Statistical Analysis Plan: C1973-202

Final Version 1.0, 15 August 2017

Study Title:	A Phase 2 Study to Compare the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of 2 Dose Regimens of IW-1973 in Patients with Stable Type 2 Diabetes and Hypertension
Study Number:	C1973-202
Product Name:	IW-1973 Tablet
Sponsor:	Ironwood Pharmaceuticals, Inc. 301 Binney Street Cambridge, MA 02142

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

Abbreviation	Full Term
ABPM	ambulatory blood pressure monitoring
ADP	adenosine 5'-diphosphate
AE	adverse event
AI	augmentation index
AI-75	augmentation index adjusted to a heart rate of 75 beats per minute
ALT	alanine aminotransferase
aPTT	activated partial prothrombin time
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the time curve
BID	twice daily
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
[redacted]	[redacted]
CL/F	apparent clearance (clearance relative to bioavailability)
C_{max}	maximum observed plasma concentration
C_{trough}	trough plasma concentration observed at the end of a dosing interval (collected before the next administration)
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate (mg/mL/1.73 m^2)
FPG	fasting plasma glucose
FPI	fasting plasma insulin
GGT	gamma glutamyl transferase
GP	glycoprotein

Abbreviation	Full Term
Hemoglobin A1c	hemoglobin A1c (glycated hemoglobin)
HDH	high density lipoprotein
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment to quantify insulin resistance
HPF	high power field
ICF	informed consent form
kg	kilogram
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LLQ	lower level of quantification
MAP	mean arterial pressure
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
MPV	mean platelet volume
NO	nitric oxide
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
PRP	platelet rich plasma
PRU	P2Y12 reaction units
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell

Abbreviation	Full Term
RDW	red blood cell distribution width
RHI	reactive hyperemia index
SAE	serious adverse event
SAP	statistical analysis plan
sCr	serum creatinine
SOC	system organ class
$t_{1/2}$	apparent terminal phase half-life
tau	dosing interval
TEAE	treatment-emergent adverse event
T_{max}	sampling time of maximum observed plasma concentration
TRAP	thrombin receptor activating peptide
UACR	urine albumin creatinine ratio
US	United States
WBC	white blood cell
WB	whole blood samples

1. INTRODUCTION

Study C1973-202 is a Phase 2a, randomized, double-blind, placebo-controlled, study in patients with stable type 2 diabetes mellitus and hypertension to compare the safety, tolerability, pharmacokinetic (PK) profile, and pharmacodynamic (PD) effects of 2 treatment regimens of IW-1973 Tablet (40 mg per day) administered orally for 2 weeks.

This statistical analysis plan (SAP) provides a more technical and detailed description of the data presentations and statistical analyses of the data as outlined and/or specified in the final protocol for Study C1973-202 (C1973-202-P-03, dated 16 March 2017). Specifications of tables, figures, and data listings are contained in a separate document.

2. STUDY OBJECTIVES

The objectives of the study are to compare the safety, tolerability, PK profile, and PD effects of 2 treatment regimens of IW-1973 Tablet (40 mg per day) administered orally for 2 weeks to patients with stable type 2 diabetes mellitus and hypertension.

3. STUDY DESIGN

3.1 GENERAL DESCRIPTION

This randomized, double-blind, placebo-controlled trial will randomize 26 patients (at least 11 male and 11 female) with stable type 2 diabetes and hypertension in a 5:5:3 ratio to 1 of 2 IW-1973 treatment regimens or placebo. Patients will receive a morning (AM) dose and an evening (PM) dose for 14 consecutive days. Patients will be in clinic for 17 days, from Check-in on Day -2 to Discharge on Day 15. Total patient participation will be 35 to 73 days. The study will be performed at up to 3 US study centers.

3.2 TREATMENTS ADMINISTERED

Patients will be randomized in a 5:5:3 ratio to 1 of 2 IW-1973 treatment regimens or placebo (all regimens will be masked) as outlined in Table 1.

Table 1. Treatment Arm Dosing Regimens

Treatment Arm	Dose time	Days 1 to 7	Days 8 to 14
PBO/PBO	AM	Placebo (8 x placebo tablet)	Placebo (8 x placebo tablet)
	PM	Placebo (8 x placebo tablet)	Placebo (8 x placebo tablet)
BID/QD	AM	20 mg IW-1973 (4 x IW-1973 Tablet*) (4 x placebo tablet)	40 mg IW-1973 (8 x IW-1973 Tablet*)
	PM	20 mg IW-1973 (4 x IW-1973 Tablet*) (4 x placebo tablet)	Placebo (8 x placebo tablet)
QD/QD	AM	40 mg IW-1973 (8 x IW-1973 Tablet*)	40 mg IW-1973 (8 x IW-1973 Tablet*)
	PM	Placebo (8 x placebo tablet)	Placebo (8 x placebo tablet)

PBO = Placebo, BID = twice daily, QD = once daily
* All IW-1973 tablets are 5 mg oral tablets

3.3 METHODS OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized to treatment on Day 1. Patients will be randomized in a 5:5:3 ratio to receive BID/QD IW-1973, QD/QD IW-1973, or placebo.

The randomization schedule was generated using a block size of 13. The lowest randomization number will be assigned to the first patient that qualifies for randomization and subsequent randomization assignments will proceed in increasing sequential order within a block as patients are qualified for the study. The randomization schedule was prepared using SAS® PLAN procedure (PC SAS® Version 9.3) by an independent randomization biostatistician at Ironwood who is not involved in the conduct of the trial (i.e., allocation of subjects, assessment of endpoints, handling of withdrawals, exclusion of data from analysis, query and resolution of study data, etc.)

3.4 BLINDING

This is a double-blind, placebo-controlled study. The patients, investigators, study staff (with the exception of specifically designated unblinded Study Center pharmacy staff), and the sponsor will remain blinded to the randomization scheme until the blind is formally broken for all subjects. For this to occur, all subjects must have completed the study and the study database must be locked.

Prior to database lock, a treatment assignment may be unblinded by the site only in emergency situations and/or by the Ironwood Drug Safety and Pharmacovigilance group if the knowledge of the treatment received is essential for managing a serious adverse event (SAE).

4. DETERMINATION OF SAMPLE SIZE

The sample size in this trial was determined outside of statistical considerations. Twenty-six patients were considered adequate for point estimates with reasonable accuracy.

5. SAFETY, PHARMACODYNAMIC, AND PHARMACOKINETIC ASSESSMENTS

5.1 STUDY SCHEMATIC AND SCHEDULE OF ASSESSMENTS

The schedule of evaluations for Study C1973-202 is presented in Table 2.

