Clinical Trial Protocol: C1973-204

Amendment 3, 27 June 2018

Study Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study Evaluating the Safety and Efficacy of Different Doses of IW-1973 over 12 Weeks in Patients with Heart Failure with Preserved Ejection Fraction (CAPACITY HFpEF)
Study Number:	C1973-204
Study Phase:	2
Product Name:	IW-1973 Tablet (praliciguat)
Indication:	Heart Failure with Preserved Ejection Fraction
Investigators:	Multicenter
Sponsor:	Ironwood Pharmaceuticals, Inc.
Sponsor Contact:	[redacted]
Sponsor Medical Monitor:	[redacted]

	Date
Original Protocol:	08 June 2017
Amendment 1	03 October 2017
Amendment 2	30 May 2018
Amendment 3	27 June 2018

KEY STUDY ROLES

Table 1 summarizes key study participants. Table 2 summarizes the external data-evaluation bodies and study committees.

Table 1. Key Study Participants

Role	Contact Information
Ironwood Contact	[redacted] Ironwood Pharmaceuticals, Inc 301 Binney Street Cambridge, MA 02142 USA PPD (office) (fax)
Sponsor Medical Monitor	[redacted] (office) (mobile) (fax)
Safety Officer	[redacted] (office)
Academic Research Organization	Cardiovascular Clinical Science Foundation (CCS) 75 Kneeland Street Boston, MA 02111 USA [redacted] ext. [redacted] (office) (fax)
Contract Research Organization (CRO) Contact	[redacted] Medpace, Inc. 5375 Medpace Way Cincinnati, OH 45227 USA [redacted] ext. [redacted] (office) (fax)
CRO Medical Monitor	[redacted] , Medical Affairs ext. [redacted] (office) (fax)

CPET Core Lab	Massachusetts General Hospital Cardiopulmonary Exercise Testing Core Laboratory GRB 800, Massachusetts General Hospital 55 Fruit Street Boston, MA 02114 USA [redacted].
Echocardiography Core Lab	Medpace Imaging Core Laboratory 5365 Medpace Way Cincinnati, OH 45227 USA [redacted] (office) (fax)
Dedicated SAE Reporting Lines & Email	[redacted] (fax) [redacted]

Table 2. External Data Evaluation Bodies and Study Committees

Committee	Description
Data Monitoring Committee (DMC)	The DMC, an independent committee of experts in cardiovascular disease plus one biostatistician, will review trial safety and provide guidance consistent with the objectives of the study and appropriate ethical requirements. The DMC charter will be developed in collaboration with the DMC members and will be finalized before the first patient is randomized.
Cardiopulmonary Exercise Test (CPET) Core Lab	The independent central CPET Core Lab will qualify CPET at each study site. In addition, CPET data for eligibility and efficacy analyses will be reviewed centrally by the CPET Core Lab. Procedural details will be documented in a CPET Core Lab manual.
Echocardiography Core Lab	The independent central Echocardiography Core Lab will be blinded to treatment assignment and will review echocardiography data for efficacy analyses. Procedural details will be documented in an Echocardiography Core Lab manual.
Clinical Events Adjudicator(s)	Blinded adjudication of hospitalizations of cardiovascular etiology and all deaths will be performed by the independent Clinical Event Adjudicator(s). The adjudicator(s) will be provided with all relevant documentation related to each event. The procedures will be described in an adjudication document. Adjudication results will be the basis for the final analysis.

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SPONSOR SIGNATURE

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Study Number:	C1973-204
Final Date:	27 June 2018

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

If an electronic signature was obtained, it will appear on the final page of this document.

Signed:_____ Date:_____

[redacted], Clinical Research
Ironwood Pharmaceuticals

INVESTIGATOR'S SIGNATURE

Study Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study Evaluating the Safety and Efficacy of Different Doses of IW-1973 over 12 Weeks in Patients with Heart Failure with Preserved Ejection Fraction (CAPACITY HFpEF)
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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:_____

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
6MWT	6-minute walk test
ACE	angiotensin-converting enzyme
AE	adverse event
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AUC	area under the curve
BID	twice daily (2×/day)
BMI	body mass index (kg/m^2)
BP	blood pressure
CBC	complete blood count
CDF	cumulative distribution function
cGMP	cyclic guanosine 3',5'-monophosphate
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CPET	cardiopulmonary exercise test
CYP3A	cytochrome P450 3A
DMC	Data Monitoring Committee
DSS	Dahl salt-sensitive
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
E/e' ratio	mitral peak velocity [E]/mitral annulus early diastolic recoil velocity [e']
EF	ejection fraction
eGFR	estimated glomerular filtration rate ($mg/mL/1.73\ m^2$)
EIU	exposure in utero
FDA	Food and Drug Administration
GCP	good clinical practice
h	hour(s)
HFpEF	heart failure with preserved ejection fraction

Abbreviation	Term
HFrEF	heart failure with reduced ejection fraction
HOMA-IR	homeostatic model assessment to quantify insulin resistance
HPF	high power field
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ITT	intent to treat
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system
[redacted]	[redacted]
kg	kilogram
kg/m^2	kilograms/meters squared (body mass index)
LA	left atrial
LSM	least-squares mean
LV	left ventricular
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume
LVESV	left ventricular end-systolic volume
m	minute
mITT	modified intent to treat
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
mL	milliliter
mmHg	millimeters of mercury
MPV	mean platelet volume
MRA	mineralocorticoid receptor antagonists

Abbreviation	Term
NO	nitric oxide
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
pd	postdose
PDE	phosphodiesterase
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily (1×/day)
[redacted]	[redacted]
QOL	quality of life
RBC	red blood cell
RDW	red blood cell distribution width
RER	respiratory exchange ratio
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
sGC	soluble guanylate cyclase
SOC	system organ class
TEAE	treatment-emergent adverse event
UACR	urine albumin creatinine ratio
UGT	uridine diphosphate–glucuronosyl transferase
ULN	upper limit of normal
US	United States

SYNOPSIS

Sponsor

Ironwood Pharmaceuticals, Inc.

Name of Finished Product

IW-1973 Tablet (praliciguat)

Name of Active Ingredient

IW-1973

Study Title

A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study Evaluating the Safety and Efficacy of Different Doses of IW-1973 over 12 Weeks in Patients with Heart Failure with Preserved Ejection Fraction (CAPACITY HFpEF)

Study Number

C1973-204

Study Phase: 2

Study Objectives

Primary

- To assess the safety of oral IW-1973 when administered for approximately 12 weeks to patients with heart failure with preserved ejection fraction (HFpEF)
- To evaluate effect of oral IW-1973 on peak exercise capacity when administered for approximately 12 weeks to patients with HFpEF, both in all patients and in patients without permanent or persistent atrial fibrillation

Secondary

- To evaluate the effect of oral IW-1973 on exercise and functional capacity when administered for approximately 12 weeks to patients with HFpEF

Study Design

This Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study will evaluate the safety and efficacy of IW-1973 compared with placebo when administered daily for approximately 12 weeks (2 weeks of twice-daily [BID] dosing followed by 10 weeks of once-daily [QD] dosing) in the indicated patient population.

At the Day 1 Visit, eligible patients will be stratified by atrial fibrillation status and by baseline peak VO_2 (<60% or ≥60% of age- and sex-adjusted normal values and with respiratory exchange ratio [RER] ≥1.0 as determined by cardiopulmonary exercise test [CPET]). Patients will be randomized in a 1:1 ratio to daily 40 mg IW-1973 or placebo (see Study Treatment below). All patients will receive their first morning BID dose in the clinic on Day 1 and their first QD dose at the Week 2 Visit (Day 15 [±3]); for these 2 visits, patients must stay in the clinic for approximately 4 hours postdose and will be released at the Investigator's discretion

after undergoing safety, efficacy, and pharmacokinetic (PK) assessments per the Schedule of Events. At the Week 4, Week 8, and End of Treatment visits, patients will again return to the clinic for study drug administration; for safety, efficacy, and PK assessments; and to receive additional study drug and other supplies, as applicable. Patients will return to the clinic 28 days (Day 113 ±7) after their last study drug dose for the final Follow-up Visit.

Study Treatment

Patients will receive study drug for up to 89 days.

For patients randomized via Protocol Amendment 2 (or earlier): On Day 1, patients will be randomized in a 1:1:1:1 ratio to the following 4 regimens:

Dose	Weeks 1 and 2, BID Dosing	Weeks 3 through 12, QD Dosing
10 mg	one 5-mg IW-1973 Tablet, orally twice daily	two 5-mg IW-1973 Tablets, orally once daily
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

For patients randomized starting with Amendment 3 to the protocol: Patients will be randomized on Day 1 in a 1:1 ratio to the following 2 regimens:

Dose	Weeks 1 and 2, BID Dosing	Weeks 3 through 12, QD Dosing
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

Study Population and Planned Number of Patients

The study will enroll approximately 184 adult patients with established heart failure and limited exercise capacity with ejection fraction of at least 40% and who have at least 2 of 4 risk factors for HFpEF (diabetes/prediabetes, hypertension, obesity, advanced age [≥70 years]). The number of patients admitted with permanent or persistent atrial fibrillation will be limited to approximately 36 in the study.

See Eligibility Criteria for full inclusion and exclusion criteria.

Study Assessments

Safety: Medical history, prior and concomitant medications and surgeries/procedures, and adverse events will be collected. Physical examination, vital sign measurements including orthostatic blood pressure, clinical laboratory tests, pregnancy tests, and electrocardiograms will be performed.

Efficacy: CPET, 6-minute walk tests (6MWT), and echocardiography will be performed. New York Heart Association (NYHA) functional classification will be determined. Cardiac events will be analyzed. Blood and urine will be collected for biomarker determinations.

Patient-reported outcomes: Patients will self-administer the following questionnaires: Kansas City Cardiomyopathy Questionnaire (KCCQ), Sheehan Disability Scale (SDS), EuroQol-5D-5L (EQ-5D-5L), and Quick Inventory of Depressive Symptomatology (QIDS)-SR-16.

Pharmacokinetics: Blood will be collected to determine plasma concentrations of IW-1973.

Dose Reduction, Individual Stopping Criteria, and Data Monitoring Committee (DMC)

Per Investigator discretion, a dose reduction for an individual patient is allowed after consultation with the Medical Monitor. If approved, the patient will reduce his or her daily dose by half, ie, from 2 to 1 tablet daily. It is recommended that the patient to be evaluated in the clinic in association with any dose modification. Each patient's dose may only be reduced once and will not be increased after reduction.

Also on an individual basis, a patient will be discontinued from study drug dosing if any of the following are reported: a study drug-related serious adverse event (SAE) of spontaneous bleeding; a life-threatening symptomatic hypotension-related SAE; or 2 study drug-related symptomatic hypotension-related SAEs.

An independent DMC will review trial safety data both periodically and on an ad hoc basis. After each periodic or ad hoc review of safety data, the DMC will recommend trial continuation, continuation with modification, or termination. Details will be provided in a DMC charter, which will be developed in collaboration with the DMC members and will be finalized before the first patient is randomized.

Statistical Methods

There will be no statistical adjustment for multiple testing. All reported p-values will be considered nominal. Ninety-two patients per arm will provide approximately 90% power to detect a clinically meaningful difference between the 40-mg IW-1973 treatment arm and the placebo treatment arm in change from baseline at Week 12 peak VO_2 in all patients and/or in patients without permanent or persistent atrial fibrillation.

Final Date: 27 June 2018

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 ≥45 years old at the Screening Visit.
3. Patient has heart failure with ejection fraction (EF) of ≥40% as assessed within 12 months of the Screening Visit, without previously documented EF of <40%. (If echocardiography results are not documented in the patient's medical history, the Investigator may perform an echocardiography at the Screening Visit.) Eligibility will be based on Investigator analysis.
4. Patient has a peak VO_2 measuring <80% of age- and sex-adjusted normal (see table) and a respiratory exchange ratio (RER) ≥1.0 at the Baseline Visit cardiopulmonary exercise test (CPET) as determined by the CPET Core Lab.

