STATISTICAL ANALYSIS PLAN

A PHASE 1, OPEN-LABEL, TWO-PART, FIXED-SEQUENCE, DRUG-DRUG INTERACTION STUDY TO EVALUATE THE EFFECT OF VOXELOTOR ON THE PHARMACOKINETICS OF SELECTED CYP AND TRANSPORTER PROBE SUBSTRATES IN HEALTHY PARTICIPANTS

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{inf}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_t	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_t M/P	Ratio of metabolite to parent AUC corrected for molecular weight
BMI	Body mass index
BLQ	Below the limit of quantitation
BP	Blood pressure
CL_{CR}	Creatinine clearance
C_{max}	Maximum observed plasma concentration
CP-I	Coproporphyrin I
$C_{predose}$	Predose plasma concentration
CRF	Case report form
CRU	Clinical research unit
CS	Clinically significant
CSR	Clinical study report
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DILI	Drug-induced liver injury
ECG	Electrocardiogram
ET	Early termination
FSH	Follicle-stimulating Hormone
GM	Geometric mean
HAV	Hepatitis A virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
MATE1	Multi-drug and toxin extrusion protein 1
mg	Milligram
mL	Milliliter
mmHg	millimeters of mercury
OATP1B1	Organic anion transporting polypeptide 1B1
PT	Preferred Term
PK	Pharmacokinetic(s)
SAE	Serious Adverse Event

SD	Standard Deviation
SOC	System Organ Class
SAP	Statistical analysis plan
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time at which the maximum plasma concentration was observed
ULN	Upper limit of normal
WHO DD	World Health Organization Drug Dictionary

TABLE OF CONTENTS

1. INTRODUCTION

This statistical analysis plan (SAP) is consistent with the statistical methods section of the final study protocol (protocol amendment 1, dated 02 March 2023) and includes additional detail to evaluate the pharmacokinetics (PK), safety and tolerability summaries to be included in the clinical study report (CSR).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The following are the study objectives.

2.1.1 Part A

2.1.1.1 Primary Objective

- To evaluate the effect of multiple doses of voxelotor on the plasma PK of a single dose of bupropion, repaglinide, flurbiprofen, omeprazole, and midazolam, which are probe substrates for CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 respectively

2.1.1.2 Exploratory Objective

- To evaluate the effect of voxelotor on midazolam and 1-hydroxymidazolam PK stratified by CYP3A5 genotype

2.1.1.3 Safety Objective

- To evaluate the safety and tolerability of voxelotor when administered in combination with bupropion, repaglinide, flurbiprofen, omeprazole, and midazolam to healthy participants

2.1.2 Part B

2.1.2.1 Primary Objective

- To evaluate the effect of multiple doses of voxelotor on the plasma PK of a single dose of metformin, furosemide, and rosuvastatin, probe substrates for multi-drug and toxin extrusion protein 1 (MATE1), organic anion transporter (OAT3) and organic anion transporting polypeptide 1B1 (OATP1B1), respectively

2.1.2.2 Exploratory Objective

- To evaluate the effect of voxelotor on coproporphyrin I (CP-I) as a biomarker of OATP1B1 transport

2.1.2.3 Safety Objective

- To evaluate the safety and tolerability of voxelotor when administered in combination with metformin, furosemide, and rosuvastatin to healthy participants

2.2 Endpoints

The following are the study endpoints.

2.2.1 Part A

2.2.1.1 Primary PK Endpoints

- Maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC_t) and AUC from time 0 extrapolated to infinity (AUC_{inf}) for bupropion, repaglinide, flurbiprofen, omeprazole, and midazolam

2.2.1.2 Secondary PK Endpoints

- C_{max}, AUC_t and AUC_{inf} for 6-hydroxybupropion, 5-hydroxyomeprazole, and 1--hydroxymidazolam

- The time that C_{max} is observed (t_{max}) and terminal elimination half-life ($t_{½}$) for bupropion, 6-hydroxybupropion, repaglinide, flurbiprofen, omeprazole, 5--hydroxyomeprazole, midazolam, and 1-hydroxymidazolam in plasma. Ratio of metabolite to parent AUC_t corrected for molecular weight (AUC_t M/P) for bupropion, omeprazole, and midazolam

2.2.1.3 Exploratory PK Endpoints

- C_{max}, AUC_t, and AUC_{inf} of midazolam and 1-hydroxymidazolam with and without voxelotor stratified by CYP3A5 genotype

- Predose (Days 2-7, 12-13) and postdose observed concentration at 2 hours (Days 2, 4, 6, and 12) for voxelotor in whole blood and plasma

2.2.1.4 Safety Endpoints

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

- Results of clinical laboratory tests, physical examination findings, and vital signs