Table 2. Schedule of Events

Study Period→		**Screening Period**	**Clinic Period**				
Visit Days → **Study Procedure ↓**		**Screening Visit** **Day -28 to -3**	**Check-in** **Day -2**	**Day -1**	**Day 1**	**Day 2**	**Days 3-6**
ICF Signed		X					
Demographics		X					
Medical History		X					
Inclusion/Exclusion Evaluation		X	X				
Physical Exam		X	X				
Hepatitis (HBsAg, HCV) & HIV Screen		X					
Drug & Alcohol Screen (a)		X	X				
Pregnancy Test (b)		X	X				
Weight (W) & Height (H) (c)		W, H		W			
12-lead electrocardiogram (d)		X	X		preAM: 0 (≤30m) pdAM: 4 (±15m)		
Respiratory rate (R) & oral temperature (T)		X	X	X	T,R preAM: 0 (≤30m) T pdAM: 1, 4 h (±15m)	X	X
Supine/standing BP & pulse (e) [3] indicates triplicate supine BPs supine only	AM	X [3]	X	preD1: 0 (≤30m) [3] pdD1: 1, 4h (±5m)	pre: 0 (≤30m) pd: 1, 4, 8h (±5m)	pre: 0 (≤15m) pd: 1, 4h (±5m)	pre: 0 (≤15m)
	PM			preD1: 0 (≤15m) pdD1: 1, 4h (±5m)	pre: 0 (≤15m) pd: 1, 4h (±5m)	pre: 0 (≤15m) pd: 1, 4h (±5m)	
Hemoglobin A1c		X	X		preAM: 0 (≤15m)		
Fasting plasma glucose & serum insulin (f)		X	X		preAM: 0 (≤15m)		
Clinical chemistry, coagulation, hematology, urinalysis (f)		X	X		serum creatinine only preAM: 0 (≤15m)		
Urine albumin & creatinine (g)		X		first void			
AE Evaluations		X	X	X	X	X	X
Prior & concomitant medications		X	X	X	X	X	X

Table 2. Schedule of Events

Study Period→		**Screening Period**	**Clinic Period**				
Visit Days → Study Procedure ↓		**Screening Visit Day -28 to -3**	**Check-in Day -2**	**Day -1**	**Day 1**	**Day 2**	**Days 3-6**
[redacted]			[redacted]				
Ambulatory BP monitoring (i)				Start: preD1: 0 (≤ 15m)	Continue	End: pd 12h [= preAM: 0(≤15m)]	
EndoPAT (j)				pre D13: 0 (end ≥30 m)			
[redacted]					[redacted]		
Randomization					X		
Study drug administration (l)	AM				X	X	X
	PM				X	X	X
PK blood samples (m)	AM				pre: 0 (≤ 15m) pd: 1, 3, 6h (± 5m)	…pd 6h (± 5m) pre: 0 (≤ 5m)	
	PM				pre: 0 (≤ 5m) pd: 1, 3h (± 5m)…	pre: 0 (≤ 5m)	
Platelet function (n)					preAM: 0 (≤15m)		
Confined to clinic			X	X	X	X	X
Discharge from clinic							
Study completion							

AM = morning; BP = blood pressure; h = hour; H = height; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; m = minute; msec = millisecond; pd = postdose; pdD1 = corresponding to postdose Day 1; PM = evening; pre = predose; preD1 = corresponding to predose Day 1; R = respiratory rate; T = oral temperature; W = weight

a. Urine drug screen for selected drugs of abuse and alcohol breathalyzer screen
b. For female patients, a negative serum pregnancy test must be documented at the Screening Visit, at Check-in with results available before randomization, and at the Follow-up Visit. A urine pregnancy test must be documented at the End of Trial Visit.
c. On in-clinic days, in the morning after voiding, before any water or food intake
d. Patients must be supine for ≥ 5 minutes before the ECG recording (Note: If on initial ECG, QTcF is ≥ 450 msec for male patients or is ≥ 470 msec for female patients, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the patient's eligibility).

e. Triplicate supine to standing assessment (Screening Visit, predose on Day -1, and on Day 15) after the subject has been lying quietly for ≥ 5 m supine BP and pulse is the average of 3 measurements obtained at 2-m intervals, after final supine measurement subject assume sitting position for 1 m, and finally assume standing position for 2 m before standing measurements are taken Note: The change in blood pressure from supine to standing will be determined using the third supine blood pressure and pulse measurements in comparison to the standing blood pressure and pulse measurements. Single supine to standing measurement assessed after the patient has been lying quietly for ≥ 5 m before supine measurements are taken, then assume sitting position for 1 m, and finally assume standing position for 2 m before standing measurements are taken. Single supine measurements are assessed after the subject has been laying quietly for ≥ 5 m. Predose measurements should precede all oral and any antihypertensive concomitant medications. All measurements before blood draws where applicable. Note: Supine-only (without standing) pulse and BP may be taken at the 4-h post PM dose timepoints (approximately midnight) if, in the Investigator's clinical opinion, earlier postdose orthostatic (supine and standing) pulse and BPs for the given dosing and for previous dosings at the 4-hour postdose timepoint indicate it is safe to eliminate the standing (orthostatic) pulse and BP measurement.
f. After ≥ 8-h fast, after EndoPAT (when applicable) and BP/pulse measurements and before dosing, where applicable. Does not apply to urine collection.
g. At the Screening and Follow-up Visit, single urine sample, which may not be first void; during Clinic Period, first-void urine sample
[redacted]
i. ABPM assessments should be performed on the same arm of the subject throughout the study; non-dominant arm is preferred.
j. If EndoPAT is available at the Study Center, for each patient, the Day -1 and Day 13 assessments should be at approximately the same time of day (± 15 m). Before all oral and any antihypertensive concomitant medications and study drug, BP/pulse measurements (for PD/Safety), and blood collections; after opportunity to void and then resting quietly in a temperature-controlled room for ≥ 15 m; occlusion/finger measurement right arm/hand. See Protocol Section 3.7.4.2
[redacted]
l. 2 orally administered 8-tablet doses: an AM 8-tablet dose at ~ same time (± 15 m) every day after overnight fast of ≥ 8 hours on Days 1 to 12 and on Day 14. On Day 13, first dose may be administered in the morning between 7 and 10:30AM, after the EndoPAT assessment (if applicable). Breakfast should begin within 30 m after dosing. PM 8-tablet dose, 12 hours (± 30 minutes) after AM dose and ≥ 30 minutes after completing dinner. May take multiple tablets together. Permitted concomitant medications may be taken at the same time as study drug.
m. ≈ 2-mL blood sample in one K_2EDTA tube at each timepoint; each sample divided into 2 equal plasma aliquots
n. CPRS assessment ≈ 1.8-mL blood sample in one 3.2% citrate tube at each timepoint as well as ≈ 4.5-mL blood sample in one 3.2% citrate tube at each timepoint; VerifyNow Aspirin Test and VerifyNow PRU Test ≈ 2-mL blood sample in 3.2% citrate tube at each timepoint for each test.

