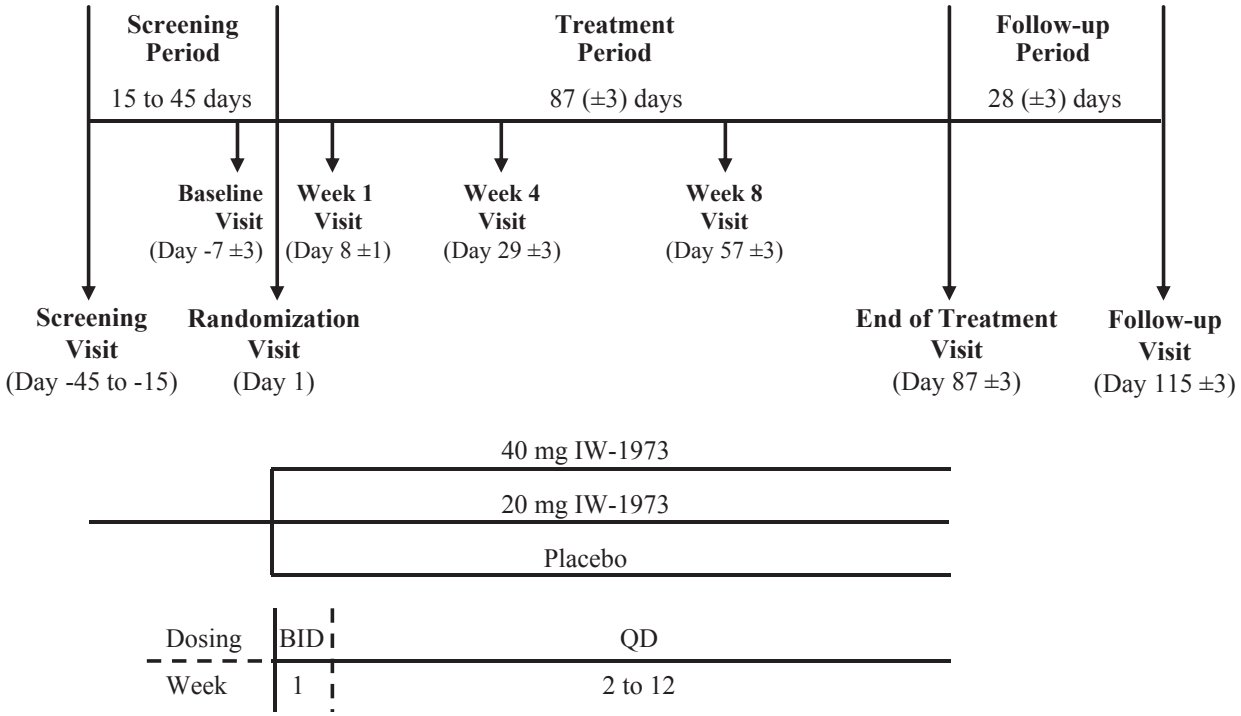
3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study will evaluate 2 dose levels of IW-1973 compared with placebo. The study will enroll approximately 150 patients with type 2 diabetes mellitus and albuminuria who are on a steady regimen of a RAAS inhibitor, such as an ACEi or an ARB (see Eligibility Criteria). Patients will be stratified by baseline eGFR (ie, eGFR 30 to 45, >45 to 60, and >60 to 75 mL/min/1.73 m^2) and randomized in a 1:1:1 ratio to receive daily 20 mg IW-1973 Tablets, 40 mg IW-1973 Tablets, or placebo tablets for daily for approximately 12 weeks.

Each patient will progress through 3 distinct study periods (Figure 1).

Figure 1. Study Schematic



Screening Period: The Screening Period will begin with the signature of the informed consent form (ICF) at the Screening Visit and may last up to 45 days. At the Screening Visit (which can occur from Day -45 to Day -15), patients will undergo preliminary screening procedures to determine their eligibility. Eligible patients will return to the clinic for the Baseline Visit (Day -7 ±3) for baseline and eligibility assessments including 24-hour ambulatory blood pressure

monitoring (ABPM). The end of the Screening Period will coincide with the beginning of the Treatment Period.

Treatment Period: The Treatment Period will begin on Day 1 at Randomization and will end after the End of Treatment Visit on Day 87 (±3). Patients will be stratified by baseline eGFR (ie, eGFR 30 to 45, >45 to 60, and >60 to 75 mL/min/1.73 m^2) and randomized in a 1:1:1 ratio to receive daily 20 mg IW-1973, 40 mg IW-1973, or placebo daily for approximately 12 weeks; each daily dose will comprise 2 tablets. Dosing on Days 1 to 7 (±1) will be BID (twice daily), 1 tablet in the morning and 1 tablet approximately 12 hours later in the evening; dosing on Day 8 (±1) onward will be QD (once daily), 2 tablets in the morning.

At the Randomization Visit on Day 1, patients will receive their morning dose of study drug in the clinic and will undergo safety, efficacy, and PK assessments, including blood and urine collections at prespecified times (see Schedule of Events). Patients must stay in the clinic at least 6 hours postdose and may leave the clinic at the Investigator's discretion following all study procedures.

At the Week 1 Visit on Day 8 (±1), patients will return to the clinic and receive their first QD dose of study drug in the clinic. Patients will undergo safety, efficacy, and PK assessments, including blood and urine collections at prespecified times (see Schedule of Events). Patients must stay in the clinic at least 6 hours postdose and may leave the clinic at the Investigator's discretion following all study procedures.

At the Week 4 (Day 29 ±3), Week 8 (Day 57 ±3), and End of Treatment (Day 87 ±3) Visits, patients will return to the clinic for study drug administration; safety, efficacy, and PK assessments; and study drug, if applicable (see Schedule of Events).

Follow-up Period: The Follow-up Period will begin immediately after the End of Treatment Visit and will last for 28 (±3) days. At the Follow-up Visit on Day 115 (±3), patients will return to the clinic for final study assessments (see Schedule of Events).

3.2 DISCUSSION OF STUDY DESIGN AND CONTROL GROUP

A double-blind, placebo-controlled, randomized study design was chosen to provide comparable treatment groups and minimal chance of selection or investigator bias in accordance with the concepts in ICH E10, Choice of Control Groups and Related Issues in Clinical Trials (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2001). Placebo was chosen as the control so that the rate of spontaneously occurring AEs can be determined and to reduce the potential for bias in the reporting of AEs.

This study has a 12-week Treatment Period to compare the effects of IW-1973 to a placebo control. The treatment duration of 12 weeks is sufficient in length to observe changes in UACR and hemodynamic measures, and in addition to establish a difference in treatment effect between IW-1973 and placebo in these measures.(29)

Patients will be stratified by baseline eGFR to minimize the potential impact of baseline disease severity imbalance between treatment groups. Individual stopping criteria and Data Monitoring Committee safety reviews (Section 3.7) have been established to ensure that dosing will stop should a safety signal be detected. Patients will have a Follow-up Visit 28 (±3) days after the final dose of study drug to determine if any AEs have developed and if any AEs that were ongoing at the time of Discharge have resolved. In addition, at the Follow-up Visit as well at each study visit, female patients of reproductive potential will have a pregnancy test.

3.3 STUDY DURATION

Patients will receive daily oral study drug for up to 90 days. Total patient participation will be 131 to 163 days, including the Screening, Treatment, and Follow-up Periods.

3.4 STUDY POPULATION

3.4.1 Study Population Description

This study will enroll approximately 150 adult patients with type 2 diabetes mellitus and albuminuria at multiple sites in the US. Patients must have type 2 diabetes diagnosed by a physician or nurse practitioner no fewer than 6 months before the Screening Visit and must have been taking at least 1 medication specifically for control of glycemia, either oral or injectable, for

at least 12 weeks before the Randomization Visit and have been on a stable regimen (ie, same drug and same dose) for at least 28 days preceding the Randomization Visit. To be eligible, patients must have a hemoglobin A1c (HbA1c) level of ≤12%. At Screening, patients must also have an eGFR of 30 to 75 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine equation), UACR >200 and <5000 mg/g, and serum albumin >3.0 g/dL. In addition, patients must have been on a stable regimen (ie, same drug and dose) of an ACEi or an ARB, for at least 28 days before the Randomization Visit. Patients must have systolic BP of 110 to 160 mm Hg, and if taking medications for hypertension, regimen must be stable for at least 28 days preceding the Randomization Visit. Patients with known nondiabetic renal disease are not eligible.

Refer to Eligibility Criteria for full inclusion and exclusion criteria.

3.4.2 Removal of Patients from Therapy or Assessment

A premature discontinuation will occur when a patient who has signed the ICF and has been randomized ceases participation in the study.

A patient will be considered to have completed the study after completing the Follow-up Visit.

Patients will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator may remove a patient from the study if, in the Investigator's opinion, it is not in the best interest of the patient to continue the study. Patients may also be discontinued from the study by the Investigator or the Sponsor at any time for any reason, including the following:

- Adverse event(s)
- Protocol violation, including lack of compliance
- Lost to follow-up (every effort should be made to contact the patient; a certified letter should be sent)
- Withdrawal of consent (attempts should be made to determine the reason for the patient withdrawing consent if possible)
- Study termination by the Sponsor
- Other reasons (eg, administrative reasons or pregnancy)

The Sponsor will be notified of any patient discontinuation after Randomization. The date the patient is withdrawn from the study and the reason for discontinuation will be recorded on the study termination form of the electronic case report form (eCRF). Patients who discontinue from the study will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator to have stabilized.

If a patient does not return for a scheduled visit, the study center should contact the patient. An effort should be made to contact the patient, including sending a certified letter. In every case, the patient outcome, including lost to follow-up information, will be documented.

3.4.3 Early Termination Procedures

Patients who prematurely discontinue study drug for any reason should complete the assessments required at the End of Treatment Visit at the time of their discontinuation and should complete the Follow-up Visit 28 ±3 days after their final dose of study drug.

3.4.4 Replacement Procedures

Patients withdrawing from the study after Randomization will not be replaced.

3.5 STUDY TREATMENT(S)

3.5.1 Description of Treatment(s)

3.5.1.1 Investigational Product

IW-1973 Tablets are 10 mg or 20 mg oral tablets and are white and round in appearance.

3.5.1.2 Placebo

Placebo will match IW-1973 Tablets in appearance. The number of placebo tablets administered will match the number of tablets used for the IW-1973 treatment arm.

3.5.1.3 Packaging and Labeling

IW-1973 and placebo tablets will be provided by PCI Pharma Services (Rockford, IL) on behalf of Ironwood in 100cc high-density polyethylene (HDPE) induction-sealed bottles, 35 tablets per bottle, containing two 1-gram mole desiccant sieves and 4-6 inches of purified polyester coil.

The bottles will be compatible with a Medication Event Monitor System cap (MEMSCap™, WestRock®; Sion, Switzerland) that will be interchanged at the clinical site.

3.5.1.4 Dosage

Table 2 summarizes the dosage and dosing regimen for each treatment arm by Treatment Period week.

Table 2. Dosage by Week

Dose	Week 1, BID Dosing	Weeks 2 through 12, QD Dosing
20 mg	one 10-mg IW-1973 Tablet, orally twice daily	two 10-mg IW-1973 Tablets, orally once daily
40 mg	one 20-mg IW-1973 Tablet, orally twice daily	two 20-mg IW-1973 Tablets, orally once daily
Placebo	one matching placebo tablet, orally twice daily	two matching placebo tablets, orally once daily

BID=twice daily; QD=once daily

3.5.1.5 Storage and Accountability

IW-1973 Tablet and placebo to match must be stored under refrigerated conditions, 2° to 8°C (36° to 46°F) at the clinical sites. Any deviation from these storage conditions must be reported to Ironwood, and use of the study drug suspended until re-authorization has been provided by Ironwood. If a temperature excursion occurs above 8°C (46°F) up to a maximum temperature of 30°C (86°F) for not longer than 24 hours, the clinical site is authorized by Ironwood Pharmaceuticals to continue using the study drug after documentation of the excursion has been completed. If a temperature excursion occurs below 2°C or above 30°C (<36°F or >86°F) for any amount of time, or from 8°C to 30°C for periods longer than 24 hours, the use of the study drug is suspended until authorization for its continued use has been provided by Ironwood.