Age- and Sex-adjusted Normal Peak VO_2

Age (years)	Sex	Normal Peak VO_2 (mL O_2/kg/min)	80% of Normal Peak VO_2 (mL O_2/kg/min)
50-59	M	36	28.8
50-59	F	29	23.2
60-69	M	33	26.4
60-69	F	27	21.6
>70	M	29	23.2
>70	F	27	21.6

Source: Fletcher et al, 1995 (1)
F=female; M=male

5. Patient may have permanent or persistent atrial fibrillation; total number of patients with permanent or persistent atrial fibrillation will be limited to approximately 36. (Note: Patients with intermittent [paroxysmal] atrial fibrillation must be in normal sinus rhythm at the time of the baseline CPET; these patients will not count toward the limit of 36 patients with permanent or persistent atrial fibrillation.)
6. Patient has evidence in medical history supporting clinical heart failure syndrome consisting of at least 1 of the following:
   a. Hospitalization or emergency department visit for heart failure within the past year, with at least 2 of the following documented:
      - Volume overload on presentation as evidenced by at least 2 of the following 5 signs: jugular venous distension, pitting edema ≥1+, ascites, pulmonary congestion on chest x-ray, or pulmonary rales

- B-type natriuretic peptide (BNP) (≥100 [sinus rhythm], ≥200 pg/mL [atrial fibrillation]) or N-terminal pro BNP (NT-proBNP) (≥300 [sinus rhythm] or ≥600 pg/mL [atrial fibrillation])
- Treatment with intravenous (IV) diuretics with clinical response

b. BNP (≥100 [sinus rhythm], ≥200 pg/mL [atrial fibrillation]) or NT-proBNP (>300 [sinus rhythm], >600 pg/mL [atrial fibrillation]) within the past 6 months. (If needed for eligibility, a sample for NT-proBNP level may be collected at the Screening Visit.)

c. Echocardiographic evidence within the past 12 months of at least 2 of the following: left ventricular (LV) hypertrophy, left atrial (LA) enlargement, or diastolic dysfunction (medial E/e' ratio ≥15)

d. Hemodynamic evidence of elevated filling pressures, as indicated by pulmonary capillary wedge pressure ≥15 mmHg at rest or >25 mmHg with exercise within the past 12 months, or left ventricular end-diastolic pressure ≥15 mmHg

7. Patient has New York Heart Association (NYHA) Class II-IV symptomatology as assessed at the time of the Screening Visit. The classifications are described in Section 3.8.7 (Table 6).
8. Patient is on stable dose(s) of any current cardiovascular medication (eg, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], beta-blockers, mineralocorticoid receptor antagonists [MRAs]) for at least 1 month before the Baseline and Randomization Visits with the regimen expected to remain unchanged for the duration of the trial. Diuretic doses do not need to be stable.
9. Patient meets at least 2 of the following criteria at the Screening Visit:
   a. Diagnosis of type 2 diabetes mellitus or prediabetes (currently treated **or** hemoglobin A1c ≥5.6)
   b. History of hypertension (on at least 1 antihypertensive medication **or** has current seated blood pressure [BP] >140/90 mmHg)
   c. Body mass index (BMI) >30 kg/m^2
   d. Age ≥70 years
10. Female patient must be postmenopausal (no menses for ≥12 consecutive months) or surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal sterilization [tie, clip, band, or burn]). Female patients of reproductive potential 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 and/or an intrauterine device (IUD), or
    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] combined with a barrier method, partner with vasectomy [conducted ≥60 days before the Screening Visit or confirmed via sperm analysis] plus a hormone or barrier method).

11. 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 highly effective birth control method (eg, condom with spermicide; partner IUD; partner diaphragm or cervical cap; partner hormonal contraceptive [including progesterone implant]; or postmenopausal partner [no menses for ≥12 consecutive months]) starting from the Screening Visit through 60 days after the final dose of study drug.
12. 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 had acute coronary syndrome or percutaneous coronary intervention within 30 days before Randomization.
2. Patient has had cardiac transplantation or has cardiac transplantation planned during the study.
3. Patient has had coronary artery bypass graft, cardiac mechanical support implantation, or other cardiac surgery in the 3 months before the Screening Visit or planned during the study.
4. Patient has severe chronic obstructive pulmonary disease (COPD) as defined by chronic oxygen dependence. Nighttime oxygen is not exclusionary.
5. Patient had had heart failure hospitalization with discharge within 30 days before the Baseline Visit.
6. Patient has hypertrophic cardiomyopathy (obstructive or nonobstructive), restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, cardiac sarcoidosis, or known amyloid cardiomyopathy.
7. Patient has uncontrolled arrhythmias other than permanent or persistent atrial fibrillation.
8. Patient has history of uncorrected congenital cardiac disease affecting LV function.
9. Patient has evidence of severe chronotropic incompetence, as indicated by a heart rate response <55% of predicted maximum heart rate (220 – age) per Baseline Visit CPET.
10. Patient has any history of platelet dysfunction, hemophilia, von Willebrand disease, coagulation disorder causing a bleeding diathesis, other bleeding diathesis, or significant, nontraumatic bleeding episodes, such as from a gastrointestinal source.

11. Patient has uncorrected thyroid disease.
12. Patient has severe aortic stenosis or severe mitral regurgitation.
13. Patient has seated systolic BP <110 mmHg at the Screening Visit and on Day 1 before Randomization. For these determinations of eligibility, BP will be the average of 3 measurements obtained at approximately 2-minute intervals after the patient has been sitting quietly for ≥5 minutes.
14. Patient has estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 at the Screening Visit and/or is receiving dialysis.
15. Patient has direct bilirubin >2 times upper limit of normal (×ULN, as defined by laboratory) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3×ULN at the Screening Visit.
16. Patient has received IV inotropic therapy within 30 days before the Screening Visit.
17. Patient is unable to take oral medications.
18. Patient has active or treated malignancies within 12 months of the Screening Visit, except for basal cell carcinoma.
19. Patient has previously received IW-1973, has received any other investigational drug during the 30 days or 5 half-lives of that investigational drug (whichever is longer) before the Screening Visit, is planning to receive another investigational drug at any time during the study, has an active investigational medical device currently implanted, and/or is planning to have an investigational medical device implanted at any time during the study.
20. Patient has comorbid condition with an expected survival less than 6 months.
21. Patient has any medical condition that, in the Investigator's opinion, could lead to difficulty complying with protocol procedures (eg, 6-minute walk test, CPET) or could prohibit completion of the study. Specifically, patients should not be primarily limited in their physical activity by joint, leg, hip or back pain, or gait unsteadiness.
22. Patient has evidence of active hepatitis or human immunodeficiency virus antibody at the Screening Visit.
23. Patient has clinically significant (per Investigator judgment) history of viral or bacterial infection within 4 weeks of the Baseline Visit.
24. Patient has had surgery with general anesthesia in the 6 weeks before the Screening Visit or has scheduled or planned surgery with general anesthesia during the study.
25. Patient has a history of active alcoholism or drug addiction during the 12 months before the Screening Visit and/or has a positive drug screen at the Screening Visit for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, propoxyphene without a prescription for a medically defined condition.

26. 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, and/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 medicines and supplements.
27. Patient has a history of clinically significant hypersensitivity or allergy to any of the ingredients contained in the active or placebo drug products.
28. Female patient is pregnant (positive urine pregnancy test) or is breastfeeding. Breastfeeding is not allowed from Screening Visit through 60 days after the final dose of study drug.
29. Female patient who may wish to become pregnant and/or plans to undergo egg donation or egg harvesting for current or future in vitro fertilization during the study and/or within at least 60 days after the final dose of study drug.
30. Male patient unwilling to refrain from sperm donation during the study and for at least 60 days after the final dose of study drug.
31. Patient will not be able to adhere to the trial assessment schedule or, in the clinical judgment of the Investigator, is otherwise not suitable for the trial.

NOTES:

- Patients may be rescreened should they discontinue in the Screening Period due to visit window deviations or other administrative reasons.
- 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.
- The Screening and Baseline Visits can be combined if the visit occurs within 14 days of Randomization and the patient has fasted for ≥8 hours.
- With prior approval by the Medical Monitor, local laboratory results may be used to determine study eligibility. In this instance, patients must have fasted for ≥8 hours prior to collection of the laboratory samples and duplicate samples must be drawn—1 set will be used for determination of study eligibility by the local laboratory and the second set will be sent to the Central laboratory for inclusion in the study database. The Randomization Visit can then occur on the next day.

SCHEDULE OF EVENTS

	Screening Period		Treatment Period					FU Period
Visit Days → Study Procedure ↓	**Screening Visit* (Day -45 to -3)**	**Baseline*Visit (Day -14 to -3)**	**Randomization Visit (Day 1)**	**Week 2 Visit (Day 15 ±3)**	**Week 4 Visit (Day 29 ±3)**	**Week 8 Visit (Day 57 ±3)**	**Week 12/ EOT Visit (Day 85 -7/+4)**	**FU Visit (Day 113 ±7)**
ICF signed	X							
Demographics	X							
Medical history	X							
Inclusion/exclusion	X	X	X					
Prior & concomitant medications and procedures	X	X	X	X	X	X	X	X
Physical exam (a)	complete	pre CPET	predose	predose	predose	predose	predose	complete
Vital signs (BP, pulse, RR, & oral temperature) (b)	X	pre CPET	pre: 0 (≤1h) pd: 1,3,4h (±20m)	pre: 0 (≤1h) pd: 1,3,4h (±20m)	pre: 0 (≤1h)	pre: 0 (≤1h)	pre: 0 (≤1h)	X
Weight, height	W, H	W	W	W	W	W	W	W
NYHA classification	X		X				X	X
Hepatitis, HIV screen	X							
Urine drug screen	X							
Urine pregnancy (c)	X	pre CPET	predose	predose	predose	predose	predose	X
Urinalysis sample (d)	X		predose	predose	predose	predose	predose	X
Serum chemistry, CBC, coagulation (d)	X	pre CPET	predose	predose	predose	predose	predose	X
Hemoglobin A1c	X	pre CPET				predose	predose	X
12-lead ECG (e)	X	pre CPET	predose	predose	predose	predose	predose	
Adverse events	X	X	X	X	X	X	X	X
CPET (f)		X				postdose >1h (or ±3 days) (f)	postdose >1h	
6MWT (g)		post CPET >1h				post CPET >1h (g)	post CPET >1h	
NT-proBNP sample (d,h)	X (if needed)	pre CPET					predose	
Echocardiography (i)	X (if needed)	X (for baseline)					X	

Visit Days → Study Procedure ↓	Screening Period		Treatment Period					FU Period
	Screening Visit* (Day -45 to -3)	Baseline*Visit (Day -14 to -3)	Randomization Visit (Day 1)	Week 2 Visit (Day 15 ±3)	Week 4 Visit (Day 29 ±3)	Week 8 Visit (Day 57 ±3)	Week 12/ EOT Visit (Day 85 -7/+4)	FU Visit (Day 113 ±7)
Fasting plasma glucose & insulin (d)		pre CPET	predose			predose	predose	X
[redacted]								
UACR sample supplies dispensed		X				X		
First-void urine samples (j)			preVisit				preVisit	
[redacted]								
Pharmacokinetic blood samples			predose pd:1,2,4h (±20m)	predose pd:1,2,4h (±20m)	predose	predose	predose pd:1,2,4h (±20m)	X
[redacted]								
Orthostatic (sitting to standing) pulse, BP (k)			pre: 0 (≤1h) pd: 2,4h (±20m)	pre: 0 (≤1h) pd: 2,4h (±20m)			pre: 0 (≤1h)	
Randomization			X					
Study drug dispensed			X	X	X	X		
In-clinic study drug (l)			X	X	X	X	X	
Study drug return				X	X	X	X	
Study completion								X

6MWT=6-minute walk test; BP=blood pressure; CBC=complete blood count; CPET=cardiopulmonary exercise test; CV=cardiovascular; ECG=electrocardiogram; EOT=end of treatment; [redacted] FU=follow-up; h=hour; H=height; HIV=human immunodeficiency virus; ICF=informed consent form; [redacted] m=minute(s); NT-proBNP=N-terminal pro B-type natriuretic peptide; NYHA=New York Heart Association; opt=optional; pd=postdose; pre=predose; QD=once daily; [redacted] RR=respiratory rate; [redacted] UACR=urine albumin creatinine ratio; W=weight

* Screening and Baseline Visits may be combined if the visit occurs within 14-day period before Randomization and if patient has fasted ≥8h. With prior approval from the Sponsor's Medical Monitor, the Screening and Baseline Visits can be combined and can occur 1 day prior to the Randomization Visit; in these instances, local laboratory values can be used to determine study eligibility, with duplicate samples sent to the Central laboratory for inclusion in the study database. Patients must have fasted for ≥8 hours prior to collection of the laboratory samples.

a. For Treatment Period visits, physical exam may be symptom directed or limited to cardiovascular system at the Investigator's discretion.
b. For eligibility at the Screening and Randomization Visits, BP will be the average of 3 measurements obtained at approximately 2-m intervals after the patient has been sitting quietly for ≥5 m; otherwise, 1 measurement after the patient has been sitting quietly for ≥5 m.
c. For female patients, a pregnancy test (by urine dipstick) must be documented at all visits and confirmed negative before dosing when applicable. Pregnancy tests are not required for 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]).
d. Pre CPET and predose samples require ≥8-h fast; fasting not required for the Screening Visit unless combined with Baseline Visit; blood collections after ECG or ≥10 m before ECG, when applicable. [redacted]
e. Patients must be supine for ≥5 minutes before the ECG recording. ECGs conducted before blood collections or ≥10 m after blood collections, when applicable.
f. CPETs should be performed at the same time of day (±2 h) and be timed to occur at ≥1 h postdose, when applicable. CPET will precede 6MWT by ≥1 h, when applicable. The Week 8 CPET can be conducted on a separate day (±3 days) from the other Week 8 assessments, as dictated by logistical considerations.
g. When applicable, 6MWT must be performed ≥1 h after CPET.
h. At Screening Visit only if needed for eligibility determination.
i. Echocardiography may be performed at the Screening Visit to confirm eligibility; if performed at the Screening Visit, it can be used for baseline and does not need to be repeated at the Baseline or Randomization Visit. If not performed at the Screening Visit, echocardiography for baseline may be performed at either the Baseline or Randomization Visit. Echocardiography performed at Baseline and EOT Visits must be before or ≥1 h after exercise (CPET, 6MWT).
j. One patient-collected, first-void urine sample from the morning before or the morning of the scheduled visit. Patients will be supplied with specimen collection supplies at the preceding study visit.
k. Patient must sit quietly for ≥5 m before sitting BP and pulse measurements are taken, and then assume standing position for 2 m (±1 m) before standing BP and pulse measurements are taken.
l. Study drug will be administered in the clinic on study visit days after predose assessments. On Day 1, only the morning dose will be administered in clinic. For at home dosing, patients will be instructed to take study drug with water at approximately the same time each day. Patients may take with or without food and, for QD dosing (Week 2 Visit onward), may swallow the 2 tablets together.