2.2.2 Part B

2.2.2.1 Primary PK Endpoints

- C_{max}, AUC_t and AUC_{inf} for metformin, furosemide, and rosuvastatin

2.2.2.2 Secondary PK Endpoints

- t_{max} and $t_{½}$ for metformin, furosemide, and rosuvastatin in plasma

2.2.2.3 Exploratory PK Endpoints

- Predose plasma concentration ($C_{predose}$), C_{max}, t_{max} and AUC from time 0 to 24 hours (AUC_{0-24}) for CP-I
- Predose (Days 4, 5, 6) and postdose observed concentration at 2 hours (Day 4) for voxelotor whole blood and plasma concentration

2.2.2.4 Safety Endpoints

- TEAEs and SAEs
- Results of clinical laboratory tests, physical examination findings, and vital signs

3. STUDY DESIGN

3.1 General

This is a Phase 1, open-label, two-part, fixed-sequence, drug-drug interaction study to evaluate the effect of voxelotor on the pharmacokinetics of selected CYP and transporter probe substrates in healthy participants.
This study is comprised of 2 parts, Parts A and B.

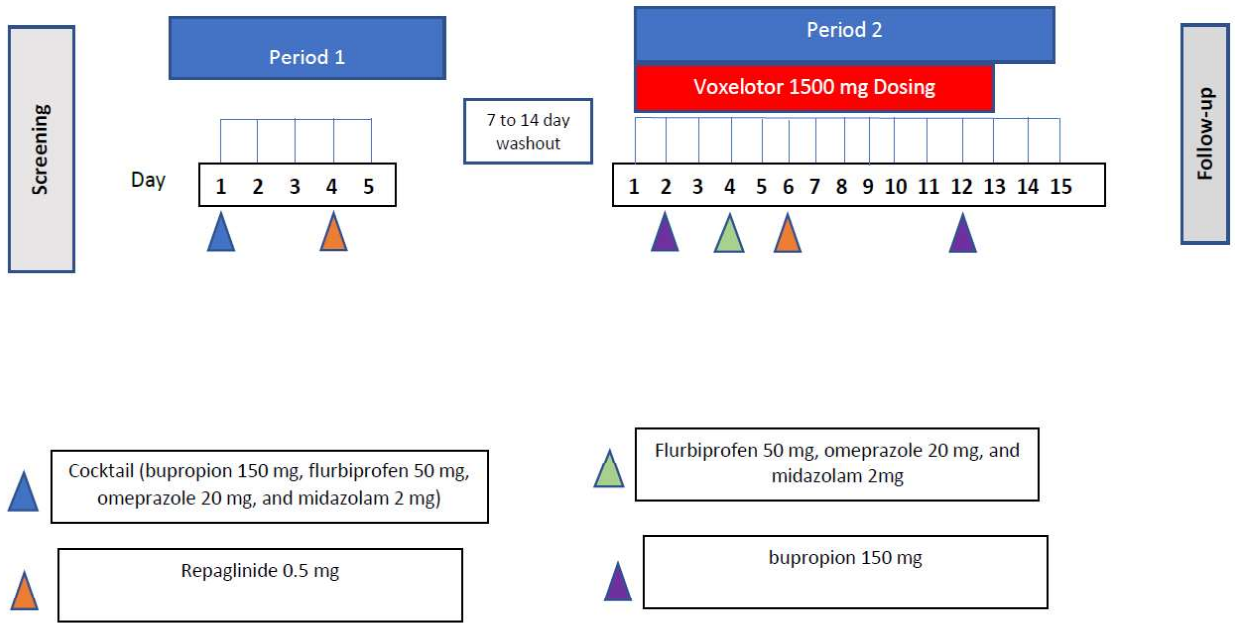
PART A

Part A is an open-label, fixed-sequence, two-period study to evaluate the effect of concomitant administration of voxelotor on bupropion (a CYP2B6 probe substrate), repaglinide (a CYP2C8 probe substrate), flurbiprofen (a CYP2C9 probe substrate), omeprazole (a CYP2C19 probe substrate), and midazolam (a CYP3A4 probe substrate) plasma concentrations. Participants will be admitted to the clinical research unit (CRU) on Day -1 and will remain resident in the CRU until discharge on Day 5 of Period 1. There will be a washout (7 to 14 days) between the last probe substrate dose of Part A, Period 1 and dosing on Day 1 of Part A, Period 2. Participants will be admitted into the CRU on Day -1 and will remain resident in the CRU until discharge on Day 15 of Part A, Period 2. Participants will return to the CRU for a Follow-up visit on Day 28 (± 1 day).

Participants in Part A are ineligible to participate in Part B.

Figure 3-1 summarizes the design of Part A.