Table 2. Schedule of Events (…Continued)

Study Period→		**Clinic Period**				**Follow-up Period**	
Visit Days → Study Procedure ↓		**Day 7**	**Days 8-13**	**Day 14**	**Discharge Day 15**	**Follow-up Visit Day 21 (± 2)**	**End of Trial Visit Day 42 (± 3)**
ICF Signed							
Demographics							
Medical History							
Inclusion/Exclusion Evaluation							
Physical Exam					X		X
Hepatitis (HBsAg, HCV) & HIV Screen							
Drug & Alcohol Screen (a)						X	
Pregnancy Test (b)						X	X
Weight (W) & Height (H) (c)			Day 13 W		W	W	W
12-lead electrocardiogram (d)					X		
Respiratory rate (R) & oral temperature (T)		X	X	X	X	X	X
Supine/standing BP & pulse (e) [3] indicates triplicate supine BPs supine only	AM	pre: 0 (≤15m) pd: 1, 4h (±5m)	Days 8 & 13 pre: 0 (≤ 15m) pd: 1, 4 (± 5m) Days 9-12 pre: 0 (≤15m)	pre: 0 (≤15m)	pd: 12h (±15m) [3]	X	X
	PM		Day 8 & 13 pre: 0 (≤15m)				
Hemoglobin A1c			Day 8 preAM: 0 (≤15m)	preAM:0 (≤15m)	X		X
Fasting plasma glucose & serum insulin (f)			Day 8 preAM: 0 (≤15m)		X		
Clinical chemistry, coagulation, hematology, urinalysis; (f)					X		X
Urine albumin & creatinine (g)					first void		X
AE Evaluations		X	X	X	X	X	X
Prior & concomitant medications		X	X	X	X	X	X

Table 2. Schedule of Events (…Continued)

Study Period→		**Clinic Period**				**Follow-up Period**	
Visit Days → Study Procedure ↓		**Day 7**	**Days 8-13**	**Day 14**	**Discharge Day 15**	**Follow-up Visit Day 21 (± 2)**	**End of Trial Visit Day 42 (± 3)**
[redacted]							
Ambulatory BP monitoring		Start: pre: 0 (≤15m)	End: Day 8 preAM: 0 (≤15m)	Start: preAM: 0 (≤15m)	End: pd: 12h (±15m)		
EndoPAT (j)			Day 13 preAM 0 (end ≥30m)				
[redacted]					[redacted]	[redacted]	[redacted]
Randomization							
Study drug administration (l)	AM	X	X	X			
	PM	X	X	X			
PK blood samples (m)	AM	pre: 0 (≤5m) pd: 1, 3, 6h (±5m)	Day 8 pre: 0 (≤5m) pd: 1, 3, 6h (±5m)	pre: 0 (≤5m) pd: 1,3,6h (±5m)	pd: 12h (±15m)	X	X
	PM	pre: 0 (≤5m)	Day 8 pre: 0 (≤5m)	pre: 0 (≤5m)			
Platelet function (n)			Day 8 preAM: 0 (≤15m)	preAM: 0 (≤15m)			
Confined to clinic		X	X	X			
Discharge from clinic					X		
Study completion							X

5.2 SAFETY ASSESSMENTS

The following safety assessments are performed throughout the study, as indicated in the Schedule of Events.

- Adverse Events
- Physical Examination
- Height and Weight
- Vital Signs including oral temperature, respiratory rate, supine and standing pulse, and cuff BP measurements
- Laboratory Parameters
    - Serum Chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, cholesterol, creatinine, gamma glutamyl transferase (GGT), glucose, HDL-c, lactate dehydrogenase (LDH), LDL-c (calculated), magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, triglycerides, uric acid.
    - Hematology: hematocrit, hemoglobin, platelet count, RBC count, WBC count, WBC differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils [% and absolute]), RBC indices (mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], and mean corpuscular volume [MCV], red blood cell distribution width [RDW]).
    - Coagulation: activated partial thromboplastin time (aPTT), Prothrombin time, INR.
    - Urinalysis: pH and specific gravity, bilirubin, glucose, ketones, leukocytes, nitrates, occult blood, protein, urobilinogen, microscopic, including bacteria, RBCs, WBCs per high power field (HPF) only if dipstick is abnormal.
    - Additional tests: Hemoglobin A1c, fasting plasma glucose, fasting plasma insulin, urine albumin, urine creatinine
- 12-lead Electrocardiogram (ECG)
- Urine Creatinine Ratio (UACR)
- Estimated Glomerular Filtration Rate (eGFR)

5.3 PHARMACODYNAMIC ASSESSMENTS

The following hemodynamic, endothelial function, metabolic function, and platelet function assessments will be performed throughout the study, as outlined in the Schedule of Assessments.

Ambulatory Blood Pressure (BP) Monitoring:

Patients will undergo 24-48 hour ambulatory BP monitoring on Days -1, 7 and 14. The 48 hour monitoring will begin on Day -1 at the time that corresponds to "just before dosing" on Day 1 and will end on Day 2, 24 hours after dosing on Day 1. The 24-hour assessments will be performed on Day 7 and Day 14. The 30-minute, 4-hour, 24-hour, daytime, and nighttime averages of systolic BP, mean arterial pressure (MAP), and diastolic BP, and pulse measurements will be calculated.

Supine Pulse and BP Assessments:

Supine and standing BP and pulse measurements will be obtained after both the AM and PM doses, as outlined in Table 2 - Schedule of Events.

Endothelial Function Assessments:

Endothelial function in the finger will be measured using the noninvasive EndoPAT™ (Itamar Medical; Caesarea, Israel) device on Day -1 and 13 at approximately the same time of day. All measurements will precede all antihypertensive concomitant medications and will be performed in a quiet, dimly lit, temperature controlled room after the patient has been resting quietly for 15 minutes. The right arm will be used for occlusion and finger measurements. Endothelial function will be assessed using the Reactive Hyperemia Index (RHI) parameter. Exploratory vascular physiology parameters such as Augmentation Index (AI) and AI adjusted to a heart rate of 75 beats per minute (AI-75) will also be assessed by the EndoPAT device.

Metabolic Function Assessments:

Homeostatic Model Assessment to Quantify Insulin Resistance (HOMA-IR)

Blood samples for determination of fasting blood glucose and insulin levels collected at Screening, Days -2, 1, 8 and 15 will be used to estimate insulin resistance using the Homeostatic Model.