Once distributed to patients, patients will be instructed to keep the bottles at room temperature (15°C to 30°C/59°F to 86°F).

The Investigator must ensure that the receipt and use of all study drug supplied is recorded. All study drug supplies must be retained in a locked room that may only be accessed by the pharmacist, Investigator, or other duly designated persons. Study drug must not be used outside the context of this protocol, and under no circumstances should the Investigator or study center

personnel allow the supplies to be used other than as directed by this protocol without prior authorization from Ironwood.

Study drug accountability should be performed at the medication level. Patients will be instructed to return all unused study drug to the study center. All returned and unused study drug must be retained at the site. At the end of the study, a complete reconciliation of the study drug supplies will be performed. A copy of the final Drug Accountability Log will be provided to Ironwood, or accountability will be completed electronically within the product returns module of an interactive response technology system when available. All unused and reconciled drug supplies will be returned to PCI Pharma Services or destroyed according to standard institutional policy or per written instruction from Ironwood should an alternate disposition be requested. No study drug is to be destroyed without prior written permission of Ironwood. A copy of the Certificate of Destruction or equivalent shall be provided to Ironwood once available.

In addition, study drug will be dispensed to patients in bottles equipped with a MEMSCap, which will record the dates and times the bottle is opened and closed.

3.5.2 Method of Assigning Patients to Treatment Groups

Approximately 150 patients who meet all of the inclusion criteria and none of the exclusion criteria will be stratified by Baseline eGFR (ie, eGFR 30 to 45, >45 to 60, and >60 to 75 mL/min/1.73 m^2) and randomized 1:1:1 to 20 mg IW-1973, 40 mg IW-1973, or placebo at the Randomization Visit on Day 1.

Patients will be randomized through central randomization. The computer-generated randomization schedule will be prepared by an independent statistician not otherwise associated with the study.

Patients and Investigators will be blinded to treatment assignments in this study (see Section 3.5.6 for more details on blinding in this study).

3.5.3 Selection of Dosage in the Study

This Phase 2 study will evaluate 2 dose levels of oral IW-1973 administered daily for 12 weeks: 20 mg and 40 mg. In the Phase 1b MAD study (ICP-1973-102), 40 mg IW-1973 was considered

adequately tolerated and produced pharmacodynamic (PD) effects (including reduced BP and increased plasma cGMP levels). It was therefore chosen as the high dose for evaluation in this patient population. For comparison to 40 mg, 20 mg IW-1973 was chosen for evaluation because it demonstrated pharmacodynamic effects following 2 weeks of dosing in the MAD study and was associated with a lower incidence of AEs. The plasma concentrations achieved in humans at the 20- and 40-mg dose levels were within the range associated with renal efficacy in the Dahl salt-sensitive rat model (reduced albuminuria, attenuated kidney weight gain, and improved renal histology).

3.5.4 Selection and Timing of Dose for Each Patient and Dose Reduction

3.5.4.1 Study Drug Administration

During Week 1, all patients will take study drug BID (2×/day), 1 tablet in the morning and 1 tablet approximately 12 hours later in the evening, preferably at approximately the same times each day. From Day 8 (±1) on, patients will take study drug QD (1×/day), 2 tablets in the morning, preferably at approximately the same time each day. Patients should take study drug with water, may take study drug with or without food, and, for QD dosing, may swallow tablets together, if desired. On study visit days, study drug will be administered in the clinic after predose BP/pulse measurements and blood/urine sampling (on Randomization Day, patients will receive only their morning dose in the clinic); therefore, study visits should be scheduled in the morning to accommodate patients' regular dosing schedules.

3.5.4.2 Dose Reduction

Per Investigator discretion, on a per-patient basis, dose may be reduced by half, ie, from 2 tablets daily to 1 tablet daily (in the morning). Each patient's dose may only be reduced once and may not be increased after reduction. Investigators should notify the Medical Monitor of all decisions to dose reduce on a per-patient basis.

3.5.5 Treatment Compliance

The appropriate amount of study drug will be dispensed to patients in prelabeled bottles at the Randomization, Week 1, Week 4, and Week 8 Visits. Patients will be asked to return all bottles

(including unused tablets) at the Week 1, Week 4, Week 8, and End of Treatment Visits for assessment of compliance with the dosing regimen.

Treatment compliance will be based on count of pills.

3.5.6 Blinding

This study is double blind and placebo controlled. The investigational product and placebo will be identical oral tablets.

Unblinding of a patient's treatment assignment is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is necessary for the proper handling of the patient. Except in a medical emergency, the Investigator and study center staff will remain blinded during the conduct of the study and until, at a minimum, all discrepancies in the clinical database are resolved (ie, at the time of the database lock). Individual patient treatment assignment unblinding is available to the Investigator through the interactive web response system (IWRS) in the event of an emergency. The Investigator should make all reasonable efforts to notify and discuss the circumstances requiring unblinding with the Medical Monitor or designee in advance of breaking the blind. If the treatment blind is broken, the reason and the date should be recorded and signed by the Investigator and information regarding the unblinding should be submitted as soon as possible to the Sponsor. If the Investigator is unblinded to the treatment assignment of a patient, the patient will be immediately withdrawn from study drug dosing and should follow early termination procedures (Section 3.4.3).

The Sponsor may also break the blind in circumstances where unblinding is necessary for the safety of the patients.

To allow ongoing safety monitoring during the conduct of the study, members of an external DMC will review summaries of AE data by treatment groups randomly masked as A, B, and C and may request unblinded safety data. Please refer to Section 5.13 for more details.

3.5.7 Prior and Concomitant Therapy

At the Screening Visit, the following information will be recorded for each patient:

- All medications the patient is taking (ongoing)
- All prior medications taken during the 30 days before the Screening Visit

Beginning at the Screening Visit, any medication or change in medication taken by a patient during the study will be documented in the source documents and the eCRF along with the start and stop date and the reason for use.

Patients will be on a stable regimen of at least 1 antihyperglycemic medication and an ACEi or an ARB (see Inclusion Criteria for details), which may be modified during the study if medically necessary. Patients may be on a stable regimen of medication(s) for hypertension, which may be modified during the study if medically necessary. Permitted concomitant medications should be taken at the same time each day and may be taken at the same time as study drug.

Pharmacological stimulation of sGC by IW-1973 produces an increase in cGMP production. Concomitant administration of IW-1973 with an angiotensin receptor neprilysin inhibitor (ie, sacubitril/valsartan) should be allowed with caution as neprilysin inhibition results in increased cGMP concentrations via protection of natriuretic peptides.

Prohibited medications and supplements are listed in Sections 3.6 and Appendix 1.

3.6 RESTRICTIONS

3.6.1 Prohibited Medicines and Supplements

Specific inhibitors of phosphodiesterase 5 (PDE5) (including sildenafil and tadalafil), nonspecific inhibitors of PDE5 (including dipyridamole and theophylline), any supplements for the treatment of erectile dysfunction, riociguat, and nitrates or NO donors in any form are prohibited from 7 days before the Randomization Visit on Day 1 through the duration of the trial.

Strong inhibitors of CYP3A are prohibited from 14 days before Randomization through the duration of the trial. Examples include azole antifungals, macrolide antibiotics, protease inhibitors, diltiazem, and concentrated grapefruit supplements.

See Appendix 1 for a more detailed list of prohibited medicines and supplements.

3.6.2 Fluid and Food Restrictions

Patients should fast overnight (at least 8 hours) before predose blood and urine sample collections at all study visits, except for the Screening Visit.

Excessive grapefruit intake is prohibited from 14 days before Randomization through the duration of the trial.

Patient must agree not to make any major changes to their diet from the Screening Period through the Follow-up Visit.

3.6.3 Patient Activity

Patient must agree not to make any major changes to their exercise routine from the Screening Period through the Follow-up Visit.

3.6.3.1 Sexual Activity and Birth Control

Female patients who are not postmenopausal for at least 1 year (ie, 12 months of spontaneous amenorrhea [not induced by a medical condition or medical therapy]) or are not surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal sterilization [tie, clip, band, or burn]) must agree to completely abstain from heterosexual intercourse or, if heterosexually active, must agree to use 1 of the following methods of birth control from the date she signs the ICF until 60 days after the final dose of study drug:

- Progesterone implant or an intrauterine device (IUD)
- Combination of 2 highly effective birth control methods (eg, diaphragm with spermicide plus a condom, condom with spermicide plus a diaphragm or cervical cap, hormonal contraceptive [eg, oral and transdermal patch] plus a barrier method, partner with vasectomy [conducted ≥60 days before the Screening Visit or confirmed via sperm analysis] plus a hormone/barrier method).

Female patients must wait at least 60 days after the final dose of study drug to try to become pregnant and/or to undergo egg donation or egg harvesting for current or future in vitro fertilization.

Male patients who are not surgically sterile by vasectomy (conducted ≥60 days before the Screening Visit or confirmed via sperm analysis) must agree to completely abstain from heterosexual intercourse or, if heterosexually active, must agree to use a combination of 2 highly effective birth control methods (eg, condom with spermicide plus partner IUD, condom with spermicide plus a partner diaphragm/cervical cap, partner use of hormonal contraceptive [including progesterone implant] plus a barrier method, or postmenopausal partner [for ≥1 year] plus barrier method) from the Screening Visit through 60 days after the final dose of study drug.

Male patients must refrain from sperm donation during the study through at least 60 days after the final dose of study drug.

3.7 INDIVIDUAL STOPPING CRITERIA AND DMC REVIEWS

If any events included in Table 3 are reported during the study and are judged to be both study drug related and an SAE (per causality and SAE definitions in Section 3.8.9.3), individual stopping criteria or DMC review will be triggered per the criteria in Sections 3.7.1 and Table 3, respectively. The inclusion of these AEs is based on the clinical experience with IW-1973, the prescribing information for riociguat, and the patient population for this study.

Table 3. Categories of SAEs Triggering Individual Stopping Criteria and Safety Committee Review

Treatment-emergent Study Drug-related SAE Category	# of patients to trigger DMC review
Renal failure (eGFR <15 mL/min/1.73 m^2; dialysis or renal transplant indicated)	2
Spontaneous bleeding events (eg, hemoptysis, subarachnoid or subdural hemorrhage, hematemesis, hematochezia)	2
Symptomatic hypotension-related events (eg, syncope)	2

DMC=Data Monitoring Committee; eGFR=estimated glomerular filtration rate; SAE=serious adverse event

3.7.1 Individual Stopping Criteria

On an individual basis, a patient will be discontinued from study drug dosing if 1 SAE from Table 3 is reported. At the Investigator's or Sponsor's discretion, any AE(s) of concern can likewise be the basis for patient discontinuation from the trial.

3.7.2 Data Monitoring Committee Reviews

An independent DMC comprising experts in cardiovascular and/or renal disease and/or diabetes and a biostatistician will review trial safety data both periodically and if SAEs from the same category in Table 3 are reported at the incidence indicated in the table (eg, 2 patients with spontaneous bleeding SAEs). After review of safety data, the DMC will recommend trial continuation, continuation with modification, or termination. Refer to Section 5.13 for details regarding the DMC, the scheduled and ad hoc reviews, the data that will be provided for review, and Sponsor decision-making.

3.8 STUDY PROCEDURES AND ASSESSMENTS

3.8.1 Informed Consent

Informed consent procedures will comply with the Code of Federal Regulations (CFR) 21, Parts 50 and 312.

The written ICF must be approved by the Institutional Review Board (IRB) for the purposes of obtaining and documenting consent.