1. INTRODUCTION

1.1 HEART FAILURE WITH PRESERVED EJECTION FRACTION

Heart failure with preserved ejection fraction (HFpEF) is a significant source of morbidity and mortality in the United States (US) and globally.(2, 3) It currently comprises approximately 50% of new heart failure diagnoses in the US, and the prevalence is estimated to be at least 1% of the population, or more than 3 million Americans.(2, 4) Patients with HFpEF account for approximately half of hospitalizations for heart failure and are frequently re-admitted following discharge.(5) Mortality rates over 5 years for patients diagnosed with HFpEF have been reported to range from 55% to 74%.(6) Patients with HFpEF have the signs and symptoms of heart failure, which may include dyspnea, orthopnea, lower extremity edema, pulmonary congestion, and cardiomegaly; tend to have low activity levels and a suboptimal quality of life (QOL); and frequently experience depression.(7) Although there are approved treatments for heart failure with reduced ejection fraction (HFrEF) that reduce death and hospitalization for heart failure, currently there are no approved chronic medications specifically for HFpEF. Given the lack of approved therapies, there is significant unmet medical need for the large population of HFpEF patients.

1.2 PATHOPHYSIOLOGY OF HFpEF

Diastolic dysfunction has long been recognized as a key element of impaired cardiac function in HFpEF. Hypertension likely plays a role in diastolic dysfunction, but more recently other factors have been proposed to contribute to HFpEF. Microvascular inflammation has been hypothesized to play an important role in HFpEF pathophysiology.(8) HFpEF patients often have comorbid obesity and diabetes mellitus, which may contribute to a systemic inflammatory state. Microvascular inflammation is associated with reduced nitric oxide (NO) bioavailability that in turn results in reduced production of cyclic guanosine 3',5'-monophosphate (cGMP) by soluble guanylate cyclase (sGC).(9) Decreased cGMP levels result in impaired activation of protein kinase G with multiple resultant effects, including impaired phosphorylation of titin, leading to increased myocardial compliance and increased synthesis of collagen.(10) This cascade of effects, stemming from reduced NO bioavailability, may be important in the reduced ventricular compliance and myocardial remodeling that is sometimes seen in HFpEF.

Other mechanisms of derangement in NO-sGC-cGMP signaling may also contribute to the pathophysiology. For example, endothelial dysfunction can result in vascular stiffness and an inability to properly regulate vascular flow to skeletal muscle, which may lead to impaired oxygen extraction and diminished exercise capacity.(11) Furthermore, many patients with HFpEF also exhibit pulmonary artery hypertension.

1.3 RATIONALE FOR USE OF AN sGC STIMULATOR IN HFpEF

Based on the key role of NO deficiency leading to impaired NO-sGC-cGMP signaling in the pathophysiology of the disease, the potential value of sGC stimulators in the treatment of HFpEF is plausible.(12, 13) Administration of a single dose of the sGC stimulator riociguat to patients with pulmonary hypertension secondary to HFpEF did not have an acute effect on pulmonary artery pressures (the primary variable) or pulmonary arterial wedge pressure, but did result in improvements in stroke volume and a reduction in systemic vascular resistance.(14) Chronic administration of an sGC stimulator may reduce pulmonary arterial pressures, an effect that would be beneficial in patients with HFpEF.

In a Phase 2b trial in HFpEF patients, the investigational sGC stimulator vericiguat improved QOL parameters, an effect that was most prominently demonstrated by an improvement in physical limitation subscale scores; a beneficial effect on the biomarker N-terminal pro B-type natriuretic peptide (NT-proBNP) or in left atrial (LA) dimension by echocardiography was not demonstrated.(15)

Studies of other drugs with effects on intracellular cGMP, such as sildenafil, have been studied for the treatment of HFpEF, and the results have been mixed.(16) In contrast, 2 small studies of inorganic nitrates administered as beetroot juice improved the submaximal aerobic endurance in HFpEF patients after acute administration in 1 study, and after 1 week of treatment in the other.(17, 18) The use of the organic nitrate isosorbide mononitrate in patients with HFpEF has demonstrated no benefit.(19) Organic nitrates release NO nonspecifically, potentially resulting in systemic sGC activation and untargeted smooth muscle relaxation. Furthermore, released NO can react with superoxide to form highly reactive and damaging peroxynitrite ion. In contrast, sGC stimulators increase local cGMP signaling in tissues and do not generate peroxynitrite.

1.3.1 IW-1973

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.

1.3.1.1 Nonclinical Data in Support of Clinical HFpEF Investigations

Pharmacologic activation of sGC with NO donors has shown cardiac benefit in animal models and in the clinic.(20) The effects of IW-1973 on cardiac morphology, function, and biomarkers have been explored in models of HFrEF and HFpEF. In the Dahl salt-sensitive (DSS) rat model, 6 weeks of treatment with IW-1973 resulted in lower levels of the cardiac stress marker NT-proBNP, lower cardiac weight, higher ejection fraction (EF), and increased left ventricular (LV) end systolic internal dimension compared to the vehicle-treated control group. IW-1973 treatment also led to a dose-dependent reduction in systemic blood pressure (BP), improvements in renal function and histology, and a reduction in expression of fibrotic markers in the DSS model. Exposures achieved with repeated administration of 40 mg/day IW-1973 to healthy subjects in clinical study ICP-1973-102 were comparable to the exposures associated with cardiac effects in the DSS rat model. In a rat post-myocardial infarction (MI) model of HFrEF, treatment with IW-1973 (10 mg/kg/day) for 8 weeks resulted in significant decrease in levels of NT-proBNP and improvements in echocardiographic measures LV end systolic area, LV end-systolic volume (LVESV), and LV fractional area change compared to the control group. Together, these data support investigation of IW-1973 as a potential therapy for HFpEF.

2. STUDY OBJECTIVES

Primary

- To assess the safety of oral IW-1973 when administered for approximately 12 weeks to patients with HFpEF
- To evaluate the effect of oral IW-1973 on peak exercise capacity when administered for approximately 12 weeks to patients with HFpEF, both in all patients and in patients without permanent or persistent atrial fibrillation

Secondary

- To evaluate the effect of oral IW-1973 on exercise and functional capacity when administered for approximately 12 weeks to patients with HFpEF

Exploratory

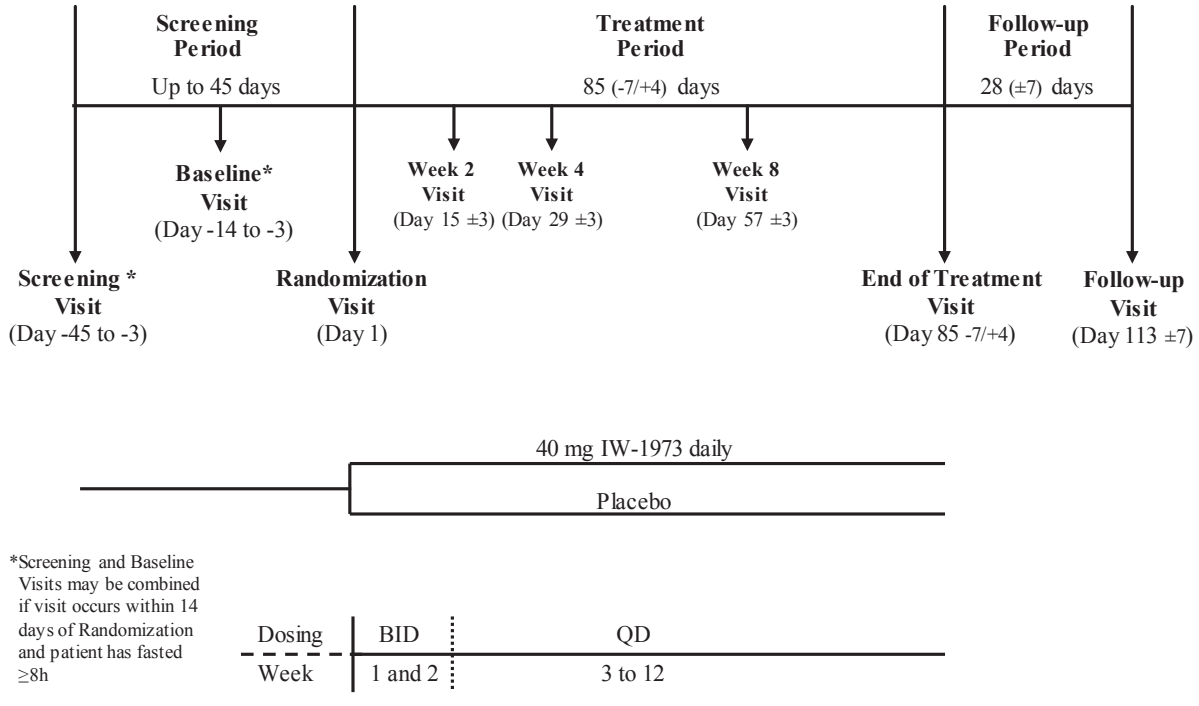
3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study will evaluate the safety and efficacy of IW-1973 compared with placebo. The study will enroll approximately 184 adults with established heart failure and limited exercise capacity with EF of at least 40% and who have at least 2 of 4 risk factors for HFpEF (diabetes/prediabetes, hypertension, obesity, advanced age) (see Eligibility Criteria). Patients will be stratified by atrial fibrillation status and by baseline peak VO_2 (<60% or ≥60% of age- and sex-adjusted normal values with respiratory exchange ratio [RER] ≥1.0 as determined by cardiopulmonary exercise test [CPET]) and randomized in a 1:1 ratio to daily IW-1973 or placebo, as described in Section 3.5.2. The number of patients admitted with permanent or persistent atrial fibrillation will be limited to under 20% of target enrollment (≤36 patients).

The study will consist of 3 distinct periods, a Screening Period, a Treatment Period, and a Follow-up Period (Figure 1).

Figure 1. Study Schematic



***Screening Period*:** The Screening Period will begin with the signature of the ICF at the Screening Visit and may last up to 45 days. At the Screening Visit, patients will undergo screening procedures to determine their initial eligibility. At the Baseline Visit, patients will return to the clinic for additional screening procedures to determine their eligibility, including CPET, vital sign measurements, and blood and urine sample collections, and to receive supplies to take home. The end of the Screening Period will coincide with the beginning of the Treatment Period. The Screening Visit may be combined with the Baseline Visit if the patient is fasted for blood and urine collections. CPET and 6-minute walk test (6MWT) must occur within the 14-day period before Randomization.

Treatment Period: The Treatment Period will begin on Day 1 at Randomization and will end after the End of Treatment Visit on Day 85 (-7/+4 days). At the Day 1 Visit, eligible patients will be stratified as described in Section 3.1 and randomized as described in Section 3.5.2 to receive daily IW-1973 or placebo for approximately 12 weeks. Dosing on Days 1 to 14 (±3) will be BID (twice daily); dosing on Day 15 (±3) onward will be QD (once daily).

At the Randomization (Day 1) Visit, patients will receive their morning BID dose of study drug in the clinic. At the Week 2 Visit (Day 15 [±3]), patients will return to the clinic and receive their 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) and will receive study drug supply. At both visits, patients must stay in the clinic a minimum of approximately 4 hours postdose and thereafter may be allowed to leave the clinic at the Investigator's discretion.

At the Week 4 Visit, Week 8 Visit, and End of Treatment Visit, patients will return to the clinic for study drug administration; safety, efficacy, and PK assessments; and study drug and other supplies, as applicable.

Follow-up Period: The Follow-up Period will begin immediately after the End of Treatment Visit on Day 85 (-7/+4 days) and will last for 28 (±7) days. On Day 113 (±7 days), patients will return to the clinic for the final Follow-up Visit (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 to determine the rate of spontaneously occurring treatment-emergent adverse events (TEAEs) 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 functional assessments, CPET and 6MWT, as well as hemodynamic measures. Noninvasive CPET provides detailed physiologic information during exercise including data on respiratory gas exchange, ventilation, BP, heart rate, and oxygen saturation. CPET also provides an objective measure of volition and is highly reproducible, which enables assessment of treatment effect in a relatively small number of patients.(21) The 6MWT (Appendix 6) provides a simple assessment of functional capacity that is easy to perform, requires no equipment or advanced training, and is based on an activity of daily living. Because subjects select their own exercise intensity, the 6MWT reflects everyday functional capacity and provides a global evaluation of the organ/physiologic systems involved in exercise.(22) Assessments will also include patient-reported questionnaires that assess health status, generic and disease-specific QOL, symptoms of depression, and functional disability. These assessments allow a better understanding of the trial population at baseline as well as an evaluation of the potential impact of IW-1973 treatment on patients' own assessments of their health and QOL.

Patients will be stratified by baseline peak VO_2 (CPET) to minimize the potential impact of baseline disease severity imbalance between treatment groups. In addition, patients will be stratified by atrial fibrillation status to minimize imbalance between treatment groups.

Enrichment is utilized in this study design by limiting enrolling patients with permanent or persistent atrial fibrillation at screening to under 20% of target enrollment. This design ensures

that a standalone study population of patients without permanent or persistent atrial fibrillation is adequately powered to evaluate efficacy.

Individual stopping criteria and Data Monitoring Committee (DMC) safety reviews (Section 3.7) ensure that individual and/or all dosing will stop should an unacceptable safety signal be detected. Patients will have a Follow-up Visit at the clinic 28 (±7) days after their 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 study drug for up to 89 days. Total patient participation will be 109 to 165 days, including the Screening, Treatment, and Follow-up Periods.