Hemoglobin A1C, cholesterol, HDL, LDL, and triglyceride levels will be determined from blood samples collected as part of the safety laboratory assessments as specified in Section 5.2.

Platelet Function Assessments:

Blood samples for platelet function assessment using Verify Now® instrument and evaluation of platelet function markers will be collected prior to dosing on Day 1, 8, and 14. Additional platelet function testing may also be performed.

[redacted]

5.4 PHARMACOKINETIC ASSESSMENTS

Blood samples for PK assessments will be collected as outlined in the Schedule of Events, and PK parameters may be calculated if systemic levels of IW-1973 are detectable, and data support the calculations.

6. STATISTICAL METHODS

6.1 GENERAL METHODOLOGY

Descriptive statistics (number of patients, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum) will be calculated for continuous variables. For summaries of continuous PK parameters, the geometric mean and the coefficient of variation (CV) will also be presented. For categorical variables, frequencies and percentages for each category will be presented. Percentages will be based on the total number of patients with non-missing values. If there are missing values, the number missing will be presented, but without a percentage. Data from screen failure subjects will be presented in subject data listings.

Inferential statistics, if calculated, will only be used for descriptive purposes.

All statistical analyses will be performed using SAS® Version 9.3 or later (1). Additional analyses using alternative software may be performed as part of the PK analysis.

Summary data for safety, PD and PK parameters will be presented by treatment group and IW-1973 overall, unless otherwise indicated:

- Placebo
- IW-1973 40 mg Total Daily Dose BID/QD
- IW-1973 40 mg Total Daily Dose QD/QD
- IW-1973 40 mg Total Daily Dose Overall

Summary data for PK parameters on Day 1 will be presented only for the 2 active treatment groups.

Definition of Baseline:

The following definitions of baseline will be used to calculate change from baseline parameters, unless specified otherwise:

- Study baseline is defined as the last non-missing assessment before first administration of study drug.

- For PD parameters obtained from ambulatory BP monitoring, time-matched baseline is calculated using the predose assessments on Day -1 that correspond to the respective postdose assessment timepoints.
- Trough baseline for supine BP and pulse assessments is defined as the Day 1 AM predose assessment.

6.2 ADJUSTMENTS FOR COVARIATES

Baseline will be included as a covariate in the analysis of covariance (ANCOVA) models used for the change from baseline PD parameters.

6.3 HANDLING OF DROPOUTS OR MISSING DATA

No imputation will be performed for missing PD observations. All safety and tolerability data will be summarized and analyzed when data values are available for a patient. Data handling for missing dates and other key safety data are described in Section 9. With respect to PK data, parameters will be derived as defined in Section 7.8. Although these methods may employ some inherent estimation of missing values such as substitution of concentration values below the level of quantification for concentration summaries or calculation of the area under the time curve (AUC), no formal imputation methods will be performed for the study other than those specified in Section 9.7.

6.4 INTERIM ANALYSIS AND DATA MONITORING

No formal interim analyses are planned to compare treatment arms with respect to efficacy or safety prior to formal completion of the trial.

6.5 MULTICENTER STUDIES

This study will be conducted at up to 3 study centers.

6.6 MULTIPLE COMPARISONS/MULTIPLICITY

No multiple comparison adjustments are planned for the safety and tolerability analyses, which are qualitative in nature. No multiple comparison adjustments will be employed for the PK or PD analyses, as the analyses of these endpoints focus more on estimation rather than inferential testing.

6.7 USE OF AN EFFICACY SUBSET OF PATIENTS

Not applicable.

6.8 ACTIVE-CONTROL STUDIES INTENDED TO SHOW EQUIVALENCE

Not applicable.

6.9 EXAMINATION OF SUBGROUPS

Subgroup analyses of 24-hour average ABPM assessments, trough pulse and BP assessments and treatment-emergent adverse events (TEAEs) will be performed by gender.

7. ANALYSIS METHODS

7.1 ANALYSIS POPULATIONS

The following analysis populations will be defined for the study:

Safety Population: The Safety Population will consist of all patients who received at least 1 dose of study drug and will be grouped according to actual study drug taken. All safety and tolerability assessments will be performed using the Safety Population.

PD Population: The PD Population will consist of all patients who received at least 1 dose of study drug and had at least 1 postdose PD assessment. All analyses of PD data will be performed using the PD Population.

PK Population: The PK Population will consist of all patients who received at least 1 dose of IW-1973 and had at least 1 postdose PK parameter assessment without events or deviations affecting the PK results. All analyses of PK data will be performed using the PK Population.

7.2 PROTOCOL DEVIATIONS

Protocol deviations will be listed by patient.

7.3 DISPOSITION OF PATIENTS

The number and percentage of patients who were included in each of the 3 analysis populations (Safety, PK, and PD), completed the study or discontinued early (along with the reasons for discontinuation) will be presented. A patient who has signed the ICF and has been randomized ceases participation in the study, regardless of circumstances, before completion of the Clinic Period will be considered to have discontinued early from the study. A patient will be considered to have completed the study after completing the Clinic Period and the End of Trial Visit.

In addition, data listings of patient disposition, including all patients who failed screening or terminated early, will be presented.

7.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patient demographics (age, sex, race, ethnicity, weight, height, and body mass index [BMI, defined as weight in kg divided by height in meters squared]) and other baseline characteristics will be summarized for the Safety Population.

If either the PD or PK Population differs from the Safety Population, the presentation will be repeated for the respective populations.

7.5 MEASUREMENTS OF TREATMENT COMPLIANCE

This is an in-clinic dosing study and, therefore, no assessment of compliance is necessary. A data listing containing the study drug dosing information will be provided.

7.6 EXTENT OF EXPOSURE

This is an in-clinic dosing study and therefore no assessment of exposure is necessary, other than the data listing of study drug dosing information.

7.7 PHARMACODYNAMIC (PD) ANALYSIS

7.7.1 PD Parameters

The PD parameters are described below:

Ambulatory BP Monitoring

- Change from time-matched baseline in 24-hour average systolic BP, MAP, diastolic BP, and pulse. The 24-hour average for a postdose day is defined as the average of ambulatory assessments from the time of dosing on that day to the time of dosing on the next day. Time-matched baseline is defined as the average of ambulatory assessments from the time corresponding to dosing on Day -1 to the time of dosing on Day 1.
- Change from time-matched baseline in daytime (12-hour) average systolic BP, MAP, diastolic BP, and pulse. The daytime average on any postdose day is defined as the average of the 30-minute average ambulatory assessments from the time of dosing on that day to 12 hours postdose. Time-matched baseline is defined as the average of ambulatory assessments from the time corresponding to dosing on Day -1 to the time corresponding to 12 hours postdose.