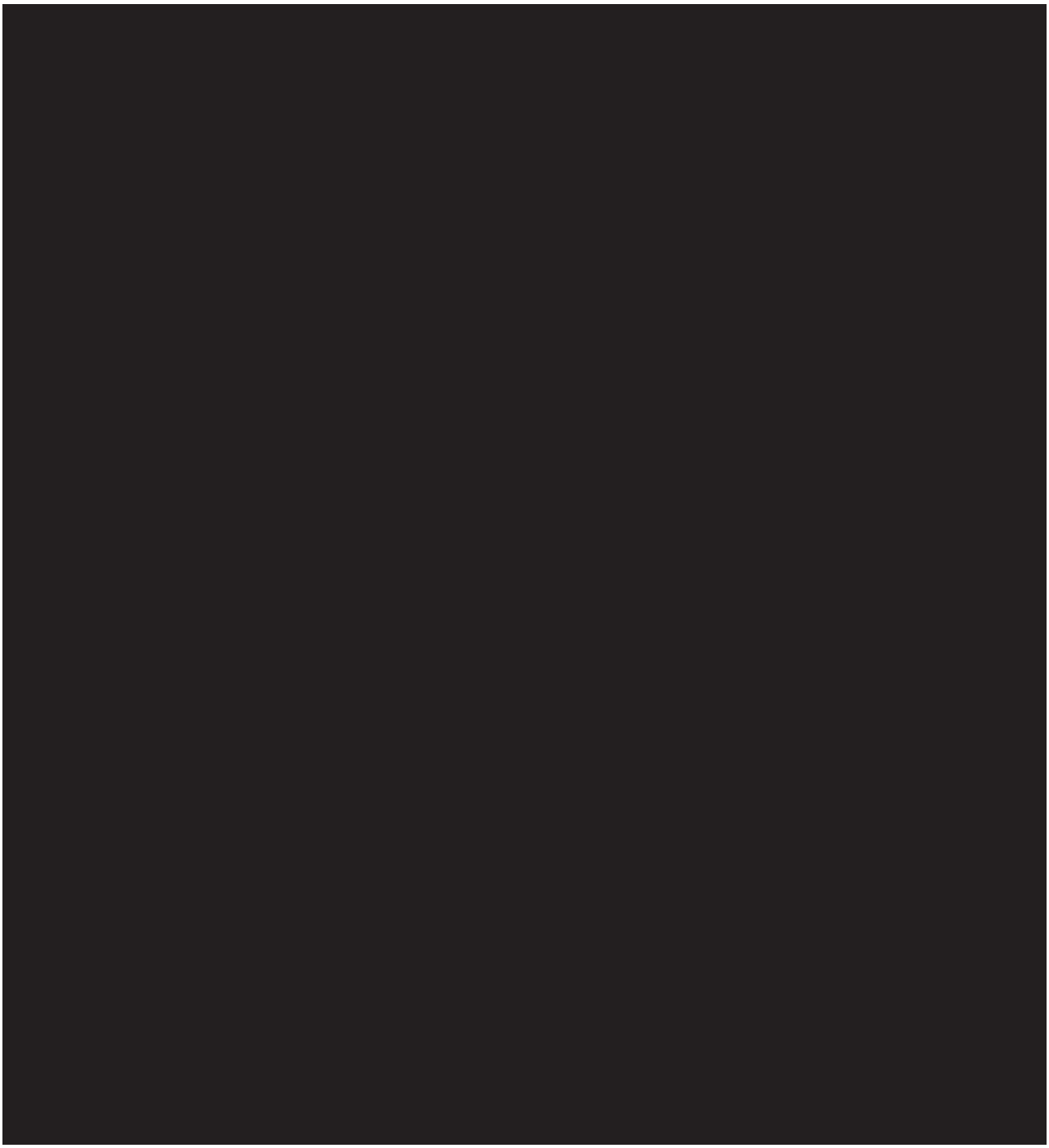
Before entry into the study, each patient will be provided with a written explanation of the study. It is the responsibility of the Investigator or appropriately trained health professional to give each patient full and adequate information regarding the objectives and procedures of the study and the possible risks involved. Patients will then be given the opportunity to ask questions and the Investigator will be available to answer questions as needed. Patients will be informed of their right to withdraw from the study at any time without prejudice. After this explanation and before entering the study, the patient will voluntarily sign the study-specific ICF. The patient will receive a copy of the signed and dated ICF. The Investigator must retain each patient's original signed ICF.

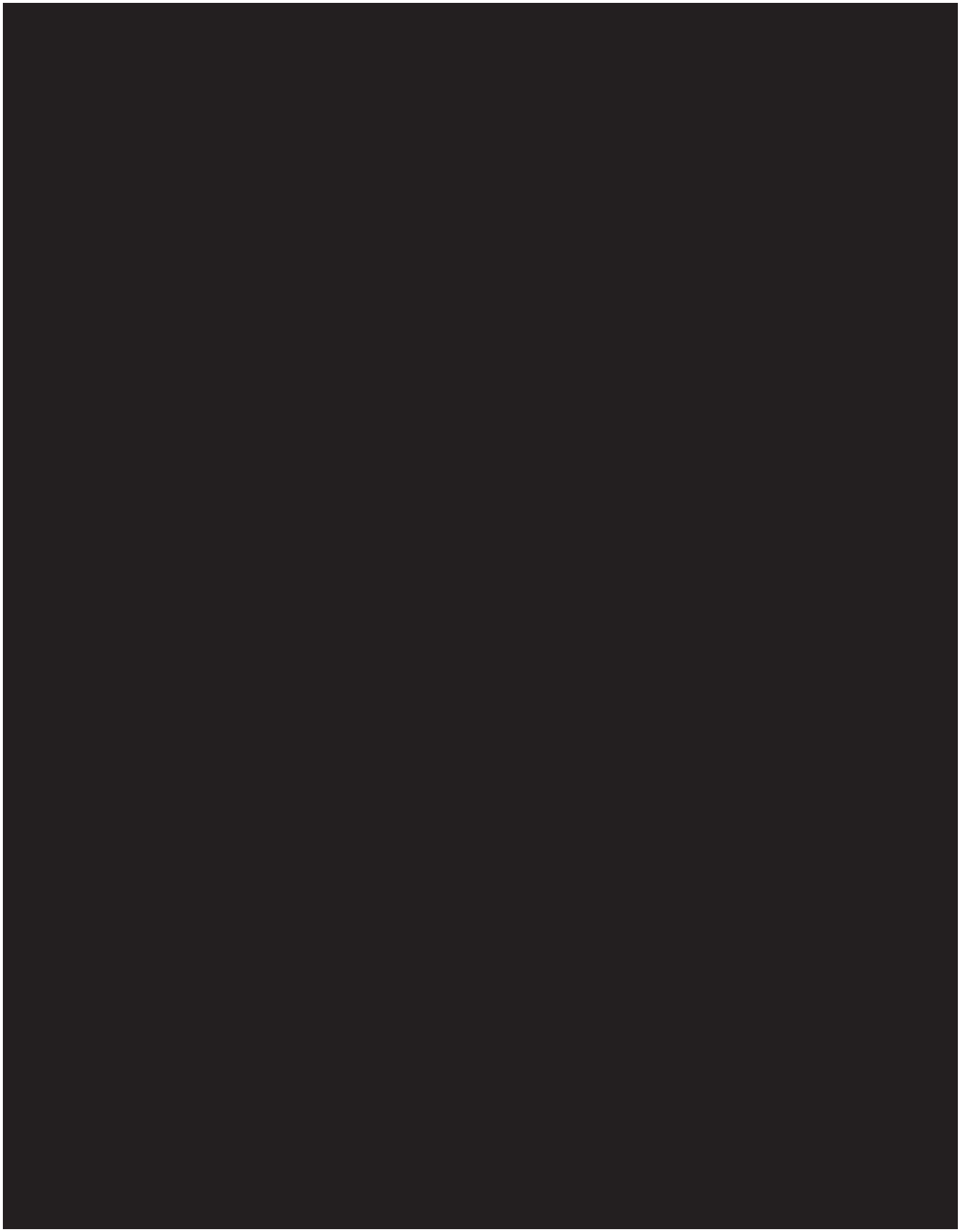
If new information becomes available that may be relevant to the patient's consent and willingness to participate in the study, the ICF will be revised. The revised ICF must be submitted to the IRB for review and approval before its use.

3.8.2 Medical History

A complete medical history, including history of smoking, will be recorded at the Screening Visit.

3.8.3 [redacted]





3.8.4 Physical Examination

A complete physical examination will be performed according to the Schedule of Events. The physical examination of each patient should include examination and assessment of the following:

General appearance	Head, eyes, ears, nose, and throat
Cardiovascular system	Neck
Respiratory system	Musculoskeletal system
Abdomen/liver/spleen	Nervous system
Lymph nodes	Skin
Neurologic status	Mental status

Breast, genitourinary, and rectal examinations are optional and may be performed at the discretion of the Investigator. Any new, clinically significant abnormal findings from the physical examination will be reported as an AE.

Each patient's weight will be recorded at each study visit; height will only be recorded at the Screening Visit.

3.8.5 Respiratory Rate and Temperature

Respiratory rate and oral temperature (°C) will be measured according to the Schedule of Events and documented on the eCRF. Respiratory rate should be measured after the patient has been seated for at least 5 minutes.

3.8.6 Hemodynamics

Hemodynamic assessments will include seated BP and pulse, orthostatic (seated-to-standing) BP and pulse, and ABPM. Outside of the ABPM assessments, all other BP and pulse measurements will be taken by automated office blood pressure (AOBP); manual measurements are allowed in cases in which an AOBP machine malfunctions or is not available.

Blood pressure and pulse measurements at the Screening and Baseline Visits will be performed with patients in the seated position. Seated BPs for study eligibility will be the average of 3 measurements obtained at 2-minute intervals after the patient has been sitting quietly for at least 5 minutes.

Blood pressure and pulse measurements at the Randomization, Week 4, Week 8, End of Treatment, and Follow-up Visits will be seated-to-standing for calculation of orthostatic BP and pulse. Patients should sit quietly for at least 5 minutes before seated measurements are taken, and then assume a standing position for 30 to 60 seconds before standing measurements are taken. At the End of Treatment visit, seated predose BP will be the average of 3 measurements.

When applicable, BP and pulse measurements should be taken before blood draws. All predose BP and pulse measurements should be taken before all oral and any antihypertensive concomitant medications.

Patients will begin 24-hour ABPM at the study site during the Baseline and End of Treatment Visits and will begin 12-hour ABPM at the study site during the Week 4 and Week 8 Visits. Patients will return the ABPM equipment to the study site at the following study visit.

Baseline Visit ABPM assessment: At least 65% compliance is preferred, with no more than 10 missed readings during the day (7 am – 10 pm) and/or 3 missed readings at night (10:30 pm – 6:30 am), and no more than 6 missed readings in succession. (If a patient's ABPM assessment does not meet these criteria, the medical monitor must be contacted PRIOR to randomizing the patient.)

At the Week 4, Week 8, and End of Treatment Visits, ABPM should begin before study drug administration.

3.8.7 Electrocardiograms

A 12-lead electrocardiogram (ECG) will be performed according to the Schedule of Events and documented on the eCRF. Electrocardiograms should be obtained after the patient has been supine for at least 5 minutes. At the Screening and Baseline Visits, if on initial ECG, QTcF is ≥450 msec for male patients or is ≥470 msec for female patients, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine eligibility.

3.8.8 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected according to the Schedule of Events. Except for the Screening Visit, patients should fast for at least 8 hours before sample collections.

The clinical laboratory evaluations will include the serum chemistry, hematology (complete blood count [CBC]), coagulation, UA, and additional tests as presented in Table 4.

Table 4. Clinical Laboratory Tests

Serum Chemistry	Hematology (CBC)	Urinalysis
Albumin	Hematocrit	Color and appearance
Alkaline Phosphatase	Hemoglobin	pH and Specific Gravity
ALT	Platelet count	Bilirubin
AST	MPV	Glucose
Bicarbonate	RBC count	Ketones
BUN	WBC count	Leukocytes
Calcium	WBC differential	Nitrites
Chloride	(% & absolute):	Occult blood
Cholesterol	Basophils	Protein
Creatinine	Eosinophils	Urobilinogen
GGT	Lymphocytes	Microscopic
Glucose	Monocytes	Including bacteria, RBCs, WBCs per HPF if dipstick is abnormal
HDL-c	Neutrophils	
LDH	RBC indices	
LDL-c (calculated)	MCH	**Additional blood tests**
Magnesium	MCHC	Hemoglobin A1c
Phosphorus	MCV	Fasting plasma glucose
Potassium	RDW	Fasting plasma insulin
Sodium		
Total Bilirubin	**Coagulation**	**Additional urine tests**
Total Protein	aPTT	Urine albumin & creatinine for UACR*
Triglycerides	Prothrombin time	Urine cotinine
Uric acid	INR	

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; GGT=gamma glutamyl transferase; HPF=high power field; INR=International Normalized Ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; MPV=mean platelet volume; RBC=red blood cell; RDW=red blood cell distribution width; UACR=urine albumin-creatinine ratio; WBC=white blood cell.