3.4 STUDY POPULATION

The study will enroll approximately 184 adult patients who have established heart failure with an EF of at least 40% and limited exercise capacity (peak VO_2 <80% of age- and sex-adjusted normal values). In addition, patients must have at least 2 of the following 4 risk factors for HFpEF: diabetes/prediabetes, hypertension, obesity, and/or advanced age (≥70 years).

The number of patients admitted with permanent or persistent atrial fibrillation will be limited to approximately 36, total, in the study.

For details, see Eligibility Criteria.

3.4.1 Removal of Patients from Therapy or Assessment

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

A patient will be considered to have completed the study after completing the Follow-up Visit on Day 113 (±7).

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 premature patient discontinuation. 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 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 will 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.

3.4.2 Early Termination Procedures

Patients who 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 ±7 days after their final dose of study drug. If the End of Treatment Visit occurs more than 7 days after the patient's final dose of study drug, the PK blood draw can be reduced to 1 sample.

3.5 STUDY TREATMENT(S)

3.5.1 Description of Treatment(s)

3.5.1.1 Investigational Product

IW-1973 Tablets are 20-mg oral tablets that are white, round, and match in appearance.

3.5.1.2 Placebo

Placebo tablets match IW-1973 Tablets in appearance.

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 100-cc high-density polyethylene (HDPE) induction-sealed bottles, 35 tablets per bottle, containing two 1-gram mole desiccant sieves and 4 to 6 inches of purified polyester coil.

3.5.1.4 Dosage

For patients randomized through Amendment 2 (or earlier), Table 3 summarizes the dosage and dosing regimen for each treatment arm by Treatment Period week.

Table 3. Dose Regimen by Treatment Period Week

Dose	Weeks 1 and 2, BID Dosing	Weeks 3 through 12, QD Dosing
10 mg	one 5-mg IW-1973 Tablet, orally twice daily	two 5-mg IW-1973 Tablets, orally once daily
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

Beginning with Amendment 3 to the protocol, new patients will be randomized to either 40 mg IW-1973 or placebo, as summarized in Table 4.

Table 4. Dose Regimen by Treatment Period Week

Dose	Weeks 1 and 2, BID Dosing	Weeks 3 through 12, QD Dosing
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 study 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 above 8°C (46°F) up to a maximum temperature of 30°C (86°F) occurs for no longer than 24 hours, the clinical site is authorized by Ironwood Pharmaceuticals to continue using study drug after documentation of the excursion has been completed. If a temperature excursion below 2°C (<36°F) or above 30°C (>86°F) occurs for any period of time, or from 8 to 30°C for a period 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 bottles at room temperature.

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.

Subjects 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 Week 2, unused study drug will be returned to the clinic, accountability will be performed, and any unused study drug will be dispensed back to the study subject. At the end of the study, a complete reconciliation of the study drug supplies will be performed (ie, tablets will be counted). A copy of the final Drug Accountability Log will be provided to Ironwood. 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.

3.5.2 Method of Assigning Patients to Treatment Groups

A centralized interactive web response system (IWRS) will be used to randomly assign patients to study treatment. The computer-generated randomization schedule will be prepared by an independent statistician not otherwise associated with the conduct of the study.

Approximately 184 patients who meet all of the Inclusion Criteria and none of the Exclusion Criteria will be stratified by permanent/persistent atrial fibrillation status (yes or no) and by baseline peak VO_2 (<60% or ≥60% of age- and sex-adjusted normal values and with RER ≥1.0 as determined by CPET). An upper limit of approximately 36 patients with permanent or persistent atrial fibrillation will be set in the IWRS.

Patients enrolled under Amendment 2 to the protocol (or earlier) were randomized 1:1:1:1 to daily 10 mg IW-1973, 20 mg IW-1973, 40 mg IW-1973, or placebo at the Randomization Visit on Day 1. Beginning with Amendment 3 to the protocol, new patients will be randomized in a 1:1 ratio to daily doses of either 40 mg IW-1973 or placebo.

3.5.3 Selection of Dosage in the Study

This Phase 2 study will evaluate oral IW-1973 (40 mg), administered daily for 12 weeks. The dose level selection was originally based on data from the following study:

- Phase 1b study ICP-1973-102: "A 2-stage Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of IW-1973 Tablet Formulation in Healthy Volunteers in an Open-label, Single-dose, Crossover Stage Followed by a Randomized, Double-blind, Placebo-controlled, Multiple-ascending-dose with Optional Up-titration Stage"

In the Phase 1b multiple-ascending-dose (MAD) study (ICP-1973-102), along with preliminary data from C1973-201 and C1973-202 that were received subsequent to finalization of the original protocol, 40 mg IW-1973 was considered adequately tolerated and was therefore chosen for evaluation in this patient population.

Administration of split doses during the first 2 weeks of dosing is expected to reduce the initial time to maximum observed plasma concentration and to minimize variations in IW-1973 plasma concentrations during the approach to steady state, which may improve tolerability.

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

3.5.4.1 Study Drug Administration

During Weeks 1 and 2, patients will be instructed to take study drug BID (2×/day), as 1 tablet in the morning and 1 tablet approximately 12 hours later in the evening, and preferably at approximately the same times each day. Starting with the Week 2 Visit (Day 15 ±3), patients will be instructed to take study drug QD (1×/day), as 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 the 2 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 study drug dosing schedules and fasting requirements (Section 3.6.2).

Permitted concomitant medications should be taken as usual, may be taken at the same time as study drug, and do not need to be taken in the clinic on study visit days.

3.5.4.2 Dose Reduction

Per Investigator discretion, dose reduction is allowed after consultation with the Medical Monitor. If dose reduction is approved, the patient will be allowed to reduce his or her daily dose by half, ie, from 2 tablets daily to 1 tablet daily (in the morning). It is recommended for the patient to be evaluated in the clinic in association with any dose modification. Each patient's dose may only be reduced once and will not be increased after reduction.

3.5.5 Treatment Compliance

The appropriate amount of study drug will be dispensed to patients in prelabeled bottles. Patients will be asked to return all bottles (including unused tablets) at the subsequent study visit 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 Investigators, patients, and Sponsor will be blinded to treatment assignments. The investigational product and placebo will be supplied as oral tablets that match in appearance.

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 safety 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 IWRS in the event of a medical emergency. In advance of breaking the blind, the Investigator should make all reasonable efforts to notify and discuss the circumstances requiring unblinding with the Medical Monitor or designee. If the treatment blind is broken, the reason and the date must 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 early termination procedures (Section 3.4.2) should be followed.

To allow ongoing safety monitoring during the conduct of the study, members of an external DMC will review summaries of unblinded safety data. Please refer to Section 5.13 for details.

3.5.7 Prior and Concomitant Therapy and Procedures

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

- All medications (including name, dosage, and schedule) the patient is taking (ongoing)

- All prior medications (including name, dosage, and schedule) taken during the 30 days before the Screening Visit
- Prior procedures and surgeries

Beginning at the Screening Visit, any medication (including name, dosage, and schedule) or change in medication taken by a patient during the study will be documented in the source documents and the eCRF along with the time of use and the reason for use. Also beginning at the Screening Visit, any medical procedure or surgery that the patient undergoes will be documented in the source documents and the eCRF along with the start and stop date and reason.

Permitted concomitant medications should be taken as prescribed, may be taken at the same time as study drug, and do not need to be taken in the clinic on study visit days.

Prohibited medications and supplements are listed in Sections 3.6.1 and Appendix 1.

3.6 RESTRICTIONS

3.6.1 Prohibited Medicines and Supplements

The following medicines and supplements are prohibited from 7 days before the Randomization Visit (Day 1) through the duration of the trial:

- 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, or any sGC stimulator
- Nitrates or NO donors in any form

The following medicines and supplements are prohibited from 14 days before the Randomization Visit (Day 1) through the duration of the trial:

- Strong inhibitors of CYP3A; 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.

Should there be an urgent need for nitrate administration, it should occur in a monitored in-patient setting.

3.6.2 Fluid and Food

Patients should fast overnight (at least 8 hours) before all study visits, except the Screening Visit, and will continue fasting until the pre-CPET and predose blood and urine samples have been collected. See Section 3.8.8 for additional details.

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 (no menses for ≥12 consecutive months) or 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 her final dose of study drug:

- Progesterone implant and/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] combined with a barrier method, partner with vasectomy [conducted ≥60 days before the Screening Visit or confirmed via sperm analysis] plus a hormone or 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 highly effective birth control method (eg, condom with spermicide, partner IUD, partner diaphragm or cervical cap, partner hormonal contraceptive [including progesterone implant], or postmenopausal partner [no menses for ≥12 consecutive months]) 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.

3.6.3.2 Breastfeeding

Breastfeeding is not allowed from Screening Visit through 60 days after the final dose of study drug.

3.7 INDIVIDUAL STOPPING CRITERIA AND DATA MONITORING COMMITTEE REVIEWS

If any events included in Table 5 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 [Section 3.8.13.3]), individual stopping criteria or DMC review will be triggered per the criteria in Sections 3.7.1 and 3.7.2. The inclusion of these events is based on the clinical experience with IW-1973, the prescribing information for the sGC stimulator riociguat (23), and the patient population for this study.

Table 5. Categories of SAEs Triggering Individual Stopping Criteria and DMC Review

Treatment-emergent Study Drug-related SAE Category	Number of patients to trigger DMC review
Symptomatic hypotension-related events (eg, syncope)	5
Spontaneous bleeding events (eg, hemoptysis, vaginal hemorrhage, ovarian hemorrhage, subdural hemorrhage, hematemesis, hematochezia)	2

DMC=Data Monitoring Committee; SAE=serious adverse event

3.7.1 Individual Stopping Criteria

On an individual basis, a patient will be discontinued from study drug dosing if any of the following is reported for that patient:

- 1 study drug-related spontaneous bleeding SAE
- 1 study drug-related symptomatic hypotension-related SAE that is life threatening per protocol definition (Section 3.8.13.3)
- 2 study drug-related symptomatic hypotension-related SAEs

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 will review trial safety data both periodically and on an ad hoc basis per the SAE criteria in Table 5 (eg, spontaneous bleeding SAEs reported in 2 patients). After each periodic or ad hoc 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

The procedures and assessments described below will be performed according to the Schedule of Events.

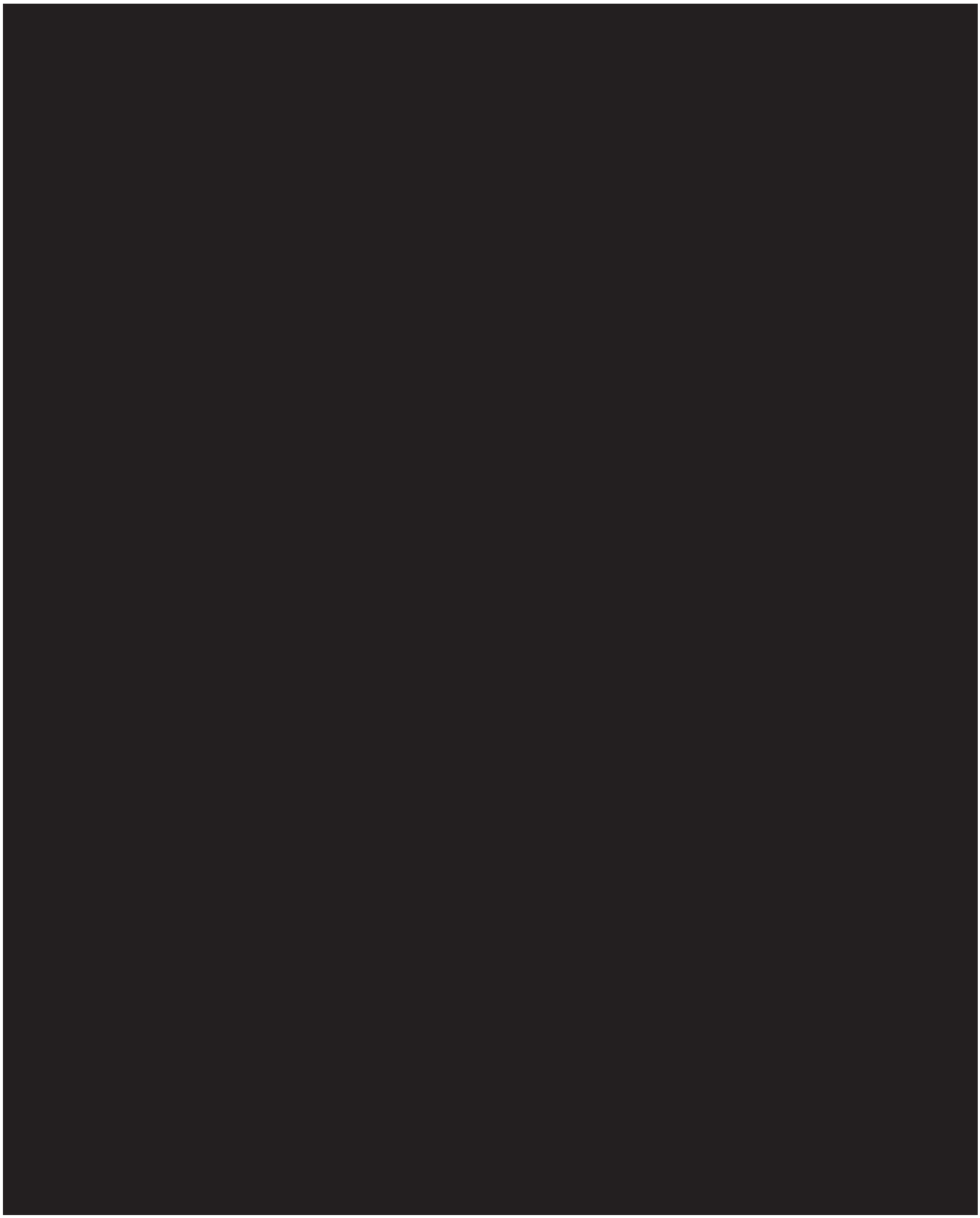
3.8.1 Informed Consent

Before a potential study participant undergoes any study-specific evaluations or procedures, he or she must provide written, informed consent. Please see Section 6.2 for more information.