- Change from time-matched baseline in nighttime average systolic BP, MAP, diastolic BP, and pulse. The nighttime average on any postdose day is defined as the average of the 30-minute ambulatory assessments from 12 hours postdose on that day to 1 hour before the time of dosing on the next day. Time-matched baseline is defined as the average of ambulatory assessments from the time corresponding to 12 hours postdose on Day -1 to 1 hour before the time of dosing on Day 1.
- Change from time-matched baseline in 4-hour averages of systolic BP, MAP, diastolic BP, and pulse. The 4-hour averages are calculated from the time of dosing on the ABPM assessment day, using the 30-minute average values. Baseline is defined as the corresponding 4-hour average on Day -1.
- Change from time-matched baseline in systolic BP, diastolic BP, MAP, and pulse at 30-minute postdose intervals. See Section 9.8 for details on calculation of assessment time intervals. Baseline is defined as the corresponding 30-minute average on Day -1.

Supine Pulse and BP Measurements

- Change from trough baseline in trough supine systolic BP, diastolic BP, and pulse. Postdose trough values are defined as the supine assessments performed 24 hours after the AM dosing. Trough baseline is defined as the Day 1 AM predose assessment.
- Change from study baseline in supine systolic BP, diastolic BP, and pulse.
- Proportion of patients meeting target postdose supine blood pressure levels of systolic BP < 130 mmHg and diastolic BP < 80 mmHg.

Endothelial Function and Exploratory Vascular Physiology Assessments

- Change from study baseline in RHI, AI and AI-75.

Metabolic Assessments

- Change from study baseline in insulin resistance (HOMA-IR). HOMA-IR will be calculated using the Homeostatic Model Assessment to estimate insulin resistance (HOMA-IR).(2,3) The HOMA-IR equation is

$$HOMA\text{-}IR = \frac{(FSI \times FPG)}{22.5}$$

  where FSI is the fasting serum insulin concentration (mU/l)

  FPG is the fasting plasma glucose (mmol/l)

- Change from study baseline in metabolic assessments, fasting plasma glucose, serum insulin, hemoglobin A1C, cholesterol, HDL, LDL, triglycerides, weight, and BMI.

Platelet Function Assessments

- Change from study baseline in platelet function assessments [VerifyNow - $P2Y_{12}$ reaction units (PRU) and Aspirin]
- Proportion of patients with decreased platelet reactivity (VerifyNow) defined as <180 for PRU and <=549 for Aspirin
- Change from study baseline in the following platelet activation markers assessed in both platelet rich plasma (PRP) and whole blood samples (WB), and for different agonists (no agonist, ADP 0.5 µM [Low ADP], ADP 20 µM [High ADP], TRAP 1.5 µM [low TRAP], and TRAP 20 µM [High TRAP]):
  - % platelets positive for activated GPIIb-IIIa
  - % platelets positive for Surface P-Selectin
  - relative abundance of activated GPIIb-IIIa on platelet surface
  - relative abundance of P-Selectin on platelet surface
- Change from study baseline in platelet count

[redacted]

[redacted]

7.7.2 PD Analysis

Descriptive statistics will be presented for the observed and change from baseline results for the PD parameters at each scheduled timepoint by treatment group. Least squares means, standard errors and 95% confidence intervals for each treatment, as well as the least squares means, standard errors and 95% confidence intervals for each IW-1973 group minus placebo difference from an ANCOVA model with treatment as a fixed effect and baseline as a covariate will be presented for all the change-from-baseline endpoints, with the exception of [redacted] and VerifyNow assessments.

Subject incidence and percentages will be presented for the proportion of patients that meet target BP criteria. Percentages will be calculated based on the total number of PD subjects.

Shifts from baseline to each later timepoint will be tabulated for patients with decreased platelet reactivity.

7.7.3 Graphical Presentation of PD Data

Boxplots of change from time-matched baseline in 24-hour, daytime, and 4-hour averages of ambulatory systolic BP, mean arterial pressure, diastolic BP, and pulse will be presented by treatment group. Least squares mean plots of change from time-matched baseline in the above parameters as well as for the 30-minute averages of ABPM assessments over time along with the corresponding 95% confidence intervals will be plotted by treatment group.

Least squares mean plots of change from trough baseline in trough supine cuff blood pressure and pulse assessments over time, along with the corresponding 95% confidence intervals will be presented by treatment group. Bar graphs will be presented by study day and treatment group for the proportion of patients meeting target supine blood pressure criteria.

Boxplots of change from study baseline will be presented by treatment group for endothelial function, HOMA-IR, metabolic, platelet function, and exploratory vascular physiology parameters. Bar graphs will be presented by treatment group for the proportion of patients with decreased platelet reactivity.

7.8 PHARMACOKINETIC (PK) ANALYSIS

7.8.1 PK Parameters

The PK parameters listed in Table 3 will be calculated for each patient, whenever possible, if systemic levels of IW-1973 are quantifiable. PK parameter calculations will be performed using noncompartmental methods with Phoenix® WinNonlin® Version 6.4, or higher, (Certara L.P., Princeton, New Jersey, United States).

Plasma concentrations that are below the lower level of quantification (LLQ) or missing will be treated as described in Section 9.7 for the calculation of PK parameters. Actual sampling times relative to IW-1973 dosing times will be used in calculations of the PK parameters. Area under the concentration-time curve will be calculated by linear up/log down trapezoidal summation.