* At the Screening Visit, a single urine sample, which may not be first void, may be collected. Thereafter, samples should be 2 first-void urine samples collected on the 2 consecutive mornings before each scheduled study visit. Patients will be supplied with specimen collection supplies at the preceding study visit.

3.8.8.1 Pregnancy Tests

For female patients, a negative pregnancy test (by urine dipstick) must be documented at all study visits with results available before dosing, where applicable. In the event of a positive pregnancy test, the test will be repeated. If pregnancy is confirmed, see Section 3.8.9.5. Female patients who are postmenopausal (no menses for ≥12 consecutive months) or surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal sterilization [tie, clip, band, or burn]) do not have to have a urine pregnancy test.

3.8.8.2 Hepatitis, HIV, and Drug Screens

Screens for a hepatitis panel (including HBsAg and anti-HCV) and human immunodeficiency virus (HIV) antibody will be performed at the Screening Visit.

A urine drug screen for the following drugs of abuse will be performed at the Screening Visit:

Amphetamines	Cocaine	Phencyclidine (PCP)
Barbiturates	Marijuana	Propoxyphene
Benzodiazepines	Opiates	

3.8.8.3 Urine Albumin Creatinine Ratio (UACR)

UACR will be calculated as urine albumin (mg/dL) / urine creatinine (g/dL).

Urine albumin and urine creatinine levels will be determined as part of the clinical laboratory tests (Table 4). At the Screening Visit, a single urine sample, which may not be first void, will be collected for determination of albumin and creatinine levels. For subsequent study visits, patients will be given urine collection supplies and will collect 2 first-void urine samples on the 2 consecutive mornings before each scheduled visit.

3.8.8.4 Estimated Glomerular Filtration Rate (eGFR)

Estimated glomerular filtration rate will be based on the serum creatinine level determined as part of the clinical laboratory tests (Table 4) and will be calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.(1)

The CKD-EPI equation, expressed as a single equation, is

$$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \_ 1.159 \text{ [if black]},$$

where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κor 1, and max indicates the maximum of Scr/κ or 1.

3.8.8.5 HOMA-IR

Blood samples for determination of fasting plasma glucose and insulin levels will be collected according to the Schedule of Events. Values will be used in the Homeostatic Model Assessment to estimate insulin resistance (HOMA-IR).(34,35)

The HOMA-IR equation is:

$$\text{HOMA-IR} = (\text{FPI} \times \text{FPG})/22.5,$$

where FPI is fasting plasma insulin concentration (mU/L) and FPG is fasting plasma glucose (mmol/L).

3.8.9 Adverse Events

All patients will be monitored for AEs throughout the study. All AEs will be recorded in accordance with the procedures outlined in this section.

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes, but is not limited to, the following:

- Any unfavorable changes in general condition
- Any clinically significant worsening of a preexisting condition
- Any intercurrent diseases and accidents

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

3.8.9.1 Causality Assessment

For all AEs, the Investigator must provide an assessment of causal relationship to study drug. The causality assessment must be recorded in the patient's source documentation and on the AE page of the subject's eCRF. Causal relationship must be assessed according to the following:

Related: An event where there is a reasonable possibility of a causal relationship between the event and the study drug

Unrelated: Any other event

3.8.9.2 Severity Assessment

The Investigator will provide an assessment of the severity of each AE by recording a severity rating in the patient's source documentation and on the AE page of the patient's eCRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality. Severity will be assessed according to the following scale:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

3.8.9.3 Serious Adverse Events

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening: the patient was at immediate risk of death from the reaction as it occurred (ie, it does not include a reaction that hypothetically might have caused death if it had occurred in a more severe form)
- Hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity: a substantial disruption of a person's ability to conduct normal daily functions
- Congenital anomaly/birth defect
- Important medical events: events that may not result in death, be life threatening, or require hospitalization. Such an event may be considered serious when, based on appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Emergency room visits that do not result in admission to the hospital should be evaluated for 1 of the other serious outcomes (eg, life-threatening, other serious [medically important] event).

3.8.9.4 Recording Adverse Events

Adverse events will be collected and recorded from the time the patient signs the ICF at the Screening Visit through the Follow-up Visit. All AEs, regardless of the assumption of a causal relationship with study procedures or study medication, must be recorded in the patient's source documentation and subsequently on the appropriate AE page of the patient's eCRF. This record includes AEs the patient reports spontaneously, those observed by the Investigator, and those elicited by the Investigator in response to open-ended questions during the study, such as "Have you had any health problems since your last visit?"

For every AE, the Investigator must:

- Provide an assessment of the severity, causal relationship to the study medication, and seriousness of the event
- Document all actions taken with regard to the study medication (ie, no action taken, treatment temporarily interrupted, or treatment discontinued)
- Detail any other treatment measures taken for the AE, including concomitant medications and/or procedures

Pretreatment AEs will be collected from the time the patient signs the ICF until the patient receives study drug. Pretreatment AEs will be captured in the patient's source documentation but will only be entered for randomized patients on the AE page of the patient's eCRF.

Laboratory abnormalities and changes in vital signs, physical examination findings, and 12-lead ECG parameters should be considered AEs and reported on the AE page of the patient's eCRF if the Investigator considers them clinically significant and/or they necessitate intervention.

Any medical condition that is present when a patient is screened and does not worsen in severity and/or frequency should be reported as Medical History and not as an AE. However, if the condition does deteriorate in severity and/or frequency at any time during the study, it should be reported as an AE.

3.8.9.5 Reporting Serious Adverse Events and Pregnancy

An AE that meets any of the serious criteria must be reported to Covance within 24 hours from the time that site personnel first learn of the event, using the SAE Report form provided for the study. All SAEs must be recorded in the subject's source documentation and, subsequently, on the appropriate AE reporting page of the subject's eCRF, whether or not they are considered causally related to study medication.

Regardless of causality, all SAEs must be recorded and reported from the time the patient signs the ICF at the Screening Visit until the final Follow-up Visit. Any SAE that occurs at any time after the specified follow-up period and which the Investigator considers study drug related should be reported immediately.

The initial SAE report should include the following information at minimum:

- Patient identification number
- Description and onset of the event
- Serious criteria
- Causality assessment to study drug

In the event that a pregnancy occurs in a patient, study drug must be stopped at once and study personnel must report the pregnancy within 24 hours from the time that site personnel first learn of the pregnancy using the pregnancy notification form provided for this study. Study personnel must also make every reasonable effort to follow the pregnancy until resolution and report the outcome using the pregnancy outcome form provided for this study. If the pregnancy is associated with an SAE (eg, if the mother is hospitalized), a separate SAE form must be submitted.

All SAE and pregnancy information should be emailed to Covance as shown below.

All SAE and Pregnancy Report Forms should be emailed or faxed to:

[redacted]

or

Fax#: [redacted]

If follow-up is obtained, or is requested by Covance, the additional information should be emailed on an SAE or Pregnancy Report Form to Covance, in a timely manner according to the procedures outlined above. Copies of discharge summaries, consultant reports, autopsy reports, and any other relevant documents may also be requested.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the subject's response to these measures should be recorded. All SAEs regardless of relationship to study drug will be followed by the Investigator until satisfactory resolution, until the Investigator deems the SAE to be chronic or stable, or until the subject is lost to follow-up. Clinical, laboratory, and diagnostic measures

should be employed by the Investigator as needed to adequately determine the etiology of the event.

The Investigator will be responsible for reporting all SAEs to the IRB. Ironwood will be responsible for reporting to the regulatory authorities.

3.8.10 [redacted]

[redacted]

3.8.11 [redacted]

[redacted]

3.8.12 Pharmacokinetic Assessments

Blood samples for PK assessments will be collected according to the Schedule of Events.

3.8.13 [redacted]

[redacted]

3.9 STUDY ACTIVITIES

3.9.1 Screening Period (Day -45 to Day -1)

3.9.1.1 Screening Visit (Days -45 to -15)

- Obtain informed consent
- Record demographics and medical history
- Review inclusion and exclusion criteria
- Review prior and concomitant medications (all medicines taken during the 30 days before the Screening Visit)
- [redacted]
- Record weight and height
- Perform physical examination
- Perform 12-lead ECG (if QTcF exceeds eligibility criterion, conduct 2 more ECGs and use average of 3 values for determination of eligibility)
- Record respiratory rate and oral temperature
- Record seated BP (average of 3 measurements) and pulse
- Collect blood and urine samples for:
  - Serum chemistry, hematology (CBC), coagulation
  - Urinalysis (may be collected at any time during study visit)
  - Urine albumin and creatinine (may be collected at any time during study visit)
  - Urine pregnancy test, as applicable (must be confirmed negative) (may be collected at any time during study visit)
  - Hemoglobin A1c
  - Urine drug screen (may be collected at any time during study visit)
  - HBsAg, HCV, and HIV screen
- Conduct AE evaluation
- Issue supplies and instructions for first-void urine sampling

Note: Screening Visit assessments may take place over more than 1 day. Patients may be rescreened should they discontinue in the Screening Period due to visit window deviations or other administrative reasons. In addition, laboratory values, ECG values, or BPs that are outside

the range specified in the protocol may be repeated to confirm eligibility during the Screening Period at the Investigator's discretion after consultation with the Medical Monitor.

3.9.1.2 Baseline Visit (Days –7 ±3)

- Return by patient:
  - 2 first-void urine samples
- Review inclusion and exclusion criteria
- Review prior and current medications
- Record weight
- Perform 12-lead ECG (if QTcF exceeds eligibility criterion, conduct 2 more ECGs and use average of 3 values for determination of eligibility)
- Record seated BP (average of 3 measurements) and pulse
- Begin ABPM; patient will wear ≥24 hours and should return monitor to clinic at next study visit
- Collect blood and urine samples for:
  - Serum chemistry, hematology (CBC), coagulation
  - Urinalysis (may be collected at any time during study visit)
  - Urine pregnancy test, as applicable (must be confirmed negative; may be collected at any time during study visit)
  - Hemoglobin A1c
  - Fasting plasma glucose and insulin
- Conduct AE evaluation
- Issue supplies and instructions for first-void urine sampling

3.9.2 Treatment Period (Day 1 to Day 87 ±3)

3.9.2.1 Randomization Visit (Day 1)

- Return by patient:
  - 2 first-void urine samples
  - ABPM cuff and monitor (may be returned outside of study visit)

- Collect predose urine samples for:
  - Pregnancy test, as applicable (must be confirmed negative before randomization)
  - Urine cotinine
  - [redacted]
- Confirm inclusion and exclusion criteria
- Review prior and concomitant medications
- Record weight
- [redacted]
- Record respiratory rate and oral temperature predose (≤30 minutes)
- Record seated-to-standing (orthostatic) pulse and BP predose (≤30 minutes)
- Collect predose (≤30 minutes) blood samples for:
  - Serum creatinine and glucose
  - [redacted]
  - PK
  - [redacted]
  - [redacted]
- Randomize patient
- Dispense study drug
- MEMS introduction
- Administer study drug (morning dose)
- Record respiratory rate and oral temperature at 1 hour (±15 minutes) postdose
- Record seated-to-standing (orthostatic) pulse and BP at 1, 2, 4, and 6 hours (±15 m) postdose
- Collect blood samples for PK at 1, 3, and 6 hours (±15 minutes) postdose
- Conduct AE evaluation
- Issue supplies and instructions for first-void urine sampling

3.9.2.2 Week 1 Visit (Day 8 ±1)

- Return by patient:
  - 2 first-void urine samples

  - Study drug (Patients will bring in study drug dispensed on Day 1. MEMS Caps will be read, and the subject will be administered the Day 8 [±1] study drug dose in the clinic from the Day 1 bottles. The subject will continue to dose from the Day 1 bottles until returning for the Week 4 Visit.)