3.8.2 Medical History

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

3.8.3 [redacted]



3.8.4 Physical Examination

Physical examinations, either complete, symptom-directed, and/or of the cardiovascular system will be performed. A complete physical examination of each patient should include assessment of the following, at minimum:

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. For Treatment Period visits, physical exam may be symptom-directed or limited to cardiovascular system at the Investigator's discretion. Any new, clinically significant abnormal findings from physical examinations 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 Vital Signs

Vital signs will include seated BP, pulse, respiratory rate, and oral temperature (°C). All vital signs should be measured after the patient has been sitting quietly for at least 5 minutes. For the Screening and Randomization Visits, BPs for eligibility will be the average of 3 measurements obtained at approximately 2-minute intervals.

3.8.6 Orthostatic Blood Pressure and Pulse

Sitting-to-standing BP and pulse measurements will be used for calculation of orthostatic BP and pulse. Patients should sit quietly for at least 5 minutes before sitting measurements are taken, then assume a standing position for 2 minutes (±1 m) before standing measurements are taken.

3.8.7 NYHA Functional Classification

At each timepoint, including for purposes of study eligibility, each patient's NYHA classification should reflect a contemporaneous assessment of functional status. Note that patients

experiencing any functional limitation whatsoever should be classified as NYHA Class II or higher.

Table 6. New York Heart Association (NYHA) Functional Classification

Class	Description
I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-56

3.8.8 Blood and Urine Sample Collection

3.8.8.1 Clinical Laboratory Tests

Blood and urine samples will be collected for clinical laboratory tests. Except for the Screening Visit, patients must fast for at least 8 hours before these sample collections. Laboratory values used for determination of eligibility must be fasted. Blood samples should be collected after electrocardiograms (ECGs) or at least 10 minutes before ECGs, when applicable.

The clinical laboratory evaluations will include the serum chemistry, hematology (complete blood count [CBC]), coagulation, urinalysis, and additional tests presented in Table 7.

Table 7. 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
Bilirubin (total and direct)	RBC indices	Leukocytes
BUN	MCH	Nitrites
Calcium	MCHC	Occult blood
Chloride	MCV	Protein
Cholesterol	RDW	Urobilinogen
Creatinine	WBC count	Microscopic:
GGT	WBC differential	Including bacteria, RBCs, WBCs
Glucose	(% and absolute):	per HPF if dipstick is abnormal
HDL-c	Basophils	
LDH	Eosinophils	**Additional blood tests**
LDL-c (calculated)	Lymphocytes	Hemoglobin A1c
Magnesium	Monocytes	Fasting plasma glucose
Phosphorus	Neutrophils	Fasting plasma insulin
Potassium		
Sodium	**Coagulation**	**Additional urine tests**
Total Protein	aPTT	Urine albumin & creatinine for UACR*
Triglycerides	Prothrombin time	
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.

* Samples should be first-void urine samples collected on the morning before or the morning of the applicable study visit. Patients will be supplied with specimen collection supplies at the preceding study visit.

3.8.8.2 Pregnancy Tests

For female patients of reproductive potential, a negative pregnancy test (by urine dipstick) must be documented at all study visits with results available before dosing, when applicable. In the event of a positive pregnancy test, the test will be repeated. If pregnancy is confirmed, see Section 3.8.13.5.

Pregnancy tests are not required for 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]).

3.8.8.3 Hepatitis, HIV, and Drug Screens

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

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

Amphetamines	Cocaine	Phencyclidine (PCP)
Barbiturates	Opiates	Propoxyphene
Benzodiazepines		

3.8.8.4 Urine Creatinine Ratio

The urine albumin creatinine ratio (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 7). Patients will be given urine collection supplies and will collect a first-void urine sample on the morning before or the morning of the specified study visit.

3.8.8.5 Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR) will be based on the serum creatinine level determined as part of the clinical laboratory tests (Table 7) and will be calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.(29)

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

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

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/κ or 1, and max indicates the maximum of Scr/κ or 1.

3.8.8.6 Homeostatic Model Assessment to Estimate Insulin Resistance (HOMA-IR)

Values from fasting plasma glucose and insulin levels (Table 7) will be used in the Homeostatic Model Assessment to estimate insulin resistance (HOMA-IR).(30, 31)

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).

3.8.8.7 [redacted]

[redacted]

3.8.9 Electrocardiograms

Twelve-lead ECGs should be obtained after the patient has been supine for at least 5 minutes. ECGs should be performed before blood collections or at least 10 minutes after blood collections, when applicable.

3.8.10 Echocardiography

Echocardiography may be performed at the Screening Visit to confirm eligibility. If performed at the Screening Visit, it can be used for baseline and does not need to be repeated. If echocardiography is not performed at the Screening Visit, the baseline echocardiography may be performed at either the Baseline *or* the Randomization Visit (predose). Echocardiography will also be performed at the End of Treatment Visit. When applicable, echocardiography should be performed before or at least 1 hour after exercise (CPET, 6MWT) is completed.

Echocardiography measurements for eligibility may be determined by the Investigator. Echocardiography measurements for efficacy analyses will be determined by an independent, central Echocardiography Core Lab that is blinded to treatment assignment.

At a minimum, the following echocardiographic variables will be determined:

- Mitral E/e' ratio (mitral peak velocity [E]/mitral annulus early diastolic recoil velocity [e'])
- LA volume
- LVEF
- LV chamber dimensions (LVESV and left ventricular end-diastolic volume [LVEDV])
- LV wall thickness (septal and posterior)

3.8.11 CPET

CPET will be performed using a study-specific protocol; details will be provided in a CPET study manual. Each study site will be CPET qualified for the study. Patients must use the same form of exercise (treadmill or bicycle) for all 3 CPETs, and the method of exercise should be recorded in the patient's eCRF. In general, patients will exercise to peak capacity beginning with unloaded exercise and continuing with a symptom-limited incremental ramp to peak VO_2 with RER ≥1. For the baseline CPET, RER must be ≥1. For Week 8 and End of Treatment CPETs, patients should exercise to maximum effort, ideally to RER ≥1.

CPET should be performed at the same time of day (±2 h) and should be timed to occur ≥1 hour postdose, when applicable. The CPET will precede the 6MWT when applicable, which will be started ≥1 hour after the CPET is completed.

CPET measurements for eligibility and for efficacy analyses will be determined by an independent central CPET Core Lab.

At a minimum, the following measures will be determined:

- Peak VO_2 (mL O_2/kg/min)
- RER
- Ventilatory efficiency (VE/VCO_2 slope)
- Peak Power Output at Ventilatory Anaerobic Threshold (watts)

Other parameters of interest may be analyzed.

3.8.12 6-minute Walk Test

The distance, in meters, travelled in 6 minutes will be measured using a study-specific 6MWT protocol (Appendix 6).

The 6MWTs should be performed at approximately the same time of day (within a 4-hour window) and must be started at least 1 hour after CPET is completed, when applicable.

3.8.13 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.

3.8.13.1 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

3.8.13.2 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.

3.8.13.3 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).

3.8.13.4 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.

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.

3.8.13.5 Reporting Serious Adverse Events

All AEs that meet any of the serious criteria must be reported to Medpace Clinical Safety within 24 hours from the time that site personnel first learn of the event. All SAEs must be recorded in the subject's source documentation and, subsequently, entered into the electronic data capture (EDC) system on the appropriate AE reporting page of the subject's eCRF, whether or not an event is considered causally related to study medication. Once the AE eCRF has been completed or updated, Medpace Safety will be notified electronically and retrieve the form.

If an event meets serious criteria and it is not possible to access the EDC system, the site should send an e-mail to Medpace Safety at [redacted] or call the Medpace SAE Reporting Line (phone number listed below), and fax the completed paper Back Up SAE form to Medpace Safety (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Contact Information for Medpace Clinical Safety:

Safety Inbox E-mail: [redacted]

SAE Reporting Line: [redacted]

Safety Fax: [redacted]

When follow-up is obtained or requested by Medpace Clinical Safety, the additional information should be recorded on AE eCRF (as applicable) or sent to Medpace Clinical Safety within 24 hours of receipt by the site. Copies of discharge summaries, consultant reports, autopsy reports, and any other relevant documents may 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 patient's response to these measures should be recorded. All SAEs, regardless of relationship to study medication, will be followed by the Investigator until satisfactory resolution, until the Investigator deems the SAE to be chronic or stable, or until the patient 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/IEC, as applicable. Ironwood will be responsible for reporting to the regulatory authorities.

Special Situation: Exposure to Study Drug During Pregnancy

A patient who reports pregnancy before study drug randomization must be withdrawn from the study. The pregnancy will be recorded as a reason for screen failure. Since there will have been no exposure to study drug, there will be no need to notify Medpace Clinical Safety of the pregnancy.

A patient who reports pregnancy after randomization must discontinue study drug at once. The site must notify Medpace Clinical Safety within 24 hours from the time that site personnel first learn of the pregnancy (via email or SAE Reporting line). Medpace Clinical Safety will send the site an Exposure in Utero (EIU) Form for completion within 24 hours. The site should make reasonable efforts to follow the pregnancy to term and notify Medpace Clinical Safety of the pregnancy outcome (within 24 hours of being informed) or if outcome is associated with an SAE (eg, if the mother is hospitalized, spontaneous abortion, congenital anomaly), the site should follow SAE reporting procedures, as discussed above.

3.8.14 Cardiac Events

Hospitalizations of cardiovascular etiology and all deaths will be classified by the central, independent, blinded cardiac events adjudicator(s).

3.8.15 Pharmacokinetic Assessments

Blood samples will be collected for PK assessments.

3.8.16 [redacted]

[redacted]

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 peak VO_2 (CPET) at Week 12

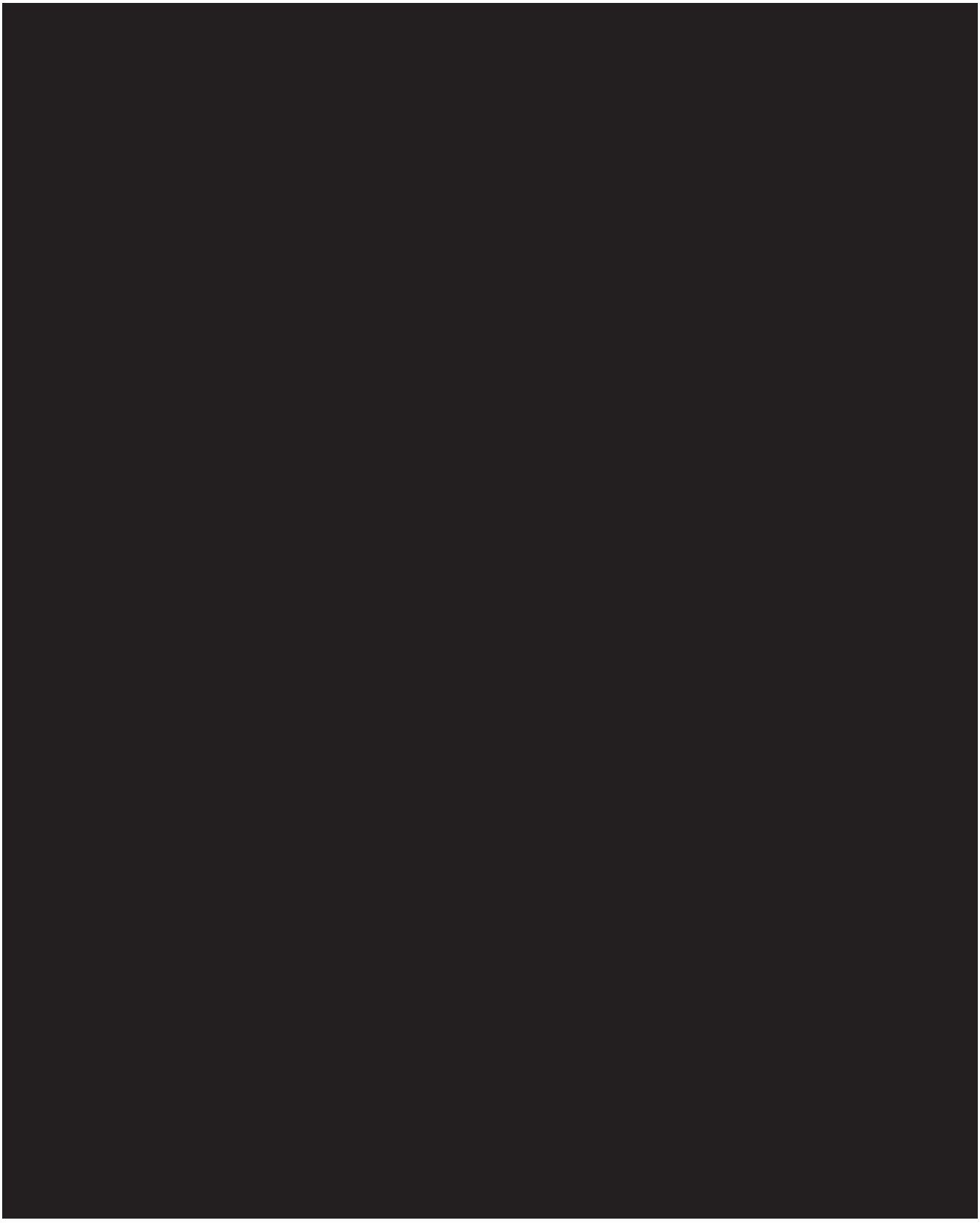
4.2 SECONDARY ENDPOINTS

4.2.1 Secondary Efficacy

- Change from baseline in 6MWT distance at Week 12
- Change in ventilatory efficiency as defined by VE/VCO_2 slope (CPET) at Week 12
- CPET Responders (Responders are subjects who improve by at least 1.5 mL O_2/kg/min in peak VO_2 from baseline to Week 12. Subjects who are hospitalized or who die due to heart failure during the study Treatment Period are considered nonresponders.)