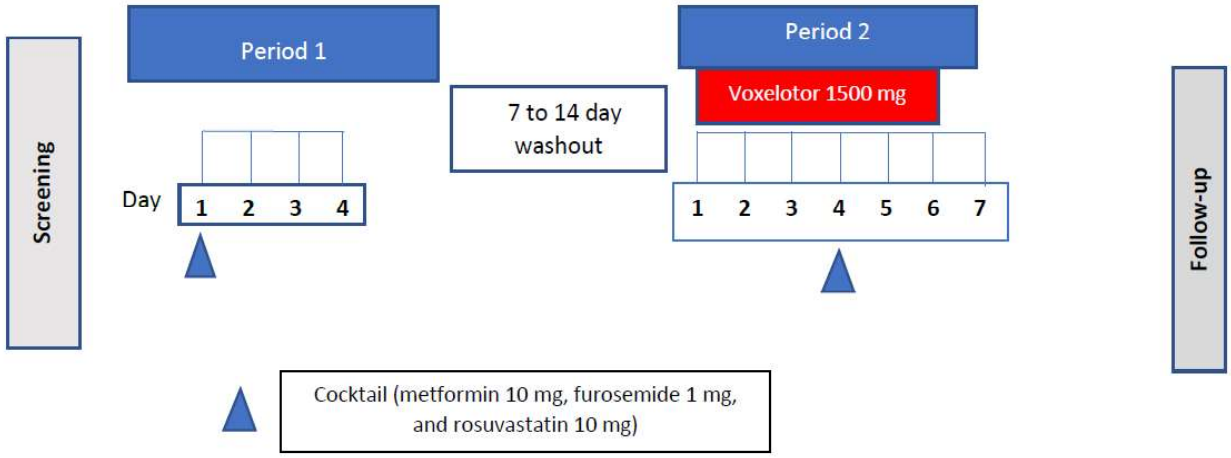
Figure 3-1: Part A Study Schema



PART B

Part B is an open-label, fixed-sequence, two-period study to evaluate the concomitant administration of voxelotor on metformin (a MATE1 probe substrate), furosemide (an OAT3 probe substrate), and rosuvastatin (an OATP1B1 probe substrate) plasma concentrations. Furthermore, the study will assess the effect of voxelotor on plasma concentrations of coproporphyrin I (CP-I), a biomarker for OATP1B1 activity. Participants will be admitted into the CRU on Day -1 and remain resident in the CRU until discharge on Day 4 of Part B, Period 1. There will be a washout (7 to 14 days) between the last probe substrate dose of Part B, Period 1 and dosing on Day 1 of Part B, Period 2. Figure 3-2 summarizes the design of Part B.

Figure 3-2: Part B Study Schema



The study schedules are presented in Tables 3.1.1 and 3.1.2 for Part A: Period 1, Tables 3.1.3 and 3.1.4 for Part A: Period 2, Tables 3.2.1 and 3.2.2 for Part B: Period 1 and Tables 3.2.3 and 3.2.4 for Part B: Period 2.

Table 3.1 Schedule of Assessments for Part A

Table 3.1.1: Schedule of Assessments, Period 1

Assessment	Screening (Days -35 to -2)	Part A, Period 1					
		Day -1 Admission	Day 1	Day 2	Day 3	Day 4	Day 5 / Discharge
Informed Consent	X						
Review Inclusion/Exclusion criteria	X	X					
Medical and Surgical History	X	X [a]					
Height/Weight/BMI [b]	X	X					
Vital Signs [c]	X	X	X	X	X	X	X
Pulse Oximetry [d]			X				
ECG (12-lead) [e]	X	X					
Physical Examination [f]	X	X					X
CYP2C9, CYP2C19, and CYP3A5 genotyping	X						
COVID-19 Test [g]		X					
Pregnancy Test (all females) [h]	X	X					
FSH (postmenopausal females only) [i]	X						
Hematology, Serum Chemistry, and Urinalysis	X	X		X			X
Coagulation Panel (PT, PTT, INR)	X						X
Creatinine Clearance [j]	X	X					
Serology Panel (Hepatitis A, B, C, and HIV)	X						

Assessment	Screening (Days -35 to -2)	Part A, Period 1					
		Day -1 Admission	Day 1	Day 2	Day 3	Day 4	Day 5 / Discharge
Screening for Drugs of Abuse, Alcohol, and Cotinine	X	X					
Overnight Stay		X	X	X	X	X	
Bupropion, Flurbiprofen, Omeprazole, and Midazolam Administration [k]			X				
Bupropion, 6-hydroxybupropion, Flurbiprofen, Omeprazole, 5-hydroxyomeprazole, Midazolam, and 1-hydroxymidazolam PK Sampling (Plasma) [l]			X	X	X	X	
Repaglinide Administration [k]						X	
Repaglinide PK Sampling (Plasma) [l]						X	X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; CL_{cr} = creatinine clearance; COVID-19 = coronavirus disease; CYP = cytochrome P450; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time.