- Collect predose urine samples for pregnancy test, as applicable
- Record concomitant medications
- Record weight
- Record respiratory rate and oral temperature predose (≤30 minutes)
- Record seated-to-standing (orthostatic) pulse and BP predose (≤30 minutes)
- Collect predose (≤30 minutes) blood samples for:
  - Serum creatinine and glucose
  - Hemoglobin A1c
  - Fasting plasma glucose and insulin
  - [redacted]
  - PK
- Review MEMS cap data
- Administer study drug
- Record respiratory rate and oral temperature at 1 hour (±15 minutes) postdose
- Record seated-to-standing (orthostatic) pulse and BP at 1, 2, 4 and 6 hours (±15 minutes) postdose
- Collect blood samples for PK at 1, 3, and 6 hours (±15 minutes) postdose
- [redacted]
- Conduct AE evaluation
- Issue supplies and instructions for first-void urine sampling

3.9.2.3 Week 4 Visit (Day 29 ±3)

- Return by patient:
  - 2 first-void urine samples
  - Study drug
- Collect predose urine sample for pregnancy test, as applicable

- Record concomitant medications
- Record weight
- [redacted]
- Record seated-to-standing (orthostatic) pulse and BP predose (≤30 minutes)
- Begin ABPM; patient will wear ≥12 hours and should return monitor at next study visit
- Collect predose (≤30 minutes) blood samples for:
  - Serum chemistry, hematology (CBC), coagulation
  - Hemoglobin A1c
  - Fasting plasma glucose and insulin
  - PK
- Review MEMS cap data
- Dispense study drug
- Administer study drug
- Conduct AE evaluation
- Issue supplies and instructions for first-void urine sampling

3.9.2.4 Week 8 Visit (Day 57 ±3)

- Return by patient:
  - 2 first-void urine samples
  - ABPM cuff and monitor (may be returned outside of study visit)
  - Study drug
- Collect predose urine samples for pregnancy test, as applicable
- Record concomitant medications
- Record weight
- [redacted]
- Record seated-to-standing (orthostatic) pulse and BP predose (≤30 minutes)
- Begin ABPM; patient will wear ≥12 hours and should return monitor to clinic at next study visit

- Collect predose (≤30 minutes) blood samples for:
  - Serum creatinine and glucose
  - Hemoglobin A1c
  - Fasting plasma glucose and insulin
  - PK
- Review MEMS cap data
- Dispense study drug
- Administer study drug
- Conduct AE evaluation
- Issue supplies and instructions for first-void urine sampling

3.9.2.5 End of Treatment Visit (Day 87 ±3)

- Return by patient:
  - 2 first-void urine samples
  - ABPM cuff and monitor (may be returned outside of study visit)
  - Study drug
- Collect predose urine samples for:
  - Pregnancy test, as applicable
  - Urinalysis
  - [redacted]
- Record concomitant medications
- Record weight
- Perform physical examination
- [redacted]
- Record respiratory rate and oral temperature
- Perform 12-lead ECG
- Record seated-to-standing (orthostatic) pulse and BP predose (≤30 minutes) (seated measurement will be the average of 3 measurements)
- Begin ABPM; patient will wear ≥24 hours and should return monitor to clinic at next study visit

- Collect predose (≤30 minutes) blood samples for:
  - Serum chemistry, hematology (CBC), coagulation
  - Hemoglobin A1c
  - Fasting plasma glucose and insulin
  - [redacted]
  - PK
  - [redacted]
- Administer study drug
- Collect blood sample for PK at 3 hours (±15 minutes) postdose
- Conduct AE evaluation
- Issue supplies and instructions for first-void urine sampling

3.9.3 Follow-up Period (Day 87 ±3 to Day 115 ±3)

3.9.3.1 Follow-up Visit (Day 115 ±3)

- Return by patient:
  - 2 first-void urine samples
  - ABPM cuff and monitor (may be returned outside of study visit)
- Record concomitant medications
- Record weight
- [redacted]
- Record respiratory rate and oral temperature
- Record seated-to-standing (orthostatic) pulse and BP
- Collect blood and urine samples for:
  - Urine pregnancy test, as applicable
  - Serum chemistry, hematology (CBC), coagulation
  - Hemoglobin A1c
  - Urinalysis
  - PK
  - [redacted]
- Conduct AE evaluation

4. STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

4.1.1 Primary Safety

- Incidence of TEAEs and study drug-related TEAEs

4.1.2 Primary Efficacy

- Change from baseline in UACR over Weeks 8 and 12

4.2 EXPLORATORY ENDPOINTS

5. STATISTICAL METHODS

5.1 GENERAL CONSIDERATIONS

Descriptive statistics (n, mean or geometric mean, standard deviation, coefficient of variation, minimum, median, maximum, 25th and 75th percentiles) will be calculated to summarize continuous variables. Frequency and percentage of patients in each category will be calculated to summarize categorical variables. Additional details regarding the statistical methods will be provided in the Statistical Analysis Plan (SAP), to be finalized before unblinding of the study.

5.2 DETERMINATION OF SAMPLE SIZE

Using an estimate of standard deviation of 0.67, (29) a sample size of 40 patients per treatment group would provide approximately 80% power to detect a mean between-group difference of -0.376 units in change from baseline in log-transformed UACR over 12 weeks, with a one-sided significance level of 0.05 for at least 1 dose versus placebo comparison. This difference corresponds to a 31% between-group reduction of geometric mean change from baseline in UACR. Assuming a drop-out rate of 20%, approximately 150 patients will be randomly assigned in a 1:1:1 ratio (approximately 50 patients per treatment group) to 20 mg IW-1973, 40 mg IW-1973, or placebo.

5.3 ANALYSIS POPULATIONS

The following populations will be defined for this study:

- **Safety Population**: The Safety Population will consist of all randomized patients who receive at least 1 dose of study drug. Patients in this population will be summarized according to the treatment they actually received.
- **Intent-to-Treat (ITT) Population**: The ITT Population will consist of all randomized patients who receive at least 1 dose of study drug. Patients in this population will be evaluated according to the treatment group they were assigned to at Randomization.
- **PK Population**: The PK Population will consist of all randomized patients who receive at least 1 dose of study drug and have at least 1 postdose PK parameter assessment.
- **Per-Protocol (PP) Population**: The PP Population will consist of all ITT patients who did not have any major protocol deviations or dose reduction.

5.4 PATIENT DISPOSITION

The total number of screened patients and the number of patients who are screen failures will be tabulated. The number of patients who were randomized and the number and percentage of patients included in each population will be presented by treatment group. The number and percentage of patients who completed the study or discontinued early, as well as the reasons for discontinuation, will be presented by treatment group.

5.5 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic parameters (eg, age, sex, race, ethnicity, weight, height, body mass index [BMI]) and other baseline characteristics will be summarized by treatment group for the Safety and ITT Populations.

The number and percentage of patients with abnormalities in medical and surgical histories in each system organ class (SOC) and preferred term (PT) will be summarized by treatment group for the Safety Population.

5.6 DRUG EXPOSURE AND COMPLIANCE

Exposure to study drug, calculated as the number of days from the first dose taken to the date of the last dose taken, inclusive, will be summarized by treatment group for the ITT Population. The total number of doses taken between each scheduled visit and overall for the entire study will be calculated for each subject. Compliance will be based on the number of doses expected to be taken. Percent compliance for study medication will be summarized by treatment group and overall for the ITT Population. Compliance rates will also be categorized as missing, <80%, ≥80% and ≤120%, and >120% and summarized by treatment group.

5.7 PRIOR AND CONCOMITANT MEDICATIONS

Prior medicines are defined as any medicines taken before the date of first dose of study drug.

Concomitant medicines are defined as any medicines taken on or after the date of first dose of study drug. Any medicines taken after the date of last dose of study drug will not be considered concomitant medicines. Both prior and concomitant medicine use will be summarized by the number and percentage of patients in each treatment group receiving each medicine within each

therapeutic class for the ITT Population. Multiple medicines used by a patient in the same category (based on Anatomical-Therapeutic-Chemical classification) will only be counted once.

5.8 MAJOR PROTOCOL DEVIATIONS

Major protocol deviations will be identified and documented based on a review of protocol deviations before database lock and treatment unblinding, and will be used to define the PP population. The categories of major protocol deviations to be reviewed include, but are not limited to, patients who:

- Did not meet key inclusion/exclusion criteria
- Received disallowed concomitant medication that could meaningfully impact results
- Had overall treatment compliance rate <80% or >120%

The number and percentage of subjects with major protocol deviations will be summarized by type of deviation and by treatment group for the ITT Population. All major protocol deviations will be presented in a data listing.

5.9 EFFICACY ANALYSES

All efficacy analyses will be based on the ITT and PP Populations.

Corresponding with the primary efficacy objective of the trial, the primary inference for hypothesis testing is the treatment difference between the placebo group and the IW-1973 groups on the change from baseline in log UACR over Weeks 8 and 12. The primary efficacy analysis will be conducted using the ITT population using a mixed-effects model repeated measures (MMRM) analysis with change from baseline in log-transformed UACR as the response variable, treatment, site, visit, treatment-by-visit interaction, and baseline eGFR stratum as fixed effects, and baseline log UACR and baseline MAP as covariates with unstructured as the variance-covariance structure. Treatment differences between the pooled IW-1973 dose groups and the placebo group will be estimated overall. The null hypothesis of the test will be interpreted as equality between the placebo and pooled treatment groups, and rejection of the null hypothesis as evidence that the pooled IW-1973 groups have a greater effect on lowering UACR than the placebo group. If the null hypothesis is rejected, the nature of these differences

will be explored further by estimating the treatment differences between each IW-1973 dose group and the placebo group overall and at each assessment timepoint. Least square (LS) means, and LS mean differences between each IW-1973 group and placebo, and their associated one-sided 95% confidence intervals will be calculated overall and for each assessment timepoint. The contrasts between each IW-1973 dose group and the placebo group at each assessment timepoint will be compared using a one-sided significance level of 0.05. If the treatment-by-visit interaction is significant at the 0.1 significance level, LS mean treatment differences relative to the previous visit will also be presented.

All change-from-baseline efficacy parameters will use the same MMRM model.

Treatment group differences in the proportion of patients who achieved a 30% or 40% reduction in UACR from baseline to Week 12 will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by baseline eGFR stratum.

Summary statistics will be presented by treatment group for the biomarker parameters. Change from baseline in these variables will also be presented, where applicable.

5.9.1 Controlling for Multiplicity

No adjustments will be made for multiple comparisons.

5.10 SAFETY ANALYSES

All safety parameters will be analyzed descriptively for the Safety Population.

5.10.1 Adverse Events

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) available at the start of the study. Treatment-emergent adverse events (TEAEs) are those AEs that started or worsened in severity after the administration of study drug. TEAEs will be summarized for each treatment group by SOC and PT; PT and severity, by SOC; PT and relationship to study drug; and by SOC, PT, and baseline eGFR. If a patient has more than 1 TEAE coded to the same preferred term, the patient will be counted only once for that preferred term by identifying those TEAEs with the highest severity and the closest relationship to study drug.

In addition, the incidence of AEs leading to premature discontinuation of study drug will be summarized by treatment group. Listings of pretreatment AEs, TEAEs, severe TEAEs, study drug-related AEs, SAEs, AEs leading to study discontinuation, and AEs leading to death (if any) will be provided.

5.10.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in standard units) and changes from the baseline values at each assessment time point will be presented by treatment group for each clinical laboratory parameter.

5.10.3 Vital Signs

Descriptive statistics for vital signs (ie, pulse rate, systolic and diastolic BP, respiratory rate, temperature, and body weight) and changes from baseline values at each visit will be presented by treatment group for the Safety Population.

5.10.4 ECGs

Descriptive statistics for ECG parameters and changes from the baseline values at the end of treatment visit will be presented by treatment group for the Safety Population.

The number and percentage of patients with ECG abnormalities will be tabulated by treatment group. A listing of all AEs for patients with ECG abnormalities will also be provided.

5.10.5 [redacted]

[redacted]

5.11 PK [redacted]

All PK analyses will be based on the PK Population. Descriptive statistics will be presented for IW-1973 plasma concentrations at each assessed timepoint.