4.3 EXPLORATORY ENDPOINTS

[redacted]



5. STATISTICAL METHODS

5.1 GENERAL CONSIDERATIONS

Descriptive statistics (n, mean or geometric mean, standard deviation, minimum, median, maximum, 25th and 75th percentiles) will be calculated to summarize continuous variables. Count and percentage of patients in each category will be calculated to summarize categorical variables.

Additionally, inferential statistical analysis will be performed on primary and secondary efficacy endpoints described in Sections 5.1.1 and 5.1.2.

5.1.1 Continuous Endpoints

For continuous endpoints (eg, absolute change from baseline and percent change from baseline), an analysis of covariance (ANCOVA) model will be fitted with treatment group and stratification factors as categorical variable terms and the corresponding baseline efficacy value as a covariate. Least squares means (LSMs) and 95% confidence intervals for each treatment group as well as LSM difference between the 40-mg IW-1973 group and the placebo group will be presented, along with the corresponding confidence intervals and p-values. The cumulative distribution function (CDF) of change from baseline will be plotted by treatment group. To aid in the interpretation of the graphical representation of the CDF across treatments, a two-sample Kolmogorov-Smirnov test will be conducted.

5.1.2 Responder Endpoints

For responder endpoints, the proportions of responders between the 40-mg IW-1973 group and the placebo group will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for stratification factors. The difference in the proportion of responders between the 40-mg IW-1973 group and the placebo group as well as the CMH estimates of odds ratio and p-values will be presented, along with the corresponding confidence intervals.

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

The study is not designed to formally test a single statistical hypothesis; however, approximately 184 subjects will provide approximately 90% power to detect a mean difference of 1.3 (mL O_2/kg/min) between the 40-mg IW-1973 treatment arm and the placebo treatment arm in change from baseline at Week 12 peak VO_2. This estimate is based on the Evaluable Population (defined in Section 5.3), including patients with permanent or persistent atrial fibrillation at Screening, and using the follow assumptions:

- 5% Type I error for a 2-sided test
- Mean Peak VO_2 change from baseline at Week 12 for Placebo arm is 0.0 (mL O_2/kg/min)
- Mean Peak VO_2 change from baseline at Week 12 for 40 mg IW-1973 is 1.3 (mL O_2/kg/min)
- Equal standard deviation for all treatment arms at 2.5 (mL O_2/kg/min) for change from baseline at Week 12
- 10% attrition prior to Week 12 CPET
- 10% of the total number of patients were randomized to either the 10- or 20-mg IW-1973 dose groups under Amendment 2 of the protocol (or earlier)
- Reduced treatment effect for IW-1973 in subjects with permanent or persistent atrial fibrillation at Screening

Additionally, under similar assumptions, this sample size will also provide 90% power to detect a mean difference of 1.5 (mL O_2/kg/min) on the same endpoint on the well-defined subgroup of a minimum of approximately 148 patients without permanent or persistent atrial fibrillation at Screening.

5.3 ANALYSIS POPULATIONS

ITT Population	All randomized subjects
Safety Population	All randomized patients who take at least 1 dose of study medication
mITT Population	All randomized patients who take at least 1 dose of study drug and have at least 1 evaluable baseline measurement.
Evaluable Population	All patients in the mITT who complete 8 weeks of dosing (±3 days) and have at least 1 evaluable postbaseline assessment. Other criteria may be established and reviewed before database lock and unblinding.
PK Population	All patients who have received at least 1 dose of IW-1973

ITT=intent to treat; mITT=modified intent to treat

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, BMI and other baseline characteristics will be summarized by treatment group for the Safety, Evaluable, and modified intent-to-treat (mITT) Populations, using descriptive statistics as defined in Section 5.1.

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 Safety 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 each scheduled visit 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 AND PROCEDURES

Prior medicines and procedures are defined as any medicine taken or procedure performed on the patient before the date of first dose of study drug.

Concomitant medicines and procedures are defined as any medicines taken or procedures performed on the patient on or after the date of first dose of study drug. Any medicines taken or procedures performed after the date of last dose of study drug will not be considered concomitant for purposes of analysis. 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 Intent-to-treat (ITT) Population. Multiple medicines within the same category (based on Anatomical-Therapeutic-Chemical classification) will only be counted once for that patient.

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. 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(s) that could meaningfully impact interpretation of study 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

5.9.1 Controlling for Multiplicity

Due to the exploratory nature of this study, there is no adjustment on the p-values for multiple testing. All reported p-values are considered nominal. A p-value ≤0.05 indicates that the 2 treatment samples are less likely to have been drawn from the same distribution by chance alone.

5.9.2 Analyses on the Primary Efficacy Endpoint

An ANCOVA analysis as described in Section 5.1.1 will be performed on the primary efficacy endpoint as defined in Section 4.1.2 with treatment group and stratification factors as categorical variable terms and the corresponding baseline CPET value as a covariate on each of the following 2 populations:

- Evaluable Population
- A subgroup of the Evaluable Population, excluding patients who had permanent or persistent atrial fibrillation at baseline

Sensitivity analyses similar to the above analysis will be performed on each of the above 2 analyses using the mITT Population. In these analyses, patients without a Week 12 CPET measurement will carry Week 8 or earlier postbaseline measurement forward. Patients with no postbaseline CPET measurement will be assigned 0 as improvement, or no change from baseline. Details of the sensitivity analysis will be included in the SAP.

5.9.3 Analyses on the Secondary Efficacy Endpoints

All secondary and exploratory analyses will be performed on the Evaluable Population and a subgroup of the Evaluable Population excluding patients with permanent or persistent atrial fibrillation at baseline.

ANCOVA models described in Section 5.1.1 will be used to compare the 40-mg IW-1973 group with the placebo group on the following secondary endpoints.

- Change from baseline in 6MWT distance at Week 12
- Change in ventilatory efficiency as defined by VE/VCO_2 slope (CPET) at Week 12

Proportions of responders based on CPET will be compared using a responder analysis as described in Section 5.1.2.

Details of other analysis, such as exploratory analysis [redacted]

5.10 SAFETY ANALYSES

All safety parameters will be analyzed with descriptive statistics as described in Section 5.1 on the Safety Population. The safety parameters will include AEs, TEAEs, clinical laboratory evaluations, vital signs, ECG, and physical examination. For each applicable safety parameter, the last nonmissing assessment made before randomization will be used as the baseline for all analyses of that safety parameter.

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 and will be summarized by MedDRA system organ class (SOC), preferred term (PT), and treatment group. Listings will be provided for pretreatment AEs, TEAEs, severe AEs, study drug-related AEs, SAEs, and AEs leading to study discontinuation.

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. If a patient has more than 1 TEAE coded to the same PT, the patient will be counted only once for that PT 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.

5.10.4 ECGs

Descriptive statistics for ECG parameters and changes from the baseline values at each assessment time point will be presented by treatment group.

The number and percentage of patients with ECG abnormalities that are considered TEAEs by the Investigator will be tabulated by treatment group. A listing of all AEs for patients with ECG-related TEAEs will also be provided.

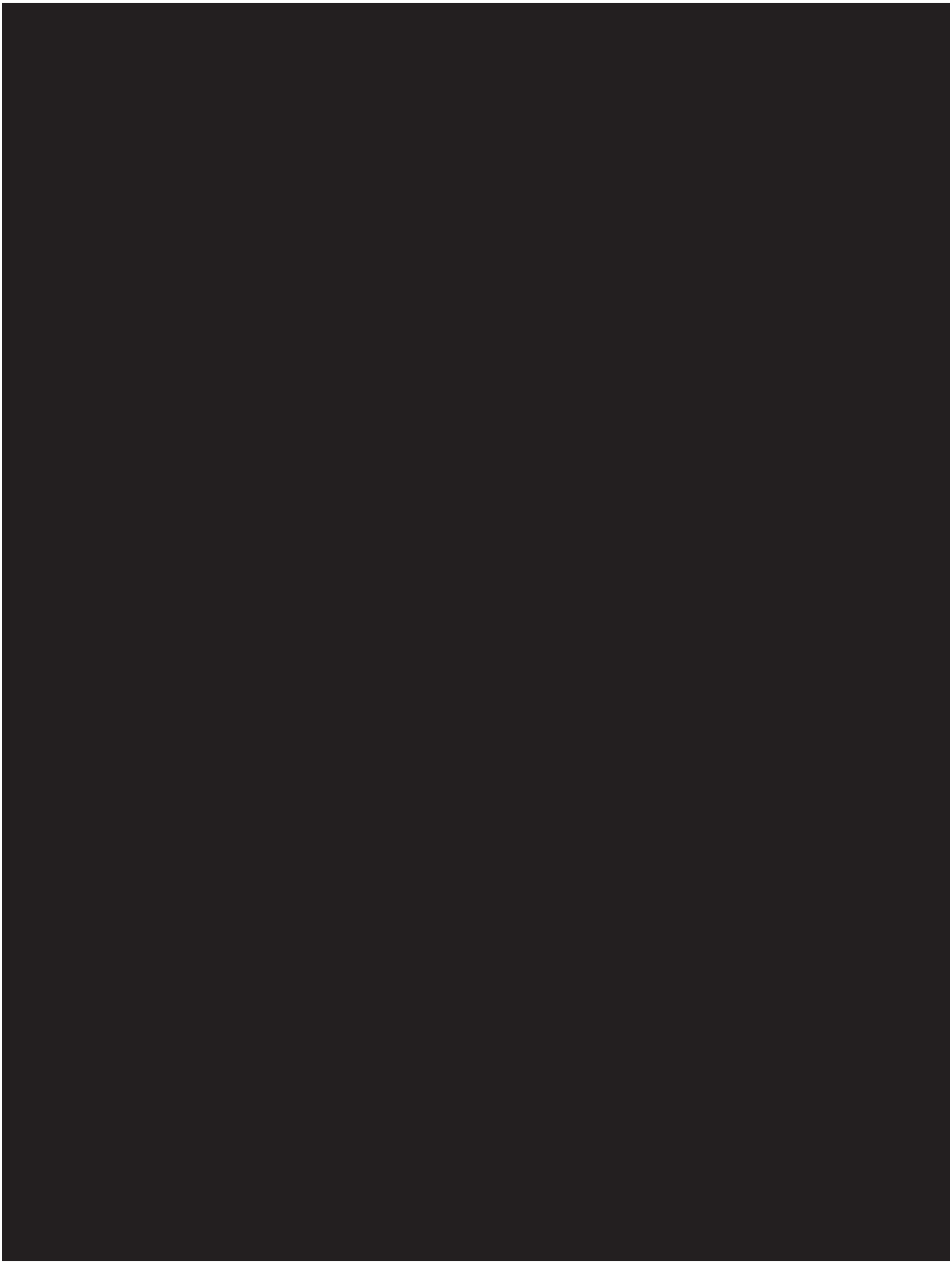
5.11 PK [redacted]

PK analyses will be based on the PK Population. Descriptive statistics will be calculated for plasma concentrations of IW-1973 at each assessed timepoint by study visit.

[redacted]

5.12 [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 recognized experts in cardiovascular disease and 1 biostatistician who have experience in clinical trials and are not otherwise 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.

Periodic safety review meetings will be scheduled after approximately 50 patients and after 100 patients have completed 2 weeks of the Treatment Period (but at least twice every 12 months, unless a different frequency is deemed appropriate by the DMC Chair). For these periodic reviews, the DMC will be provided with unblinded summaries of TEAE data by treatment groups. 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. All data that are available at the time of each analysis will be presented. If a safety/tolerability signal or concerning AE imbalance is identified at a review, the committee may request additional safety data (eg, vital signs, concomitant

medications) At each meeting, the DMC will review cumulative TEAE data and recommend trial continuation, modification, or termination.

The DMC will also be required to perform ad hoc review(s) per SAE criteria in Table 5. In this circumstance, the committee will be provided with narrative descriptions and all relevant clinical supporting documentation related to the SAEs under review. Upon request, the subjects' unblinded treatment and dose level information 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 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/unblinded data and discuss study findings with the DMC. 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 the first patient is randomized.

5.14 INTERIM ANALYSES

Planned interim safety analyses will be performed for the sole purpose of providing preliminary safety analyses to the DMC (Section 5.12.4).

An additional optional interim analysis to review unblinded efficacy data to assist with the planning of future studies may be performed after at least one half of the anticipated subjects (N≥92) have completed the last visit. If performed, details regarding the interim analysis will be included in the SAP, along with updates to the data management plan as necessary. An 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. Review of the interim analysis for planning purposes will operate independently of the study data monitoring and endpoint adjudication committees.

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/IEC) must be approved by the IRB/IEC 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/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

Deviating from the protocol will be 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/INSTITUTIONAL ETHICS COMMITTEE

Before the 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 applicable Institutional Review Board (IRB) or Institutional Ethics Committee (IEC).