a. Any updates to medical and surgical history will be recorded.
b. Height will be performed at screening only. BMI will be calculated using the height obtained at screening.
c. Vital signs (heart rate, blood pressure, respiratory rate, and oral temperature) will be measured after a participant has rested at least 5 minutes in the supine position. Vital signs will be collected as outlined in Table 3.1.2.
d. Oxygen saturation will be measured by pulse oximetry prior to and following cocktail administration as outlined in Table 3.1.2.
e. ECGs (12-lead) will be recorded after a participant has rested at least 5 minutes in the supine position.
f. Physical examinations after the screening visit may be targeted at the discretion of the Investigator, focusing on specific organ systems, abnormalities identified on the screening examination, and abnormalities related to adverse events and screening for bupropion toxicity.
g. Additional COVID-19-testing or procedures may be implemented based on the prevailing situation during study conduct, at the Investigator's discretion. Any procedure implemented will be in accordance with the local regulations and shall be documented appropriately.

h. A serum pregnancy test will be conducted at screening and urine pregnancy test at Day -1. A serum pregnancy test will also be conducted for confirmation in the event of a positive urinary pregnancy test result.
i. Postmenopausal is defined as having amenorrhea for 12 consecutive months or surgically sterile. CL_{cr} will be calculated using the Cockcroft-Gault formula (CLcr [mL/min] = [(140-age [years]) × weight (kg) × (0.85 for female participants)]/ [72 × serum creatinine (mg/dL)]).
j. Participants must remain upright or semi-recumbent (head of bed > 45 degrees) for 4 hours postdose on days of probe substrate administration.
k. Blood samples for plasma PK analysis of bupropion, 6-hydroxybupropion, flurbiprofen, omeprazole, 5-hydroxyomeprazole, midazolam, 1-hydroxymidazolam, and repaglinide will be collected as outlined in Table 3.1.2.

NOTE: If multiple postdose procedures are required to be conducted at the same nominal time point, the timing of PK blood sample collections will take priority over all other scheduled activities except for dosing. In practice, the following is the order of priority: (1) PK blood sampling; (2) clinical laboratory tests sampling; (3) ECG recording; (4) vital signs and pulse oximetry assessments; (5) physical examination and weight measurements. Electrocardiograms and vital signs may be conducted up to 15 and 10 minutes, respectively, prior to the nominal time to minimize the potential autonomic effects of blood draws on these measurements.

Table 3.1.2: Schedule of Study Procedures, Period 1

Study Day	Time Relative to Dosing [a] -Vital Signs Timepoints [b]	Time Relative to Dosing [a] -Pulse Oximetry Timepoints [c]	Time Relative to Bupropion, Flurbiprofen, Omeprazole, Midazolam Dose [a] -PK Sampling Timepoints [d]	Time Relative to Repaglinide Dose [a] -PK Sampling Timepoints [e]
1	0, 4	0, 0.5, 1, 1.5, 2, 3, 4	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12	
2	24		24	
3	48		48	
4	0, 4		72	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12
5 / Discharge	24			24

Abbreviations: PK = pharmacokinetic.

a. Time relative to dosing in hours.
b. Vital signs (heart rate, blood pressure, respiratory rate, and oral temperature) will be measured after a participant has rested at least 5 minutes in the supine position. Predose is at timepoint 0.
c. Oxygen saturation will be measured by pulse oximetry. Predose is at timepoint 0.
d. PK samples are to determine plasma bupropion, 6-hydroxybupropion, flurbiprofen, omeprazole, 5-hydroxyomeprazole, midazolam, and 1hydroxymidazolam concentrations. Predose PK blood sample (timepoint 0) will be collected within 60 minutes prior to dosing. Collection windows of ±5 minutes through 8-hour sampling and ±15 minutes for samples drawn thereafter are acceptable.
e. PK samples are to determine plasma repaglinide concentrations. Predose PK blood sample (timepoint 0) will be collected within 60 minutes prior to dosing. Collection windows of ± 5 minutes through 8-hour sampling and ± 15 minutes for samples drawn thereafter are acceptable.

NOTE: If multiple postdose procedures are required to be conducted at the same nominal time point, the timing of PK blood sample collections will take priority over all other scheduled activities except for dosing. In practice, the following is the order of priority: (1) PK blood sampling; (2) clinical laboratory tests sampling; (3) vital signs and pulse oximetry assessments; (4) physical examination and weight measurements. Vital signs may be conducted up to 10 minutes, prior to the nominal time to minimize the potential autonomic effects of blood draws on these measurements.