[redacted]

5.12 [redacted]

[redacted]

[redacted]

[redacted]

5.13 DATA MONITORING COMMITTEE

An independent DMC will be given the responsibility to review trial safety and provide guidance consistent with the objectives of the study and appropriate ethical requirements.

The DMC will comprise experts in cardiovascular and/or renal disease, diabetes, and biostatistics, who have experience in clinical trials and are not involved in the conduct of this trial. Their only role in this study will be as a member of the DMC, thus ensuring their independent review of safety data.

Three safety review meetings will be scheduled: the first after 30 patients have been randomized, or 5 months after the first subject is randomized (whichever is earlier); the second after approximately 1/3 of patients have completed or discontinued treatment; and the third after approximately 2/3 of patients have completed or discontinued treatment.

For these periodic reviews, the DMC will be provided with summaries of all available AE and blood pressure data by treatment groups randomly masked as A, B, and C. An independent statistician will be responsible for summarizing and submitting these safety data to members of the DMC. All data presentations for the DMC will be performed using the Safety Population. If a safety/tolerability signal or concerning AE imbalance is identified at a review, the committee can request unblinding of the masked treatment groups as well as additional safety data. At each meeting, the DMC will review accumulated AE data and recommend trial continuation, modification, or termination. The DMC will also be required to perform an ad hoc review if 2 or more study drug-related SAEs from 1 category in Table 3 are reported. In this circumstance, the committee will be provided with narrative descriptions and all relevant clinical supporting

documentation related to the SAEs. Upon request, the unblinded treatment and dose the subjects received will be provided to the committee.

In addition to the periodic and ad hoc reviews, during the trial, committee members will be provided with blinded reports on all SAEs.

The DMC or the Sponsor may request ad hoc meetings at any time and at their discretion.

There are no predefined stopping rules for the trial (for individual stopping rules, see Section 3.7.1). However, the DMC will be reviewing safety data as described above. The Sponsor, upon the recommendation of the DMC, may stop the study at any time for significant safety concerns. If the DMC recommends stopping or modifying the trial, a senior review team from the Sponsor will have the opportunity to review the blinded data and discuss study findings with the DMC. The senior review team will be separate from the study project teams. The Sponsor may also seek input from relevant regulatory authorities. The Sponsor will make the final decision on the recommendation and will relay its decision to the DMC and relevant regulatory authorities. Additional details will be provided in the DMC charter, which will be developed in collaboration with the DMC members and will be finalized before trial initiation.

5.14 INTERIM ANALYSIS (OPTIONAL)

After at least one half of the subjects (N≥75) have completed the last visit, an interim analysis to review unblinded efficacy data may be performed to assist with the planning of future studies. If performed, details regarding the interim analysis will be included in the SAP, along with updates to the data management plan as necessary. The independent statistician (who will not be involved in study data collection or interpretation) performing the interim analysis and Ironwood staff members, as identified in the SAP, may be unblinded. DMC reviews of safety data will be independent of this possible interim analysis of efficacy.

5.15 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided to the Investigator in writing by Ironwood or its designee. Before implementation, any protocol amendment regarding reportable deviations (as defined by the IRB) must be approved by the IRB and the signature page must be signed by

the Investigator and received by Ironwood or its designee, with the following exception: If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

Deviating from the protocol is permitted only if absolutely necessary for the safety of the patients and must immediately be reported to Ironwood or its designee.

6. ETHICAL CONSIDERATIONS

6.1 INSTITUTIONAL REVIEW BOARD

Before study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB.

All IRB approvals must be dated and signed by the IRB Chair or his or her designee and must identify the IRB by name and address, the clinical protocol by title and/or protocol number, and the date upon which approval or favorable opinion was granted for the clinical research. Copies of IRB approvals should be forwarded to Ironwood. All correspondence with the IRB should be maintained in the Investigator File.

No drug will be released to the site to dose a patient until written IRB approval has been received by Ironwood.

The Investigator is responsible for obtaining continuing review of the clinical research at least annually or more often if specified by the IRB. The Investigator must supply Ironwood with written documentation of the approval of the continued clinical research.

The IRB must be constituted in accordance with Federal and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and any relevant and applicable local regulations.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by Ironwood and by the IRB that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB for approval before patients being enrolled into the amended protocol.

6.2 PATIENT INFORMATION AND INFORMED CONSENT

Informed consent procedures will comply with the Code of Federal Regulations (CFR) 21, Parts 50 and 312.

The written ICF must be approved by the IRB for the purposes of obtaining and documenting consent.

Before entry into the study, each patient will be provided with a written explanation of the study. It is the responsibility of the Investigator or appropriately trained health professional to give each patient full and adequate information regarding the objectives and procedures of the study and the possible risks involved. Patients will then be given the opportunity to ask questions and the Investigator will be available to answer questions as needed. Patients will be informed of their right to withdraw from the study at any time without prejudice. After this explanation and before entering the study, the patient will voluntarily sign an ICF. The patient will receive a copy of the signed and dated ICF. The Investigator must retain each patient's original signed ICF.

If new information becomes available that may be relevant to the patient's consent and willingness to participate in the study, the ICF will be revised. The revised ICF must be submitted to the IRB for review and approval before its use.

7. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at multiple study sites in the US. The Investigator at the study site will be responsible for ensuring that the study is conducted according to the signed Clinical Trial Agreement, the protocol, IRB requirements, and ICH GCP guidelines.

The Investigator will be responsible for the oversight of the site's conduct of the study, which will consist of completing all protocol assessments, maintaining the study file and the patient records, drug accountability, corresponding with the IRB, and completing the eCRF.

7.1 GENERATION OF STUDY RECORDS

Ironwood or its designated representative will conduct a study site visit to verify the qualifications of each Investigator, inspect study site facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. All information recorded in the eCRFs for this study must be consistent with the patient's source documentation.

During the course of the study, the Clinical Site Monitor will make study site visits to review protocol compliance, compare eCRFs and individual patient's medical records, assess drug accountability (in a blinded manner), and ensure that the study is being conducted according to pertinent regulatory requirements. All eCRFs will be verified with source documentation. The review of medical records will be performed in a manner that ensures patient confidentiality is maintained.

The Clinical Site Monitor will discuss instances of missing or uninterpretable data with the Investigator for resolution. Any changes to the study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

7.2 DATA QUALITY ASSURANCE

Ironwood performs quality control and assurance checks on all of its clinical studies. Section 7.4 provides details regarding study monitoring procedures.

The study may be subject to audit by Ironwood, its representatives, or regulatory authorities. In the event of an audit, the Investigator must agree to allow Ironwood, representatives of Ironwood, or the Food and Drug Administration (FDA) or other regulatory agencies access to all study records.

7.3 ELECTRONIC CASE REPORT FORMS AND DATA MANAGEMENT

All data relating to the study will be recorded in the patient's source documentation and eCRF to be provided by Ironwood or designee via the electronic data capture (EDC) system. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, all observations, and patient status. The Investigator is responsible for verifying that all data entries on the eCRFs are accurate and correct and ensuring that all data are entered in a timely manner, as soon as possible after the information is collected. An explanation should be provided for any missing data. The Investigator must provide through the EDC system his or her formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for each patient.

Ironwood will retain the final eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be placed in the Investigator's study file.

A record of screen failures and pretreatment failures will be maintained for patients who do not qualify for enrollment, including the reason for the failure.

7.4 STUDY MONITORING

Ironwood performs quality control and assurance checks on all of its clinical studies. Before any patients are enrolled in the study, a representative of Ironwood or its authorized designee will meet with the Investigator and his/her staff to review relevant and important study-related information including, but not limited to, the protocol, the Investigator's Brochure, the eCRFs

and instructions for their completion using the EDC system, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs.

An Ironwood representative, the Clinical Site Monitor, will monitor the progress and conduct of the study by periodically conducting monitoring visits and by frequent communications (telephone, e-mail, letter, and fax) with the study sites. The site monitor will ensure that the study is conducted according to the protocol and regulatory requirements. During monitoring visits, the information recorded on the eCRFs will be verified against source documents. Upon request of the monitor, auditor, IRB, or regulatory authority, the Investigator should make all requested study-related records available for direct access.

All aspects of the study will be carefully monitored by Ironwood or its designee for compliance with applicable government regulations with respect to GCP and current standard operating procedures.

8. STUDY SPONSORSHIP

8.1 INVESTIGATOR AND STUDY TERMINATION

Ironwood may terminate Investigator participation at any institution for any reason. If participation is ended at the site by either Ironwood or the Investigator, the Investigator must:

- Return all study medications and any study materials to Ironwood
- In cases where the Investigator opts to self-terminate, provide a written statement describing why the study was terminated prematurely

Ironwood may terminate the study in its entirety or at a specific center at any time for any reason, including but not limited to the following:

- Failure to enroll patients
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practice
- Questionable safety of the study medication
- Suspected lack of efficacy of the study medication
- Administrative decision

8.2 REPORTING AND PUBLICATION

All data generated in this study will be the property of Ironwood. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to agreement between the Investigator and Ironwood.

9. INVESTIGATOR OBLIGATIONS

9.1 DOCUMENTATION

The Investigator must provide the Sponsor with the following documents BEFORE the enrollment of any subjects, in accordance with ICH E6 (*Note*: Ironwood must be notified if there are any changes to these documents):

1. Completed and signed Form FDA 1572 (Statement of Investigator) including all sub-investigators involved in the study
2. Financial disclosure form(s) for the Investigator and all sub-investigators listed on Form FDA 1572
3. Current, signed curricula vitae of the Investigator and all sub-investigators
4. Copy of current medical license of the Investigator and all sub-investigators (as applicable)
5. Copy of the IRB approval letter for the protocol and ICF
6. Copy of the IRB-approved ICF to be used
7. Copy of the IRB approval of recruitment advertising (if applicable)
8. A list of IRB members and their qualifications, and a description of the committee's working procedures
9. Protocol Approval Page signed by the Investigator
10. Fully executed Clinical Trial Agreement
11. Written document containing the name, location, certification number, and date of certification of the local laboratory to be used for laboratory assays and those of other facilities conducting tests
12. List of normal laboratory values and units of measurements for all laboratory tests required by the protocol. This list is required for each local laboratory to be used during the study.

During the study, the Investigator must maintain the following essential/administrative documents related to the study:

1. Copy of the signed Protocol Signature Page
2. Copy of financial disclosure form(s) for the Investigator and all sub-investigators (as applicable) if updated
3. Curricula vitae of any new Investigator(s) and/or sub-investigators involved in the study
4. Copy of current medical license of the Investigator and all sub-investigators (as applicable) if updated

5. Copy of the signed Form FDA 1572
6. IRB Approval Notification for the following:
    a. Protocol
    b. Informed consent document
    c. Recruitment advertising (if applicable)
    d. Amendment(s) (if applicable)
    e. Annual review of the protocol and the informed consent document
    f. SAEs
    g. Study closure
7. SAE Reports
8. Drug Inventory Forms (drug receipts, drug dispensing, and inventory forms)
9. Name and address of local or central laboratory, list of normal laboratory values and units of measurement, as well as laboratory certification or hospital accreditation
10. Updates of medical/laboratory/technical procedures/tests:
    a. Normal value(s)/ranges(s)
    b. Certification
    c. Accreditation
    d. Established quality control and/or external quality assessment
    e. Other validation (where required)
11. Record of retained body fluids/tissue samples (if any)
12. Correspondence with Sponsor
13. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB must also be provided to the Sponsor. Any changes in this study or unanticipated problems involving risks to the patients must be reported promptly to the IRB. An Investigator must not make any changes in a study without IRB and Sponsor approval, except when necessary to eliminate apparent immediate hazards to the subjects. All protocol amendments must be submitted to the IRB and approved.
14. Responsibility Log
15. Other logs (eg, screening, enrollment)
16. Signed ICFs
17. Patient source documentation
18. eCRFs
19. Audit certificate(s), if applicable

9.2 PERFORMANCE

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study. The Sponsor may terminate the study with any Investigator for any reason, including, but not limited to, Investigator nonperformance or Investigator noncompliance.