Table 3. PK Parameters

Parameter	Description
	To be calculated on Day 1 relative to the morning dose, unless otherwise noted
AUC_{last}	Area under the plasma concentration time curve from time zero to T_{last}, the time at which the last measurable plasma concentration (C_{last}) is observed.
AUC_{tau}	Area under the plasma concentration-time curve during a dosing interval (tau: 24 hours for QD regimen, 12 hours for BID). Actual elapsed time at tau will be used for the calculation. If the IW-1973 sample at the end of the dosing interval is missing, AUC_{tau} will not be determined. If the IW-1973 sample at the end of the dosing interval is BLQ, AUC_{all} will be used to describe AUC_{tau}. For the BID regimen, this parameter will be calculated for the morning and for the evening dose, and for the 24-hour sampling period on Day 1 (AUC_{24}).
AUC_{tau}/D	Dose-normalized AUC_{tau}, For the BID regimen, this parameter will be calculated for the morning dose and overall for the 24-hour sampling period (AUC_{24}).
T_{max}	Time of maximum observed plasma concentration, obtained directly from the concentration-time profile. For the BID regimen, this parameter will be calculated for the morning and for the evening dose.
C_{max}	Maximum observed plasma concentration, occurring at $T_{max.}$ For the BID regimen, this parameter will be obtained from the observed concentration-time data for the morning and for the evening dose as well as overall ($C_{max,24}$) for the 24-hour sampling period.
C_{max}/D	Dose-normalized C_{max}
C_{trough}	Trough plasma concentration observed at the end of a dosing interval (collected before the next administration) and will be correspond to the following sample collection times: • 24-hour trough following the QD dose on Day 1: Day 2 predose • 12-hour troughs following the BID doses on Day 1: Day 1 PM predose and Day 2 AM predose
	To be calculated on Day 7 relative to the morning dose, unless otherwise noted
AUC_{last}	Area under the plasma concentration time curve from time zero to T_{last}, the time at which the last measurable plasma concentration (C_{last}) is observed
AUC_{tau}	Area under the plasma concentration-time curve during a dosing interval (tau: 24 hours for QD regimen, 12 hours for BID). Actual elapsed time at tau will be used for the calculation. If the IW-1973 sample is missing either at the beginning or at the end of the dosing interval, AUC_{tau} will not be determined. If the IW-1973 sample at the end of the dosing interval is BLQ, AUC_{all} will be used to describe AUC_{tau}.
AUC_{tau}/D	Dose-normalized AUC_{tau}
$RAUC_{tau}$	Accumulation ratio of AUC_{tau} comparing Day 7 with Day 1
T_{max}	Time of maximum observed plasma concentration
C_{max}	Maximum observed plasma concentration, occurring at T_{max}
RC_{max}	Accumulation ratio of C_{max} comparing Day 7 with Day 1
C_{max}/D	Dose-normalized C_{max}

Table 3. PK Parameters

Parameter	Description
C_{trough}	Trough plasma concentration observed at the end of a dosing interval (collected before the next administration) and will be correspond to the following sample collection times: • 24-hour trough following the QD dose on Day 6: Day 7 predose • 24-hour trough following the QD dose on Day 7: Day 8 predose • 12-hour trough following the evening BID doses on Day 6: Day 7 predose • 12-hour troughs following the BID doses on Day 7: Day 7 PM predose and Day 8 predose
RC_{trough}	Accumulation ratio for C_{trough} comparing the trough following the IW-1973 dose on Day 7 with the trough following the IW-1973 dose on Day 1, calculated as: Day 8 morning predose concentration / Day 2 morning predose concentration. Note: for the BID regimen, this comparison is made relative to the trough following the evening doses on Days 7 and 1.
	To be calculated on Day 8
AUC_{last}	Area under the plasma concentration time curve from time zero to T_{last}, the time at which the last measurable plasma concentration (C_{last}) is observed
C_{max}	Maximum observed plasma concentration, occurring at T_{max}
SC_{max}	Ratio of C_{max} obtained after switching to the 40 mg QD regimen on Day 8 divided by C_{max} following the morning 20 mg BID dose on Day 7 (BID/QD regimen)
C_{max}/D	Dose-normalized C_{max}
T_{max}	Time of maximum observed plasma concentration
	To be calculated on Day 14
AUC_{last}	Area under the plasma concentration time curve from time zero to T_{last}, the time at which the last measurable plasma concentration (C_{last}) is observed
AUC_{tau}	Area under the plasma concentration-time curve during a dosing interval (tau: 24 hours). Should either the predose or the 24-hour postdose sample be missing, the concentration of the other sample (eg, predose for missing 24 hour) will be substituted for calculation of AUC_{tau}.
AUC_{tau}/D	Dose-normalized AUC_{tau}
$RAUC_{tau}$	Accumulation ratio of AUC_{tau} comparing Day 14 with Day 1, calculated as • QD/QD regimen: Day 14 AUC_{tau} / Day 1 AUC_{tau} • QD/BID regimen: Day 14 AUC_{tau} / Day 1 AUC_{24}
C_{max}	Maximum observed plasma concentration, occurring at T_{max}
RC_{max}	Accumulation ratio of C_{max} comparing Day 14 with Day 1 calculated for the QD/QD regimen only
C_{max}/D	Dose-normalized C_{max}

Table 3. PK Parameters

Parameter	Description
C_{trough}	Trough plasma concentration observed at the end of a dosing interval (collected before the next administration) and will be correspond to the following sample collection times: • 24-hour trough following the QD dose on Day 13: Day 14 predose • 24-hour trough following the QD dose on Day 14: Day 14 24-hours postdose
RC_{trough}	Accumulation ratio for C_{trough} comparing the trough following the IW-1973 dose on Day 14 with the trough following the IW-1972 dose on Day 1, calculated as: Day 14 24-hour postdose concentration / Day 2 morning predose concentration. Note: for the BID regimen, this comparison is made relative to the trough following the evening dose on Day 1 (ie, following the total daily dose of 40 mg)
CL/F	Apparent total body clearance after oral administration, calculate as the administered dose divided by AUC_{tau}. No dose adjustment is required in this calculation.
$t_{1/2}$	Apparent terminal phase half-life, determined by linear regression of the terminal points of the log-linear concentration-time curve. A minimum of 3 data points will be used for determination. This parameter will be calculated but not included in any summaries if goodness of fit statistic for calculation of the regression coefficient (Rsq) for the elimination rate (λ_z) is less than 0.800. Interval of the log-linear regression, number of data points, Rsq, and λ_z will be reported for diagnostic purposes.
$t_{1/2, eff}$	Effective half-life, calculated as Ln(2)*(-24) /[ln(1-{1/$RAUC_{tau}$})]
T_{max}	Time of maximum observed plasma concentration
V_z/F	Apparent volume of distribution during the terminal phase after oral administration calculated as CL/F / λ_z

7.8.2 PK Analysis

Plasma concentration of IW-1973 will be summarized using the PK Population for each assessment timepoint by active treatment groups. Concentrations that are below the limit of quantitation (BLQ) concentrations will be treated as zero for the computation of descriptive statistics. A by-subject listing of all concentration-time data for each treatment and scheduled sample collection time will be presented. A listing of PK blood sample collection times, and elapsed time relative to dose will be provided.

PK parameters will be summarized by treatment group using the PK Population. A by-subject listing of all PK parameters for each treatment and study day will be presented.

Changes to protocol procedures or events which many impact the quality of the PK data or alter the evaluation of the PK will be reviewed on a case-by case basis to determine if PK data

collected during the affected treatment period may be excluded from relevant PK summaries. Examples include, but may not be limited to, vomiting following oral dosing occurring within the time frame of 2 times the median time to maximum concentration (T_{max}), sample processing errors that lead to inaccurate bioanalytical results, missed doses and/or inaccurate dosing on or in relationship to the day of PK sampling. Deviations to procedures or events which do not impact the quality of the PK data such as a missed blood sample or deviations from blood collection times will not be considered for exclusion from PK summaries.