All IRB/IEC approvals must be dated and signed by the IRB/IEC Chairperson or his or her designee and must identify the IRB/IEC 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/IEC approvals will be forwarded to Ironwood. All correspondence with the IRB/IEC should be maintained in the Investigator File.

No drug will be released to the site to dose a patient until written IRB/IEC 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/IEC. The Investigator must supply Ironwood with written documentation of the approval of the continued clinical research.

The IRB/IEC must be constituted in accordance with ICH Good Clinical Practice (GCP) guidelines and any relevant and applicable local and national 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/IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB/IEC 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/IEC 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 and the patient will be reconsented. The revised ICF must be submitted to the IRB/IEC for review and approval before its use.

7. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at multiple study sites. The Investigator at each study site will be responsible for ensuring that the study is conducted according to the signed Clinical Trial Agreement, the protocol, IRB/IEC 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/IEC, and completing the eCRF.

7.1 GENERATION OF STUDY RECORDS

Before activating each site, Ironwood or its designated representative will verify the qualifications of each Investigator, inspect study site facilities as necessary, 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

Study data will be recorded in the patient's source documentation and entered in eCRF in Ironwood or designee's 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

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/IEC, 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; alternatively, study medication may be destroyed on site with prior approval by 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 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.

9.2 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 log provided to Ironwood as part of the site close-out report. Written approval for return of all unused and reconciled study medication or destruction by 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.

9.3 RETENTION AND REVIEW OF RECORDS

The investigator will retain records and documents pertaining to the conduct of this study, including eCRFs, source documents, ICFs, laboratory test results, and medication inventory records, for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

The Sponsor may request retention of records for a longer period of time; therefore, 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 this responsibility. Ironwood must be notified of and agree to the change in advance.

9.4 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 by patient identification 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 patient ID number and the full name, address, and telephone number of each patient is listed.

10. REFERENCE LIST

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APPENDIX 1 PROHIBITED MEDICINES AND SUPPLEMENTS

Prohibited from 7 days before Randomization 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 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 3A; NO=nitric oxide; PDE=phosphodiesterase

APPENDIX 2

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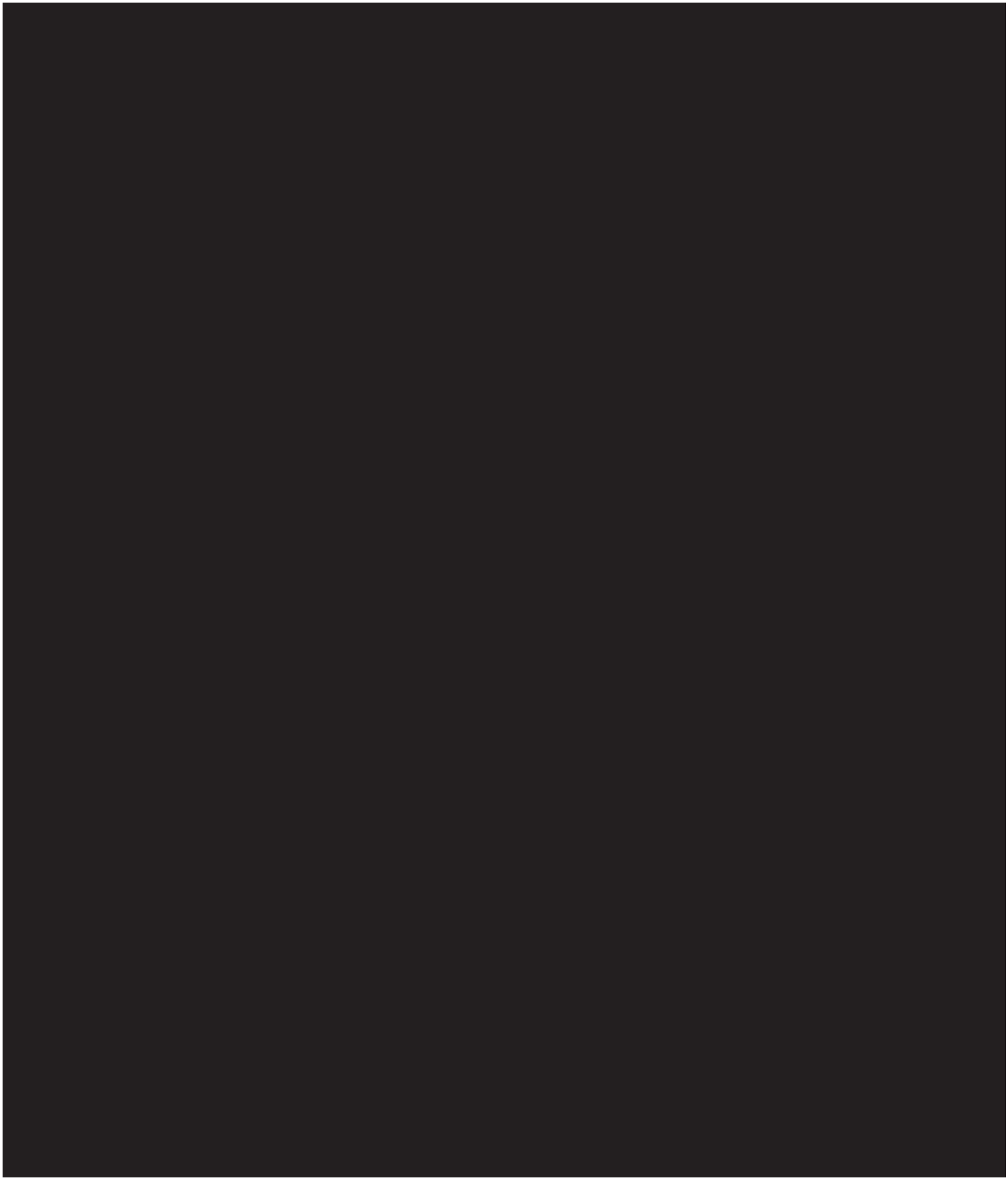