9.3 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or sub-investigators. Study medication must be stored in a safe and secure temperature-monitored location. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The study site must record the date the study medication was received and maintain a dispensing record in which to record each patient's use. A complete reconciliation of study medication will be performed at the site close-out visit with a final accountability report provided to Ironwood as part of the site close-out report. Written instructions for return of all unused and reconciled study medication to an appropriate waste handler will be provided before the end of the study. No study medication may be destroyed by study site without prior written permission of Ironwood.

9.4 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, ICFs, laboratory test results, and medication inventory records, must be retained by the Investigator in accordance with locally applicable regulatory requirements; and, in any event, for a minimum period of 5 years.

No study records shall be destroyed without notifying Sponsor and giving Sponsor the opportunity to take such study records or authorizing in writing the destruction of records after the required retention period.

If the Investigator retires, relocates, or otherwise withdraws from the responsibility of keeping the study records, custody must be transferred to another person (Ironwood, IRB, or other Investigator) who will accept the responsibility. Ironwood must be notified of and agree to the change.

9.5 PATIENT CONFIDENTIALITY

All data collected in the context of this study will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. All patient records will be identified only by initials and patient identification (PID) number. Patient names are not to be transmitted to Ironwood or its authorized designee. The Investigator will keep a Master Patient List on which the PID number and the full name, address, and telephone number of each patient is listed.

10. REFERENCE LIST

1. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of Internal Medicine 2009;150(9):604-12.

2. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 253-256. 1994. Boston, Mass., Little, Brown & Co.

3. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014 Oct;37(10):2864-83.

4. Lim AK. Diabetic nephropathy - complications and treatment. Int J Nephrol Renovasc Dis 2014;7:361-81.

5. Reidy K, Kang HM, Hostetter T, Susztak K. Molecular mechanisms of diabetic kidney disease. J Clin Invest 2014 Jun;124(6):2333-40.

6. Fineberg D, Jandeleit-Dahm KA, Cooper ME. Diabetic nephropathy: diagnosis and treatment. Nat Rev Endocrinol 2013 Dec;9(12):713-23.

7. National Kidney Foundation. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements 2013;3(1):1-150.

8. Narres M, Claessen H, Droste S, Kvitkina T, Koch M, Kuss O, et al. The Incidence of End-Stage Renal Disease in the Diabetic (Compared to the Non-Diabetic) Population: A Systematic Review. PLoS One 2016;11(1):e0147329.

9. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011 Jun 22;305(24):2532-9.

10. Toth-Manikowski S, Atta MG. Diabetic Kidney Disease: Pathophysiology and Therapeutic Targets. J Diabetes Res 2015;2015:697010

11. Nakagawa T, Tanabe K, Croker BP, Johnson RJ, Grant MB, Kosugi T, et al. Endothelial dysfunction as a potential contributor in diabetic nephropathy. Nat Rev Nephrol 2011 Jan;7(1):36-44.

12. Cheng H, Harris RC. Renal endothelial dysfunction in diabetic nephropathy. Cardiovasc Hematol Disord Drug Targets 2014;14(1):22-33.

13. Liao JK. Linking endothelial dysfunction with endothelial cell activation. J Clin Invest 2013 Feb;123(2):540-1.

14. Wharton J, Strange JW, Møller GM, Growcott EJ, Ren X, Franklyn AP, et al. Antiproliferative effects of phosphodiesterase type 5 inhibition in human pulmonary artery cells. Am J Respir Crit Care Med 2005;172:105-13.

15. Beyer C, Zenzmaier C, Palumbo-Zerr K, Mancuso R, Distler A, Dees C, et al. Stimulation of the soluble guanylate cyclase (sGC) inhibits fibrosis by blocking non-canonical TGF? signalling. Ann Rheum Dis 2014.

16. Masuyama H, Tsuruda T, Sekita Y, Hatakeyama K, Imamura T, Kato J, et al. Pressure-independent effects of pharmacological stimulation of soluble guanylate cyclase on fibrosis in pressure-overloaded rat heart. Hypertens Res 2009.

17. Ahluwalia A, Foster P, Scotland RS, McLean PG, Mathur A, Perretti M, et al. Antiinflammatory activity of soluble guanylate cyclase: cGMP-dependent down-regulation of P-selectin expression and leukocyte recruitment. Proc Natl Acad Sci U S A 2004;101:1386-91.

18. Calles-Escandon J, Cipolla M. Diabetes and endothelial dysfunction: a clinical perspective. Endocr Rev 2001 Feb;22(1):36-52.

19. Gargiulo P, Marciano C, Savarese G, D'Amore C, Paolillo S, Esposito G, et al. Endothelial dysfunction in type 2 diabetic patients with normal coronary arteries: a digital reactive hyperemia study. Int J Cardiol 2013 Apr 30;165(1):67-71.

20. Baylis C. Nitric oxide synthase derangements and hypertension in kidney disease. Curr Opin Nephrol Hypertens 2012 Jan;21(1):1-6.

21. Ito K, Chen J, Seshan SV, Khodadadian JJ, Gallagher R, El CM, et al. Dietary arginine supplementation attenuates renal damage after relief of unilateral ureteral obstruction in rats. Kidney Int 2005 Aug;68(2):515-28.

22. Griffin K, Polichnowski A, Licea-Vargas H, Picken M, Long J, Williamson G, et al. Large BP-dependent and -independent differences in susceptibility to nephropathy after nitric oxide inhibition in Sprague-Dawley rats from two major suppliers. Am J Physiol Renal Physiol 2012 Jan 1;302(1):F173-F182.

23. Ueda S, Ozawa S, Mori K, Asanuma K, Yanagita M, Uchida S, et al. ENOS deficiency causes podocyte injury with mitochondrial abnormality. Free Radic Biol Med 2015 Oct;87:181-92.

24. Stasch JP, Schlossmann J, Hocher B. Renal effects of soluble guanylate cyclase stimulators and activators: a review of the preclinical evidence. Curr Opin Pharmacol 2015 Apr;21:95-104.

25. Wang-Rosenke Y, Neumayer HH, Peters H. NO signaling through cGMP in renal tissue fibrosis and beyond: key pathway and novel therapeutic target. Curr Med Chem 2008;15(14):1396-406.

26. Ott IM, Alter ML, von WK, Kretschmer A, Tsuprykov O, Sharkovska Y, et al. Effects of Stimulation of Soluble Guanylate Cyclase on Diabetic Nephropathy in Diabetic eNOS Knockout Mice on Top of Angiotensin II Receptor Blockade. PLoS ONE 2012;7:e42623.

27. Sharkovska Y, Kalk P, Lawrenz B, Godes M, Hoffmann LS, Wellkisch K, et al. Nitric oxide-independent stimulation of soluble guanylate cyclase reduces organ damage in experimental low-renin and high-renin models. J Hypertens 2010 Aug;28(8):1666-75.

28. Dautzenberg M, Kahnert A, Stasch JP, Just A. Role of soluble guanylate cyclase in renal hemodynamics and autoregulation in the rat. Am J Physiol Renal Physiol 2014 Nov 1;307(9):F1003-F1012.

29. de Zeeuw D., Coll B, Andress D, Brennan JJ, Tang H, Houser M, et al. The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. Journal of the American Society of Nephrology : JASN 2014;25(5):1083-93.

30. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.

31. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005;43(3):203-20.

32. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34(3):220-33.

33. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the kidney disease quality of life (KDQOL) instrument. Qual Life Res 1994 Oct;3(5):329-38.

34. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes care 2004;27(6):1487-95.

35. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412-9.

11. SPONSOR SIGNATURES

Study Title:	A Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Evaluate the Safety and Efficacy of IW-1973 in Patients with Type 2 Diabetes with Albuminuria Treated with Renin-Angiotensin System Inhibitors
Study Number:	C1973-203
Final Date:	20 December 2017

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

Signed [redacted] Date: [redacted]

[redacted] Clinical Research
Ironwood Pharmaceuticals

12. INVESTIGATOR'S SIGNATURE

Study Title:	A Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Evaluate the Safety and Efficacy of IW-1973 in Patients with Type 2 Diabetes with Albuminuria Treated with Renin-Angiotensin System Inhibitors
Study Number:	C1973-203
Final Date:	20 December 2017

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Print Name:_____

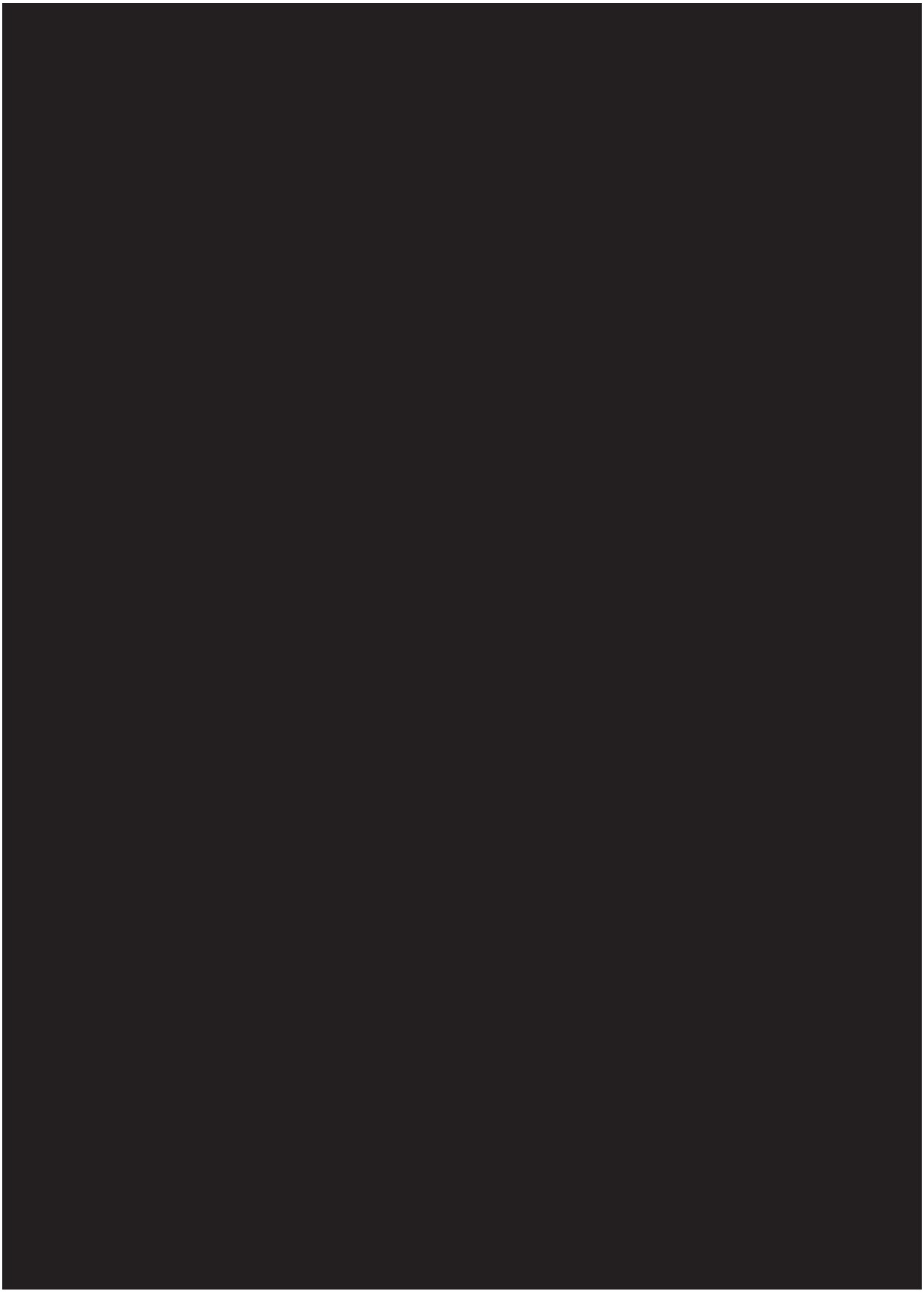
APPENDIX 1 PROHIBITED MEDICINES AND SUPPLEMENTS