7.8.3 Graphical Presentation of PK Data

Geometric mean plasma concentrations will be plotted over time by treatment group on both a linear and a semi-logarithmic scale. Individual drug plasma concentrations will also be plotted over time. Geometric mean trough concentrations will be plotted over time by treatment group and scheduled time on both linear and semi-logarithmic scales. Both morning and evening troughs will be included in the graphic presentation. In the case of an apparent diurnal difference between morning and evening trough concentration, a separate presentation including only the morning trough concentration may be prepared. Individual drug trough plasma concentrations will also be plotted over time.

Scatterplots of individual C_{max}, AUC_{tau}, C_{trough}, and T_{max} values will be presented by treatment group for the PK population, with means and medians also presented on these graphs when possible.

7.8.4 PK-PD Analysis

To assess potential relationships between IW-1973 plasma concentrations and PD assessments, mean plots of change from time-matched baseline in 30-minute averages of ambulatory blood pressure and pulse assessments and mean plots of IW-1973 plasma concentration will be presented by treatment group for the PK population.

7.9 SAFETY ANALYSIS

All safety analyses will be performed using the Safety Population.

7.9.1 Adverse Events

All adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 and will be classified by MedDRA system organ class (SOC), and preferred term (PT).

Treatment-emergent adverse events (TEAEs) are those AEs that started or worsened in severity after the administration of study drug. If it is not possible to determine when the event started due to incomplete start dates/times, it will be assumed to be treatment-emergent.

The number and percentage of patients who experience at least one TEAE as well as those who experience each specific SOC and PT will be presented by treatment group as well as for IW-1973 overall using the Safety Population. TEAEs will also be summarized by week, where TEAEs that started during Week 1 (study days 1-7) or Week 2 (study days 8-14) will be presented by treatment group for the respective week. Summaries of study drug-related TEAEs will also be presented by treatment group. For presentation of AE incidence, AEs will be sorted alphabetically by SOC, and within each SOC, by decreasing incidence of PT in the overall group.

In addition, AEs in screen failure patients, TEAEs, severe TEAEs, study drug-related AEs (those that are determined by the Investigator to be related to study drug), serious AEs, AEs that resulted in study discontinuation, and AEs that resulted in death (if any) will be presented in separate listings.

Adverse Events of Clinical Interest

Since an increased risk for bleeding may represent a class effect with sGC stimulators, bleeding events and TEAEs related to bleeding will be summarized by treatment group and presented in a data listing. Similarly, TEAEs associated with hypotension or lowering of BP will be summarized by treatment group and presented in a data listing. See Appendix 1 for details on the determination of the events for each category of interest.

7.9.2 Clinical Laboratory Parameters

For each quantitative clinical laboratory parameter, descriptive statistics of the observed values (in derived SI units) as well as change from study baseline will be presented overall for each assessment timepoint for the safety population.

Parameter values will also be categorized as low, normal, or high based on reference ranges provided by the lab, and shifts from baseline to each later timepoint will be tabulated. If there is more than one measurement for a lab parameter at a postbaseline timepoint, only the last measurement will be used.

Listings of laboratory parameters will be included.

7.9.3 Estimated Glomerular Filtration Rate (eGFR)

Change from study baseline in eGFR will be summarized by treatment group for each assessment day. eGFR (mL/min/1.73m^2) will be calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.(4)

$$GFR = 141 \times min\left(\frac{sCr}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{sCr}{\kappa}, 1\right)^{-1.209} \times 0.993^{Age} \times 1.018\, I_F \times 1.159 I_B$$

where sCr is serum creatinine (mg/dL),

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

max indicates the maximum

I_F is an indicator function for female patients

I_B is an indicator function for black patients

Boxplots of eGFR values will be presented for each treatment group and assessment day.

7.9.4 Urine Creatinine Ratio (UACR)

Change from study baseline in UACR will be summarized by treatment group for each assessment day. UACR will be calculated using the following equation:

$$UACR(mg/g) = \frac{urine\ albumin\ (mg/dL)}{urine\ creatinine\ (g/dL)}$$

Boxplots of UACR values will be presented for each treatment group.

7.9.5 Additional Vital Signs Parameters

Vital signs evaluations at each assessment timepoint not included in the PD analyses (ex. standing blood pressure and pulse assessments) and the corresponding change from study baseline will be summarized for each treatment group and presented in a data listing.

The number and percentage of patients who had a notable change from baseline in BP and pulse (based on the criteria in Table 4), will be presented by treatment group.

Table 4. Criteria for Notable Changes in Post-Baseline Vital Signs

Vital Sign Parameter	***Flag***	***Criteria****	
		Observed Value	*Change from Study Baseline*
Supine/Standing Systolic Blood Pressure (mmHg)	High	≥ 180	Increase of ≥ 30
	Low	≤ 90	Decrease of ≥ 30
Supine/Standing Diastolic Blood Pressure (mmHg)	High	≥ 105	Increase of ≥ 20
	Low	≤ 50	Decrease of ≥ 20
Supine Pulse Rate (bpm)	High	≥ 110	Increase of ≥ 20
	Low	≤ 50	Decrease of ≥ 20
Standing Pulse Rate (bpm)	High	≥ 120	Increase of ≥ 25
	Low	≤ 50	Decrease of ≥ 20

*A postbaseline value is considered as a notable value if it meets both criteria for observed value and change from baseline.

Orthostatic BP Measurements

Orthostatic changes in systolic BP, diastolic BP, and pulse will be summarized for each treatment group. An orthostatic measurement is obtained by subtracting the supine measurement from the standing measurement.

The number and percentage of patients who meet the following criteria at any postdose timepoint will also be summarized by treatment group:

- Orthostatic decrease in systolic BP of > 20 mmHg from supine to standing
- Orthostatic decrease in diastolic BP of > 15 mmHg from supine to standing
- Orthostatic increase in pulse of > 30 beats per minute from supine to standing

7.9.6 ECG Parameters

For each ECG parameter, descriptive statistics of the observed values as well as change from study baseline will be presented overall for each assessment timepoint for the safety population. Shift tables from study baseline to the discharge visit (Day 15) for the overall ECG interpretation (normal, abnormal not clinically significant, or abnormal clinically significant) will be summarized for all subjects in the Safety population.

ECG parameters will also be presented in a data listing.

7.9.6.1 Concomitant Medications

Any medication taken by patients after administration of study drug will be considered concomitant and presented in a data listing for the Safety Population.

The WHO Drug Dictionary, version September 2016 will be used to classify prior and concomitant medications by therapeutic class and drug name.

7.9.6.2 Physical Examination

Physical examination results for all patients will be presented in a data listing for the Safety Population.

8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The following analyses will be performed in addition to those described in the study protocol.