Table 3.1.3: Schedule of Assessments, Period 2

Assessment / Day	Part A, Period 2																Follow-up / ET
	-1 Admit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Day 15 / Discharge	28 (± 1 day)
Review Inclusion/Exclusion Criteria	X																
Weight/BMI [a]	X																X
Vital Signs [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse Oximetry					X												
ECG (12-lead) [c]	X																
Physical Examination [d]	X																X
COVID-19 [e]	X																
Urine Pregnancy Test (all females) [f]	X																X
Hematology, Serum Chemistry, and Urinalysis	X		X					X		X		X			X		X
Coagulation Panel (PT, PTT, INR)	X																X
Screening for Drugs of Abuse, Alcohol, and Cotinine	X																X
Overnight Stay	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Voxelotor Administration [g]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Voxelotor PK Sampling (Whole Blood and Plasma) [i]			X	X	X	X	X	X					X	X			

Assessment / Day	Part A, Period 2																Follow-up / ET
	-1 Admit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Day 15 / Discharge	28 (± 1 day)
Bupropion Administration [g, h]			X										X				
Bupropion and 6-hydroxybupropion PK Sampling (Plasma) [i]			X	X	X	X							X	X	X	X	
Flurbiprofen, Omeprazole, and Midazolam Administration [h]					X												
Flurbiprofen, Omeprazole, 5-hydroxyomeprazole, Midazolam, and 1-hydroxymidazolam PK Sampling [i]					X	X	X										
Repaglinide Administration [g, h]							X										
Repaglinide PK Sampling (Plasma) [i]							X	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease; ECG = electrocardiogram; ET = early termination; INR = international normalized ratio; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time.

a. BMI will be calculated using the height obtained at screening.
b. Vital signs (heart rate, blood pressure, respiratory rate, and oral temperature) will be measured after the participant has rested at least 5 minutes in the supine position. Vital signs will be measured following dosing and will be collected as outlined in Table 3.1.4.
c. ECGs (12-lead) will be collected after the participant has rested at least 5 minutes in the supine position.
d. Physical examinations after the screening visit may be targeted at the discretion of the Investigator, focusing on specific organ systems, abnormalities identified on the screening examination, and abnormalities related to adverse events and screening for bupropion toxicity.
e. Additional COVID-19-testing or procedures may be implemented based on the prevailing situation during study conduct, at the Investigator's discretion. Any procedure implemented will be in accordance with the local regulations and shall be documented appropriately.
f. A urine pregnancy test will be conducted. A serum pregnancy test will also be conducted for confirmation in the event of a positive urinary pregnancy test result.

g. On days when voxelotor is administered with a probe substrate, voxelotor will be administered first and will be immediately followed by the probe substrate administration.
h. Participants must remain upright or semi-recumbent (head of bed > 45 degrees) for 4 hours postdose on days of probe substrate administration.
i. PK samples will be collected as outlined in Table 3.1.4.

NOTE: If multiple postdose procedures are required to be conducted at the same nominal time point, the timing of PK blood sample collections will take priority over all other scheduled activities except for dosing. In practice, the following is the order of priority: (1) PK blood sampling; (2) clinical laboratory tests sampling; (3) ECG recording; (4) vital signs; (5) physical examination and weight measurements. Electrocardiograms and vital signs may be conducted up to 15 and 10 minutes, respectively, prior to the nominal time to minimize the potential autonomic effects of blood draws on these measurements.

Table 3.1.4: Schedule of Study Procedures, Period 2

Study Day	Time Relative to Dosing [a] - Vital Signs Timepoints [b]	Time Relative to Dosing [a] - Pulse Oximetry Timepoints [c]	Time Relative to Voxelotor Dose [a] - PK Sampling Timepoints [d]	Time Relative to Bupropion Dose [a] - PK Sampling Timepoints [e]	Time Relative to Flurbiprofen, Omeprazole, Midazolam Dose [a] - PK Sampling Timepoints [f]	Time Relative to Repaglinide Dose [a] - PK Sampling Timepoints [g]
1	0, 4					
2	0, 4		0, 2	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12		
3	0, 4		0	24		
4	0, 4	0, 0.5, 1, 1.5, 2, 3, 4	0, 2	48	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12	
5	0, 4		0	72	24	
6	0, 4		0, 2		48	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12
7	0, 4		0			24
8	0, 4					
9	0, 4					
10	0, 4					
11	0, 4					
12	0, 4		0, 2	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12		
13	0, 4		0	24		
14	24			48		
15 / Discharge	48			72		

Abbreviations: PK = pharmacokinetic.

a. Time relative to dosing in hours.
b. Vital signs (heart rate, blood pressure, respiratory rate, and oral temperature) will be measured after a participant has rested at least 5 minutes in the supine position. Predose (timepoint 0) will be collected within 20 minutes prior to dosing.
c. Oxygen saturation will be measured by pulse oximetry. Predose is at timepoint 0.
d. On days when voxelotor is administered with a probe substrate, voxelotor will be administered first and will be immediately followed by the probe substrate administration. PK samples are to determine whole blood and plasma of voxelotor. Predose PK blood samples (timepoint 0) will be collected within 15 minutes prior to dosing. Collection windows of ± 5 minutes are acceptable.
e. PK samples are to determine plasma bupropion and 6-hydroxybupropion concentrations. Predose PK blood samples (timepoint 0) will be collected within 15 minutes prior to dosing. Collection windows of ± 5 minutes through 8-hour sampling and ± 15 minutes for samples drawn thereafter are acceptable.
f. PK samples are to determine plasma flurbiprofen, omeprazole, 5-hydroxyomeprazole, midazolam, and 1-hydroxymidazolam concentrations. Predose PK blood sample (time point 0) will be collected within 15 minutes prior to dosing. Collection windows of ± 5 minutes through 8-hour sampling and ± 15 minutes for samples drawn thereafter are acceptable.
g. PK samples are to determine plasma repaglinide concentrations. Predose PK blood sample (timepoint 0) will be collected within 15 minutes prior to dosing. Collection windows of ± 5 minutes through 8-hour sampling and ± 15 minutes for samples drawn thereafter are acceptable.