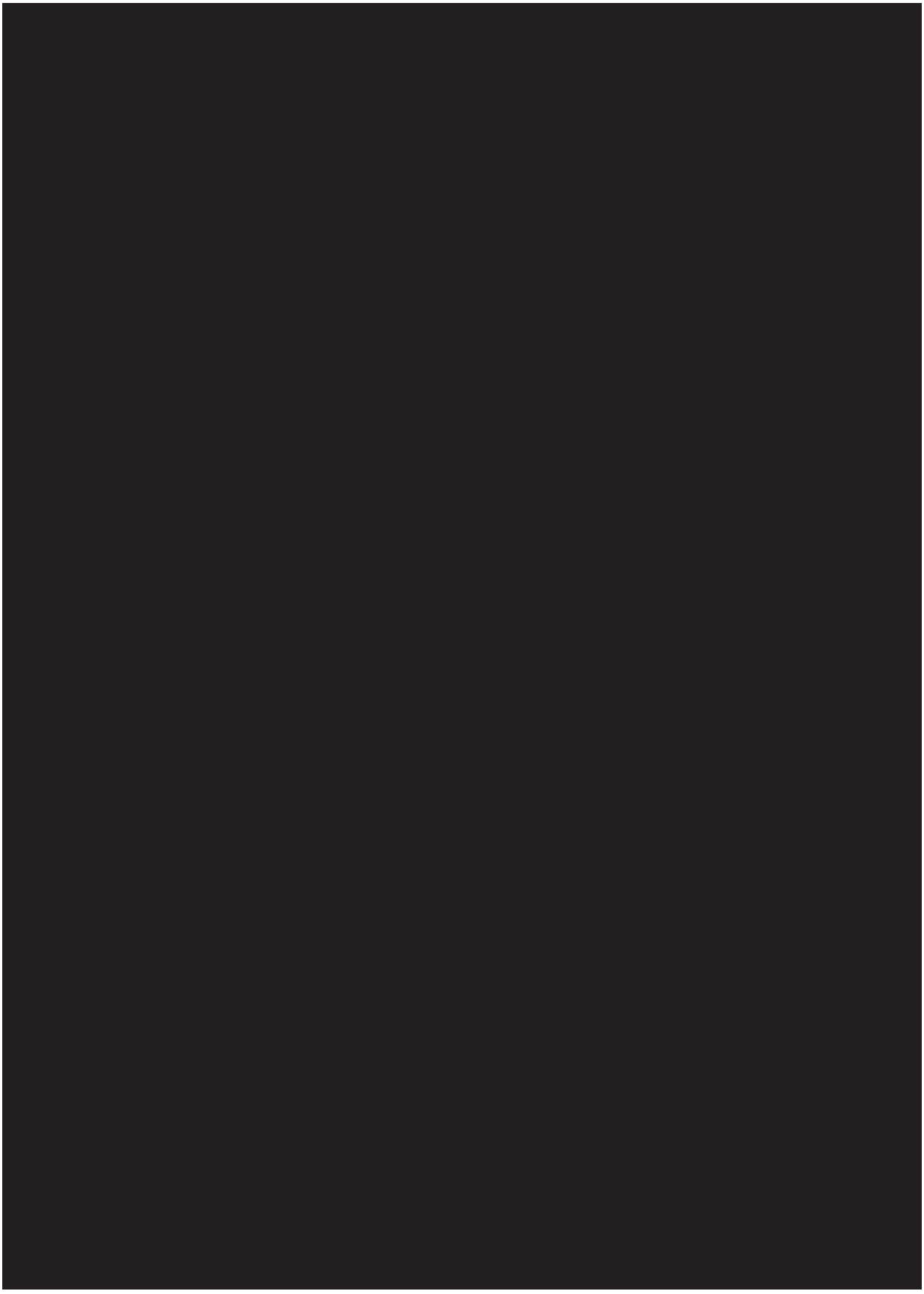
Prohibited from 7 days before Randomization (Day 1) through the duration of the study
• Specific inhibitors of PDE5, including sildenafil, tadalafil, vardenafil
• All supplements for the treatment of erectile dysfunction
• Nonspecific inhibitors of PDE5, including dipyridamole, theophylline
• Other sGC stimulators, including riociguat
• Nitrates including nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, sodium nitroprusside, amyl nitrate
• Other NO donors in any form, including beetroot
Prohibited from 14 days before Randomization (Day 1) through the duration of the study
• Strong inhibitors of CYP3A, including azole antifungals (eg, itraconazole, posaconazole), conivaptan, diltiazem, idelalisib, macrolide antibiotics (eg, clarithromycin, telithromycin), nefazodone, protease inhibitors (eg, ritonavir, boceprivir), and excessive grapefruit intake or concentrated grapefruit supplements

CYP=cytochrome P450; NO=nitric oxide; PDE=phosphodiesterase

APPENDIX 2 [redacted]

[redacted]





APPENDIX 3 [redacted]

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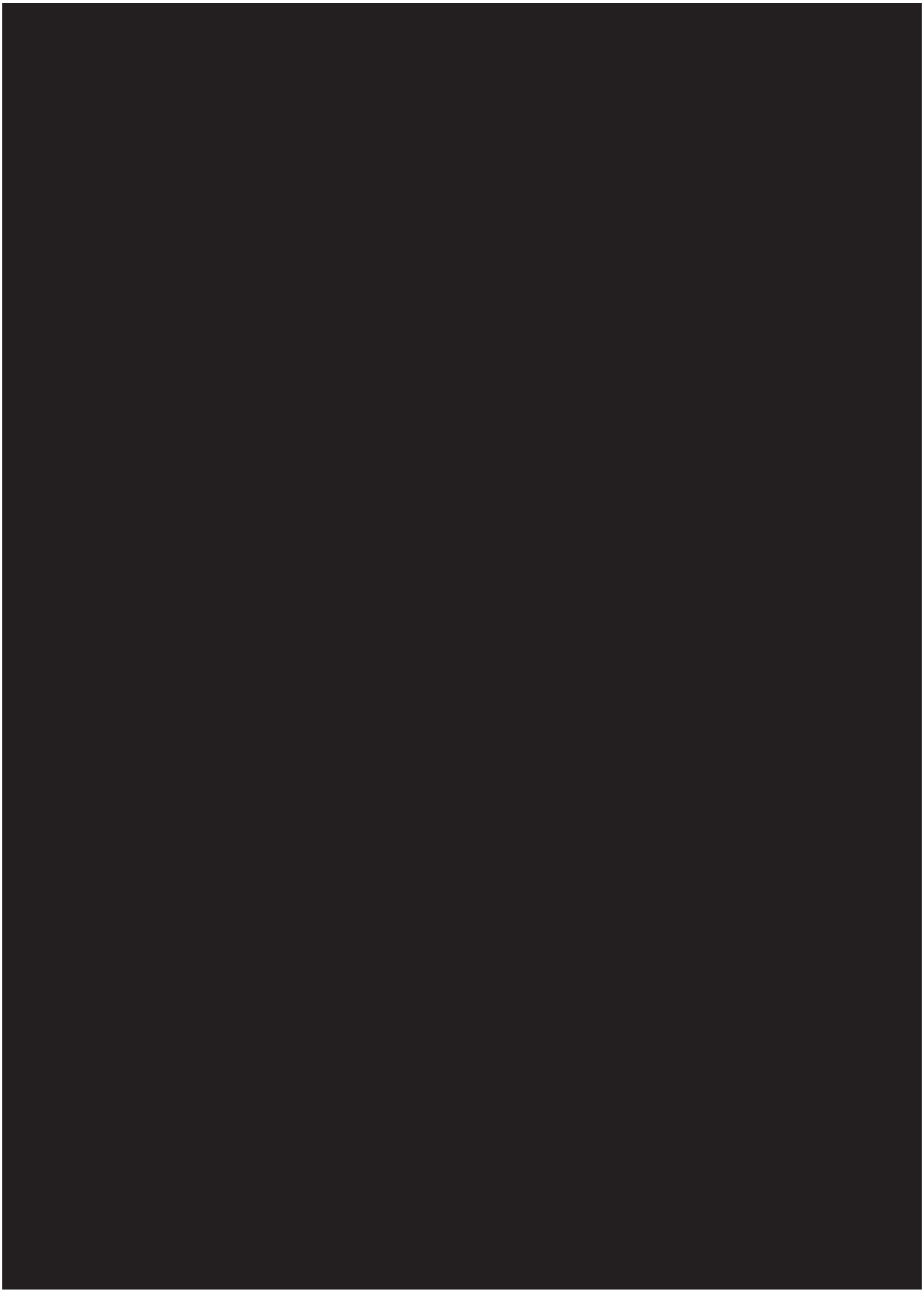

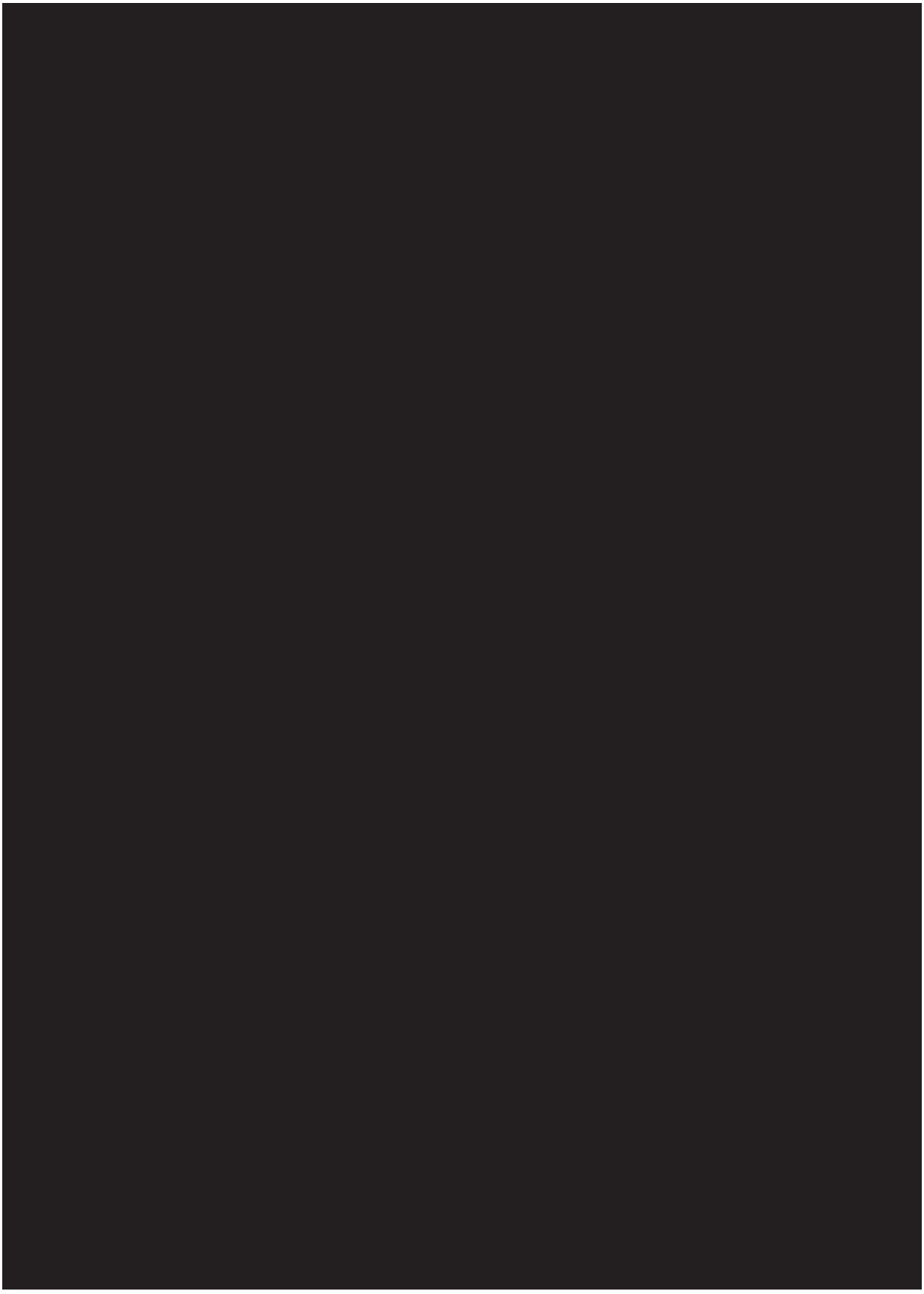

APPENDIX 4 [redacted]

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