- Change from trough baseline (defined as the Day 1 AM predose assessment) will be presented for trough supine systolic BP, diastolic BP, and pulse using the PD population.
- Change from study baseline in fasting plasma glucose, serum insulin, hemoglobin-A1C, cholesterol, HDL, LDL, triglycerides, BMI and weight that were collected as part of the safety assessments will also be analyzed using the PD population.
- Exploratory vascular physiology parameters such as Augmentation Index (AI) and AI adjusted to a heart rate of 75 beats per minute (AI-75) will also be assessed by the EndoPAT device. Change from baseline in these parameters will be analyzed using the PD population.
- Subgroup analyses of 24-hour average ABPM assessments, trough pulse and BP assessments and TEAEs by gender will be performed.
- Adverse events of clinical interest related to bleeding and hypotension will be summarized by treatment group

The following changes were made to the analyses described in the study protocol.

- Change from baseline in standing BP and pulse assessments and orthostatic changes in BP and pulse will be summarized using the Safety population instead of the PD population.
- An inadvertent typo in the unit for fasting serum insulin in the formula for HOMA-IR was revised from μU/l to mU/l.
- Area under the plasma concentration time curve extrapolated to infinity on Day 1 will not be calculated since the 24-hour concentration-time profile does not allow for adequate characterization of IW-1973 $T_{1/2}$.

9. DATA HANDLING CONVENTIONS

9.1 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated safety assessments (e.g., for a lab parameter) prior to dosing of study drug, then the results from the final non-missing assessment made prior to the start of study drug will be used as baseline. If there is more than one safety measurement (e.g., for a lab parameter) at a postbaseline timepoint, only the last measurement will be used. All postbaseline assessments including unscheduled assessments, if any, will be used for notable value determination, and all assessments will be presented in data listings.

9.2 CONVENTIONS FOR SUMMARIZING ADVERSE EVENTS

The following conventions will be followed in summarizing TEAEs within a treatment group:

- For patient incidence summaries, each patient will be counted only once within each SOC, PT, or the overall AE summary
- If a patient reported more than one AE within an SOC or PT, then the TEAE with the highest severity or strongest study drug relationship within each SOC and each PT will be included in the summaries by severity or relationship, respectively.

9.3 MISSING DATE INFORMATION FOR ADVERSE EVENTS

If it is not possible to determine when an AE started due to incomplete start dates/times, it will be assumed to be treatment emergent.

9.4 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started prior to the dosing of study drug, all efforts should be made to obtain the severity from the Investigator. If it is still missing after all efforts, then a severity of “Mild” will be assigned. If the severity is missing for an AE that started on or after the date of dosing of study drug, then a severity of “Severe” will be assigned. The imputed values for the missing severity assessment will be used for the incidence summary, while the actual missing values will be presented in data listings.

9.5 MISSING RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the relationship to study drug is missing for an AE that started on or after the date of dosing of study drug, all efforts should be made to obtain the relationship from the Investigator. If it is still missing after all efforts, a causality of "Related" will be assigned in the corresponding analysis-derived data set. The imputed values for the missing relationship to study drug will be used only for incidence summary, while the actual missing values will be presented in data listings.

9.6 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

If the start date of a medication is missing or incomplete (i.e., partially missing), then the medication will be assumed to be concomitant.

9.7 HANDLING OF LLQ OR MISSING PK DATA

- Handling of predose samples prior to the first IW-1973 administration (Day 1 – morning dose): Concentrations that are below LLQ (BLQ) or missing will be assigned a numerical value of zero for the calculation of AUC. Any anomalous concentration values observed at predose will be included in the computation of AUC. If the Day 1 predose concentration is greater than 5% of the maximum concentration (C_{max}), the data will be evaluated on a case-by-case basis to determine if exclusion of the affected profile is warranted.
- Handling of all other BLQ concentrations: any other BLQ concentrations will be assigned a value of zero if at predose (Days 7, 8, and 14) or if they precede quantifiable samples in the initial portion of the profile (all study days). A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating AUC. If BLQ values occur at the end of the collection interval (after the last quantifiable concentration), these will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.
- Handling of missing data: in general, missing data in a given profile will not be imputed. The affected profile(s) will be evaluated whether sufficient IW-1973 concentrations are available to calculate any of the planned PK parameters. Missing IW-1973 concentrations at predose (Days 7, 8, and 14) and missing IW-1973 concentrations at the end of the dosing interval are discussed in Table 3.

9.8 ASSESSMENT TIME WINDOWS FOR AMBULATORY BP ANALYSIS

Table 5 presents the timepoints used for the ambulatory BP analysis and the corresponding assessment windows during which the actual assessment may have occurred.

Table 5. Timepoint Windows for Ambulatory BP Analysis

Predose Timepoints	*Assessment Window [1]*	*Postdose Timepoints*	*Assessment Window [2]*
30 min predose	'dosing' to 0.5h + 15min on Day -1	30 min postdose	dosing to 0.5h + 15min on Day 1/7/14
1 h predose	1h ± 15min on Day -1	1 h postdose	1h ± 15min on Day 1/7/14
1.5 h predose		1.5 h postdose	1.5h ± 15min on Day 1/7/14
…		…	…
13.5 h predose	13.5 ± 15min on Day -1	13.5 h postdose	13.5h ± 15min on Day 1/7/14
…	…	…	…
23.5 h predose	23.5h ± 15min to dosing on Day 1	23.5 h postdose	23.5h ± 15min to dosing on Day 2/8/15

1. Predose timepoints are relative to the Day -1 timepoints corresponding to dosing on Day 1.
2. Postdose timepoints are relative to dosing time on Days 1, 7, or 14

10. REFERENCES

1. SAS® Institute Inc. 2015. SAS® Version 9.4 Language Reference: Concepts, Fifth Edition. SAS® Publishing, SAS® Institute Inc., Cary, NC, USA.

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

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

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

11. APPENDIX 1 – ADVERSE EVENTS OF CLINICAL INTEREST

The table below provides the criteria for identifying events within each category:

Event Category	Criteria
Bleeding Events	TEAEs with (but not limited to) the following MedDRA preferred terms: Haemoptysis Subarachnoid haemorrhage Subdural haemorrhage Haematemesis Haematochezia Upper gastrointestinal haemorrhage Lower gastrointestinal haemorrhage Melaena Haemorrhoidal haemorrhage Mucosal haemorrhage Menorrhagia Bleeding time prolonged Vessel puncture site haemorrhage Epistaxis Medical review of AEs prior to database lock will identify any additional preferred terms for this list.
Hypotension Events	TEAEs with (but not limited to) the following MedDRA preferred terms: Hypotension Blood pressure decreased Orthostatic hypotension Presyncope Syncope Dizziness Dizziness postural Medical review of AEs prior to database lock will identify any additional preferred terms for this list.