NOTE: If multiple postdose procedures are required to be conducted at the same nominal time point, the timing of PK blood sample collections will take priority over all other scheduled activities except for dosing. In practice, the following is the order of priority: (1) PK blood sampling; (2) clinical laboratory tests sampling; (3) vital signs and pulse oximetry assessments; (4) physical examination and weight measurements. Vital signs may be conducted up to 10 minutes, prior to the nominal time to minimize the potential autonomic effects of blood draws on these measurements.

Table 3.2 Schedule of Assessments for Part B

Table 3.2.1: Schedule of Assessments, Period 1

Assessment	Screening (Day -35 to Day -2)	Part B, Period 1				
		Day -1 Admission	Day 1	Day 2	Day 3	Day 4 / Discharge
Informed Consent	X					
Review Inclusion/Exclusion Criteria	X	X				
Medical and Surgical History	X	X [a]				
Height/Weight/BMI [b]	X	X				
Vital Signs [c]	X	X	X	X	X	X
ECG (12-lead) [d]	X	X				
Physical Examination [e]	X	X				X
SLCO1B1 Genotyping	X					
COVID-19 Test [f]		X				
Pregnancy Test (all females) [g]	X	X				
FSH (postmenopausal females only) [h]	X					
Hematology, Serum Chemistry, and Urinalysis	X	X		X	X	
Coagulation Panel (PT, PTT, INR)	X				X	
Creatinine Clearance [i]	X	X				
Serology Panel (Hepatitis A, B, C, and HIV)	X					
Screening for Drugs of Abuse, Alcohol, and Cotinine	X	X				
Overnight Stay		X	X	X	X	

Assessment	Screening (Day -35 to Day -2)	Part B, Period 1				
		Day -1 Admission	Day 1	Day 2	Day 3	Day 4 / Discharge
Cocktail Administration [j]			X			
Metformin and Furosemide PK Sampling (Plasma) [k]			X	X	X	
Rosuvastatin PK Sampling (Plasma) [k]			X	X	X	X
Plasma CP-I Sampling [k]			X	X		
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

Abbreviations: BMI = body mass index; CL_{cr} = creatinine clearance; COVID-19 = coronavirus disease; CP-I = coproporphyrin I; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time.

a. Any updates to medical and surgical history will be recorded.
b. Height will be performed at screening only. BMI will be calculated using the height obtained at screening.
c. Vital signs (heart rate, blood pressure, respiratory rate, and oral temperature) will be measured after a participant has rested at least 5 minutes in the supine position. Vital signs will be collected as outlined in Table 3.2.2.
d. ECGs (12-lead) will be recorded after a participant has rested at least 5 minutes in the supine position.
e. Physical examinations after the screening visit may be targeted at the discretion of the Investigator, focusing on specific organ systems, abnormalities identified on the screening examination, and abnormalities related to adverse events and screening for metformin, furosemide, and rosuvastatin toxicity.
f. Additional COVID-19-testing or procedures may be implemented based on the prevailing situation during study conduct, at the Investigator's discretion. Any procedure implemented will be in accordance with the local regulations and shall be documented appropriately.
g. A serum pregnancy test will be conducted at screening and urine pregnancy test at Day-1. A serum pregnancy test will also be conducted for confirmation in the event of a positive urinary pregnancy test result.
h. Postmenopausal is defined as having amenorrhea for 12 consecutive months or surgically sterile.
i. CL_{cr} will be calculated using the Cockcroft-Gault formula (CL_{cr} [mL/min] = [(140-age [years]) × weight (kg) × (0.85 for female participants)]/[72 ×serum creatinine (mg/dL)]).
j. Cocktail includes metformin 10 mg, furosemide 1 mg, and rosuvastatin 10 mg. Participants must remain upright or semi-recumbent (head of bed > 45 degrees) for 4 hours postdose on days of probe substrate administration.
k. Blood samples for plasma CP-I and plasma PK analysis of metformin, furosemide, and rosuvastatin will be collected as outlined in Table 3.2.2.

NOTE: If multiple postdose procedures are required to be conducted at the same nominal time point, the timing of PK blood sample collections will take priority over all other scheduled activities except for dosing. In practice, the following is the order of priority: (1) PK blood sampling; (2) clinical laboratory tests sampling; (3) ECG recording; (4) vital signs; (5) physical examination and weight measurements. Electrocardiograms and vital signs may be conducted up to 15 and 10 minutes, respectively, prior to the nominal time to minimize the potential autonomic effects of blood draws on these measurements.