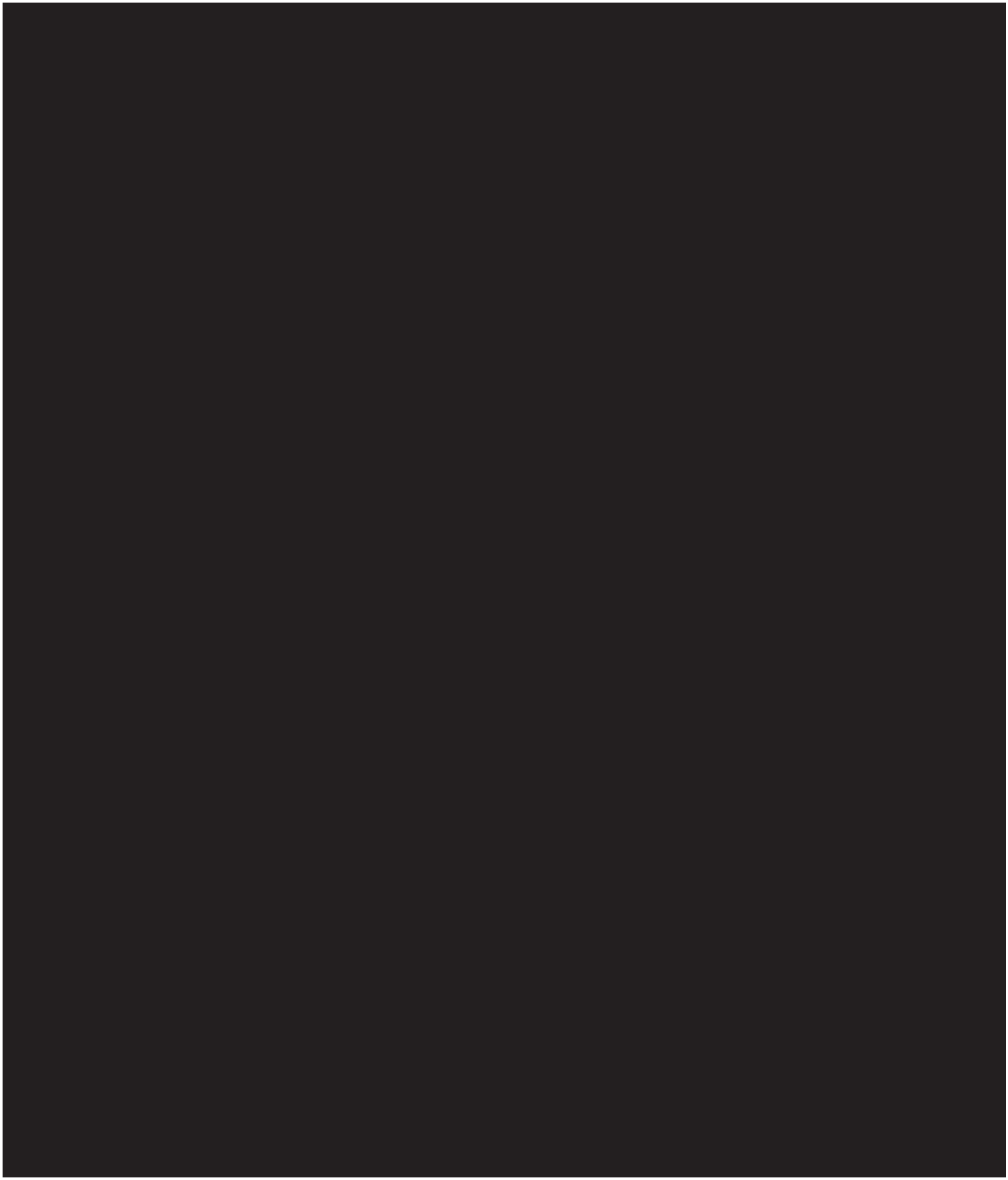

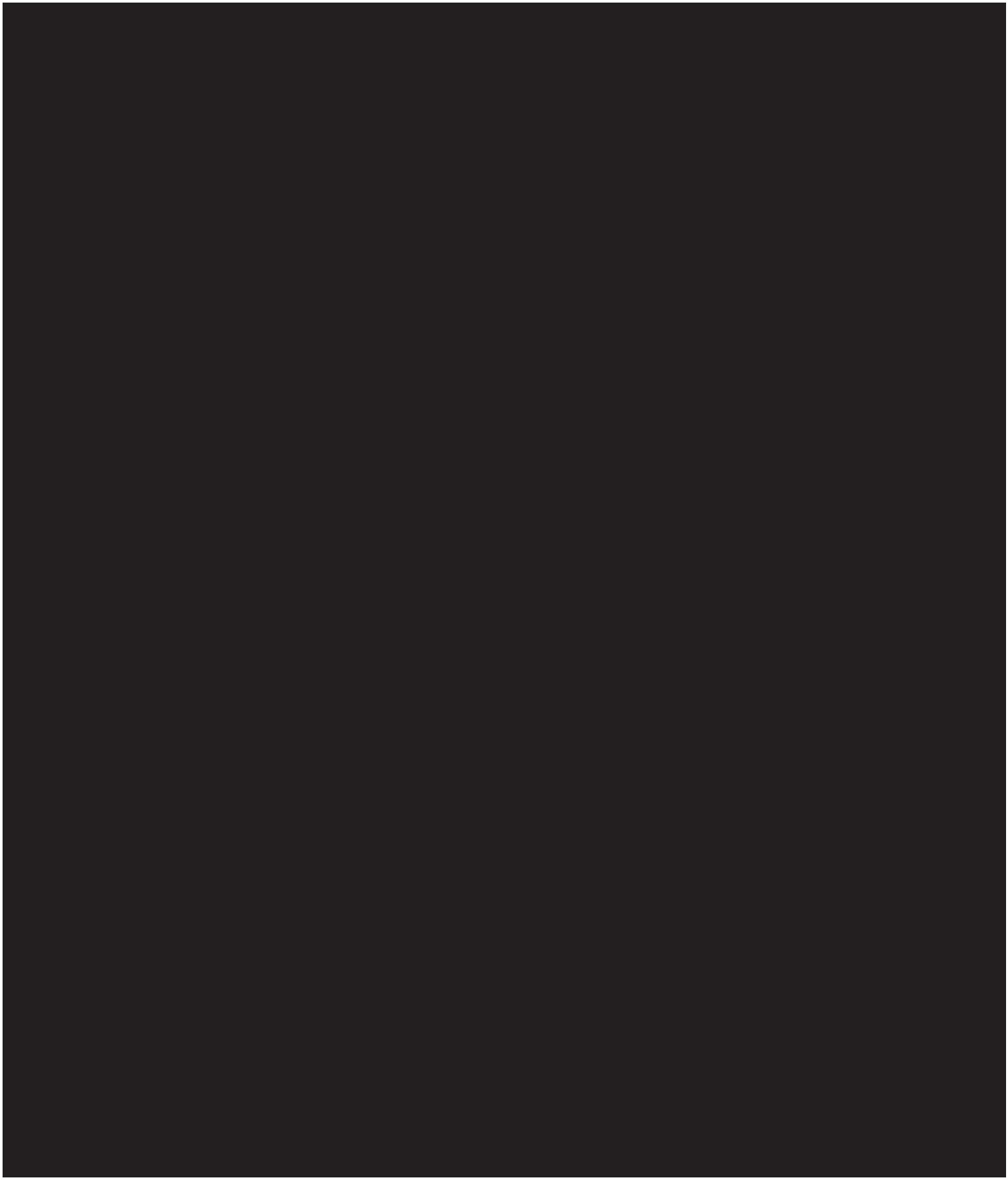

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APPENDIX 4

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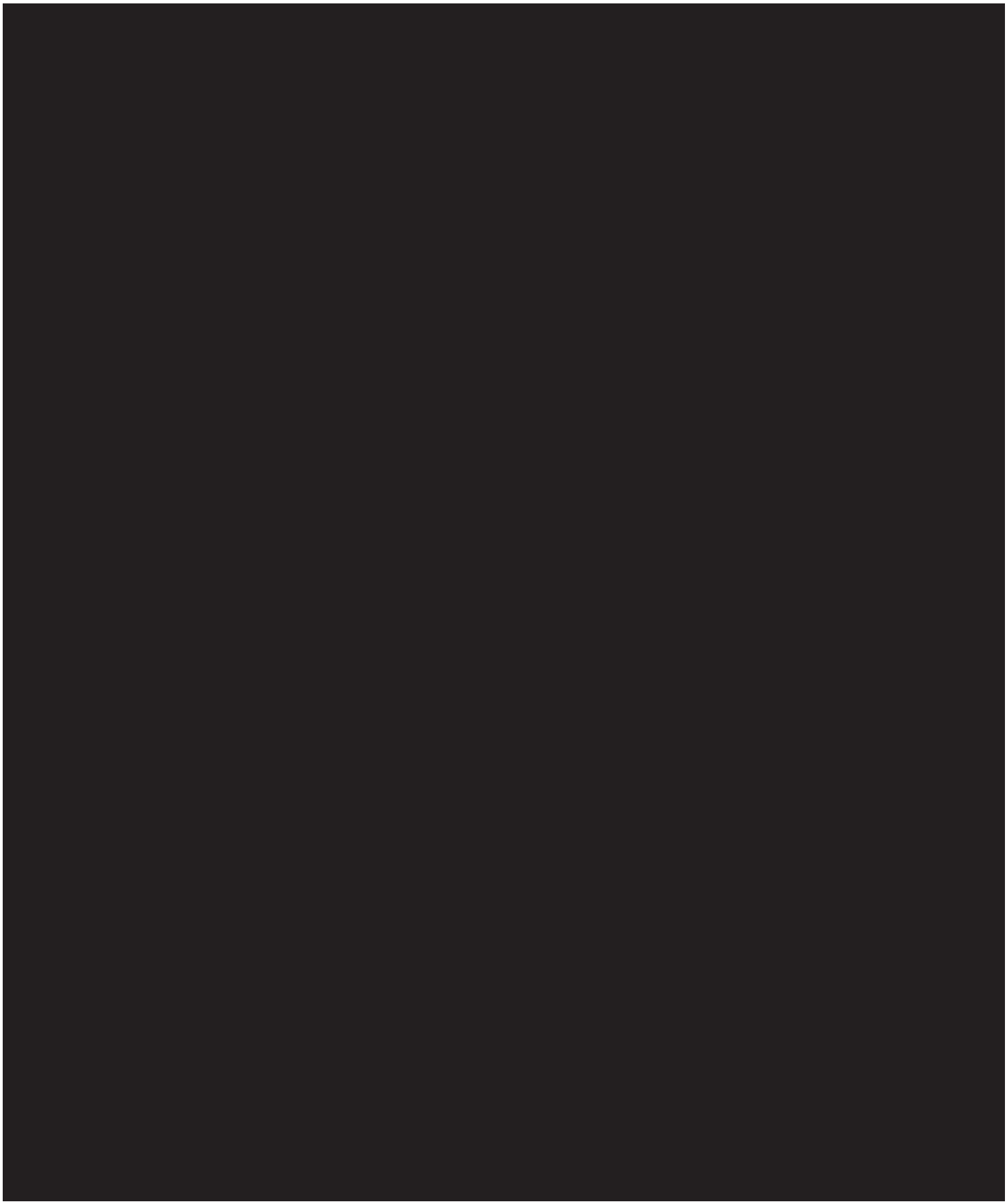

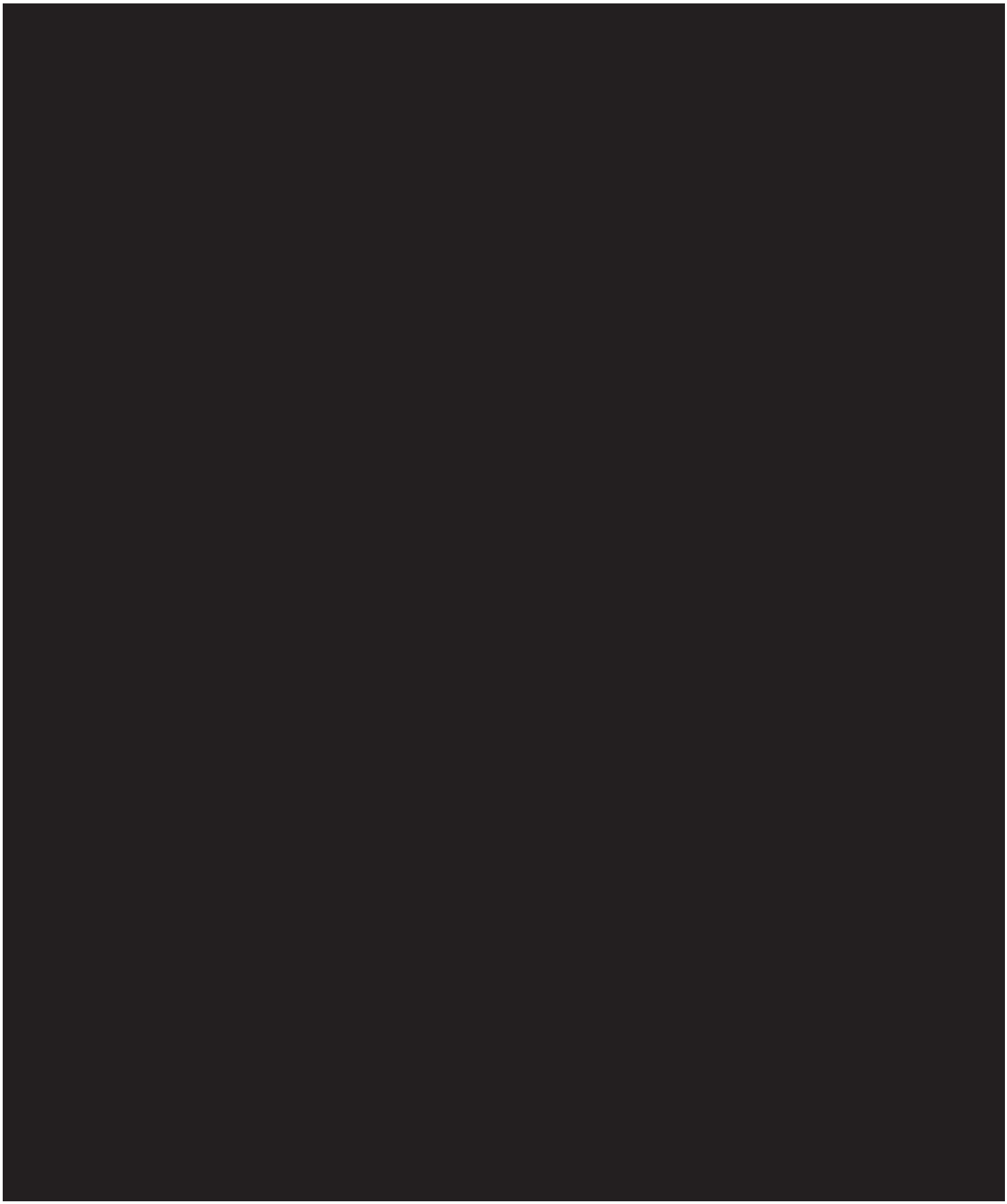

APPENDIX 5

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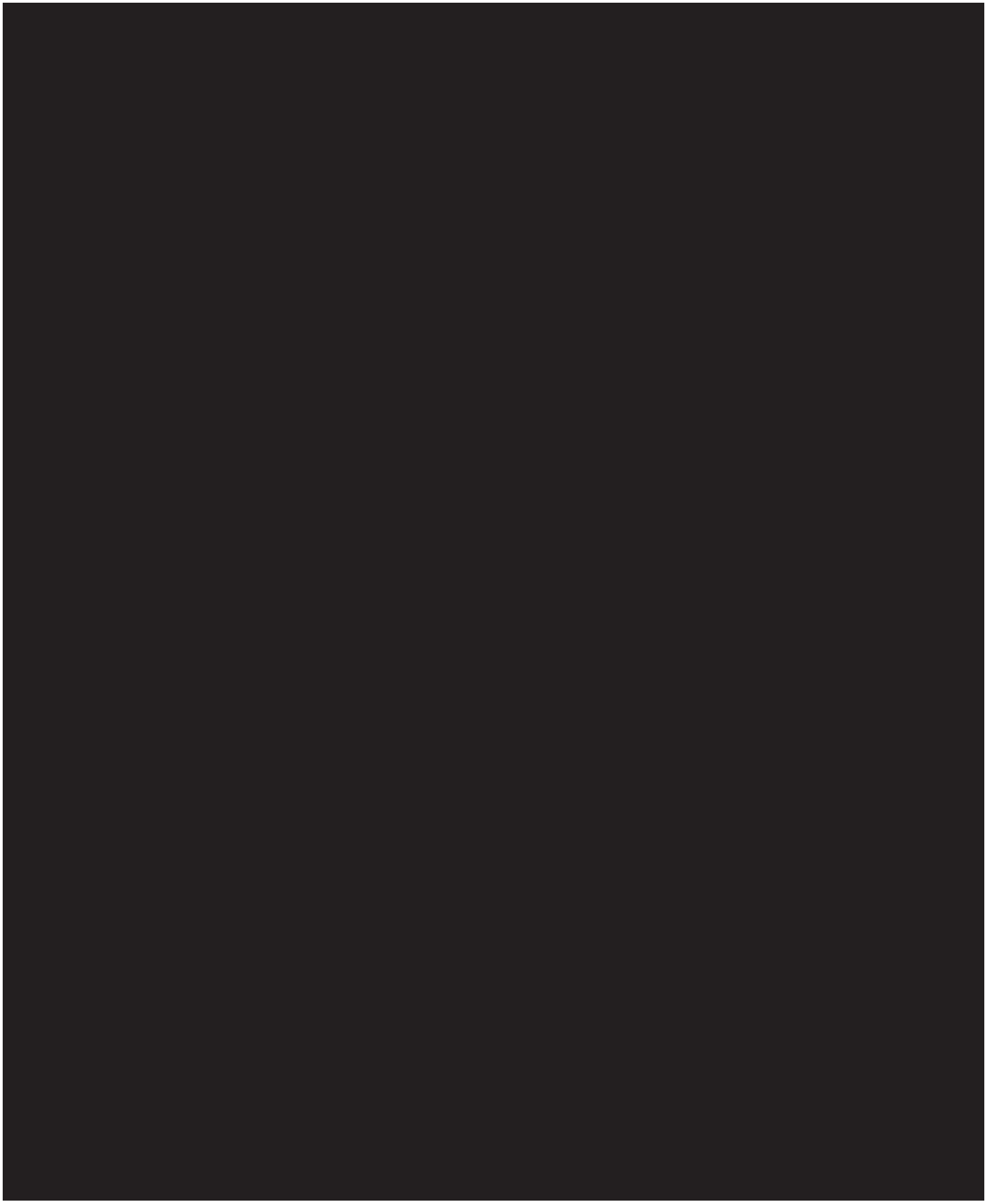

APPENDIX 6 6-MINUTE WALK TEST METHOD

The 6-minute walk test will be conducted according to the study 6-Minute Walk Manual, which is adapted from the guidelines of the American Thoracic Society.(33) It is recommended that the same study coordinator conduct each test for each applicable patient. The following recommendations should be followed:

- Ensure that the track layout remains consistent for baseline, and subsequent 6-minute walk tests. The track should be a straight corridor.
  - The track should be flat, with no steps, blind turns, or obstacles.
  - The minimum recommended length for the track is 25 meters. A 30-meter length is preferred.
  - A measuring tape should be used to measure walking distance. The track should be marked every 3 meters.
  - The same location should be used at each visit for a given patient.
  - This should be an area in which access by other people can be restricted during the test.
- Instruct the patient to dress comfortably, wear appropriate footwear, and to avoid eating for at least 2 hours before the test (where possible or appropriate).
- Any prescribed inhaled bronchodilator medication should be taken 1 hour before test or when the patient arrives for test.
- The patient should rest for at least 15 minutes before beginning the 6-minute walk test in a chair near the starting position.
- Give standardized instructions before beginning the test as specified in the study 6-Minute Walk Manual:

  "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

  Demonstrate by walking one lap yourself.

  "Are you ready to do that? I am going to use this worksheet to keep track of the number of laps you complete. I will check it off each time you turn around at this starting line.

Remember the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now or whenever you are ready."

- Give standardized verbal encouragement during the test, in an even tone of voice:
  - At 1 minute: "You are doing well. You have 5 minutes to go."
  - At 2 minutes: "Keep up the good work. You have 4 minutes to go."
  - At 3 minutes: "You are doing well. You are halfway done."
  - At 4 minutes: "Keep up the good work. You have only 2 minutes left."
  - At 5 minutes: "You are doing well. You have only 1 minute to go."
  - When the timer is 15 seconds from completion: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."
  - At 6 minutes: "Stop!"

The data and information related to my line function, which has been included with this file, are truthful and accurate.

Approval	[redacted] Approver 29-Jun-2018 19:19:42 GMT+0000

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