Table 3.2.2: Schedule of Study Procedures, Period 1

Study Day	Time Relative to Dosing [a] -Vital Signs Timepoints [b]	Time Relative to Metformin and Furosemide Dose [a] -PK Sampling Timepoints [c]	Time Relative to Rosuvastatin Dose [a] -PK Sampling Timepoints [c]	Time Relative to Dosing [a] -Plasma CP-I Sampling Timepoints [d]
1	0, 4	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12
2	24	24	24	24
3	48	48	48	
4 / Discharge	72		72	

Abbreviations: CP-I = coproporphyrin I; PK = pharmacokinetic.

a. Time relative to dosing in hours.
b. Vital signs (heart rate, blood pressure, respiratory rate, and oral temperature) will be measured after a participant has rested at least 5 minutes in the supine position. Predose is at timepoint 0.
c. PK samples are to determine plasma metformin, furosemide, and rosuvastatin concentrations. Predose PK blood sample (timepoint 0) will be collected within 60 minutes prior to dosing. Collection windows of ± 5 minutes through 8-hour sampling and ± 15 minutes for samples drawn thereafter are acceptable.
d. PK samples are to determine plasma concentrations of CP-I. Predose PK blood sample (timepoint 0) will be collected within 60 minutes prior to dosing. Collection windows of ± 5 minutes through 8-hour sampling and ± 15 minutes for samples drawn thereafter are acceptable.

NOTE: If multiple postdose procedures are required to be conducted at the same nominal time point, the timing of PK blood sample collections will take priority over all other scheduled activities except for dosing. In practice, the following is the order of priority: (1) PK blood sampling; (2) clinical laboratory tests sampling; (3) vital signs and pulse oximetry assessments; (4) physical examination and weight measurements. Vital signs may be conducted up to 10 minutes, prior to the nominal time to minimize the potential autonomic effects of blood draws on these measurements.

Table 3.2.3: Schedule of Assessments, Period 2

	Part B, Period 2								Follow-up / ET
Assessment	**Day -1 Admit**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7 / Discharge**	**Day 18 (± 1 day)**
Review Inclusion/Exclusion Criteria	X								
Weight/BMI [a]	X								X
Vital Signs [b]	X	X	X	X	X	X	X	X	X
ECG (12-lead) [c]	X								
Physical Examination [d]	X								X
COVID-19 Test [e]	X								
Urine Pregnancy Test (all females) [f]	X								X
Hematology, Serum Chemistry, and Urinalysis	X		X			X	X		X
Coagulation Panel (PT, PTT, INR)	X								X
Screening for Drugs of Abuse, Alcohol, and Cotinine	X								X
Overnight Stay	X	X	X	X	X	X	X		
Voxelotor Administration		X	X	X	X [g]	X			
Voxelotor PK Sampling (Whole Blood and Plasma) [h]					X	X	X		
Cocktail Administration [i]					X				
Metformin and Furosemide PK Sampling (Plasma) [h]					X	X	X		
Rosuvastatin PK Sampling (Plasma) [h]					X	X	X	X	
Plasma CP-I Sampling [j]					X	X			
Concomitant Medications	X	X	X	X	X	X	X	X	X

	Part B, Period 2								Follow-up / ET
Assessment	**Day -1 Admit**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7 / Discharge**	**Day 18 (± 1 day)**
Adverse Events	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease; CP-I = coproporphyrin I; ECG = electrocardiogram; ET = early termination; INR = international normalized ratio; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time.

a. BMI will be calculated using the height obtained at screening.
b. Vital signs (heart rate, blood pressure, respiratory rate, and oral temperature) will be measured after the participant has rested at least 5 minutes in the supine position. Vital signs will be measured and collected as outlined in Table 3.2.4.
c. ECGs (12-lead) will be collected after the participant has rested at least 5 minutes in the supine position.
d. Physical examinations after the screening visit may be targeted, focusing on specific organ systems, abnormalities identified on the screening and abnormalities related to adverse events and screening for metformin, furosemide, and rosuvastatin toxicity.
e. Additional COVID-19-testing or procedures may be implemented based on the prevailing situation during study conduct, at the Investigator's discretion. Any procedure implemented will be in accordance with the local regulations and shall be documented appropriately.
f. A urine pregnancy test will be conducted. A serum pregnancy test will also be conducted for confirmation in the event of a positive urinary pregnancy test result.
g. Voxelotor will be administered first and immediately followed by administration of metformin, furosemide, and rosuvastatin. h. Blood samples for voxelotor, metformin, furosemide, and rosuvastatin PK analysis will be collected as outlined in Table 3.2.4.
i. Cocktail includes metformin 10 mg, furosemide 1 mg, and rosuvastatin 10 mg. Participants must remain upright or semi-recumbent (head of bed > 45 degrees) for 4 hours postdose on days of probe substrate administration.
j. Blood samples for plasma CP-I assessment will be collected as outlined in Table 3.2.4.

NOTE: If multiple postdose procedures are required to be conducted at the same nominal time point, the timing of PK blood sample collections will take priority over all other scheduled activities except for dosing. In practice, the following is the order of priority: (1) PK blood sampling; (2) clinical laboratory tests sampling; (3) ECG recording; (4) vital signs; (5) physical examination and weight measurements. Electrocardiograms and vital signs may be conducted up to 15 and 10 minutes, respectively, prior to the nominal time to minimize the potential autonomic effects of blood draws on these measurements.

Table 3.2.4: Schedule of Study Procedures, Period 2

Study Day	Time Relative to Dosing [a] -Vital Signs Timepoints [b]	Time Relative to Voxelotor Dose [a] -PK Sampling Timepoints [c]	Time Relative to Metformin and Furosemide Dose [a] -PK Sampling Timepoints [d]	Time Relative to Rosuvastatin Dose [a] -PK Sampling Timepoints [d]	Time Relative to Dosing [a] -Plasma CP-I Sampling Timepoints [e]
1	0				
2	0				
3	0, 4				
4	0, 4	0, 2	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12
5	24	0	24	24	24
6	48	0	48	48	
7 / Discharge	72			72	

Abbreviations: CP-I = coproporphyrin I; PK = pharmacokinetic.

a. Time relative to dosing in hours.
b. Vital signs (heart rate, blood pressure, respiratory rate, and oral temperature) will be measured after a participant has rested at least 5 minutes in the supine position. Predose (timepoint 0) will be collected within 20 minutes prior to dosing.
c. Voxelotor will be administered first and will be immediately followed by administration of metformin, furosemide, and rosuvastatin. PK samples are to determine whole blood and plasma of voxelotor. Predose PK blood samples (timepoint 0) will be collected within 15 minutes prior to dosing. Collection windows of ± 5 minutes are acceptable.
d. PK samples are to determine plasma metformin, furosemide, and rosuvastatin concentrations. Predose PK blood sample (timepoint 0) will be collected within 15 minutes prior to dosing. Collection windows of ± 5 minutes through 8-hour sampling and ± 15 minutes for samples drawn thereafter are acceptable.
e. PK samples are to determine plasma concentrations of CP-I. Predose PK blood sample (timepoint 0) will be collected within 15 minutes prior to dosing. Collection windows of ± 5 minutes through 8-hour sampling and ± 15 minutes for samples drawn thereafter are acceptable.

NOTE: If multiple postdose procedures are required to be conducted at the same nominal time point, the timing of PK blood sample collections will take priority over all other scheduled activities except for dosing. In practice, the following is the order of priority: (1) PK blood sampling; (2) clinical laboratory tests sampling; (3) vital sign and pulse oximetry assessments; (4) physical examination and weight measurements. Vital signs may be conducted up to 10 minutes, prior to the nominal time to minimize the potential autonomic effects of blood draws on these measurements.

3.2 Study Population

Part A: Approximately 26 healthy male or female participants (at least 20% African Americans) with ≥18 to ≤55 years of age inclusive, with a body mass index (BMI) ≥18.0 to ≤30.0 kg/m^2, and a body weight ≥ 50 kg at the screening visit and Period 1 Day -1 will be enrolled in this part. Participants will be stratified by CYP3A5 expresser status (approximately 50% expressers).

Part B: Approximately 20 healthy male or female participants (at least 20% African Americans) with ≥18 to ≤55 years of age inclusive, with a body mass index (BMI) ≥18.0 to ≤30.0 kg/m^2, and a body weight ≥ 50 kg at the screening visit and Period 1 Day -1 will be enrolled in this part.

In total, approximately 46 male or female participants will be enrolled in the study.

3.3 Evaluations at Screening and Check-in

Screening procedures will be conducted prior to Day 1 dosing between Day -35 to Day -2 for both Part A and Part B. Refer to Table 3.1.1 and Table 3.2.1 for Part A and Part B respectively for screening and check-in procedures.

3.4 Randomization and Treatment Assignments

This is an open-label fixed sequence study, so randomization and blinding are not applicable.

3.5 Determination of Sample Size

Part A:
There will be 26 participants enrolled in Part A. A previous DDI cocktail study (GBT440--003) used several probe substrates including midazolam and omeprazole that are common with the current protocol. It was shown that voxelotor, at two 900 mg/day doses followed by a 600 mg/day dose, significantly decreased midazolam elimination in 24 healthy participants but had no effect on the PK of omeprazole. Thus, we anticipate that an approximately similar number of healthy participants (n=24, adjusting for a potential 10% dropout rate, out of 26 enrolled participants) would facilitate characterization of the magnitude of DDI when 1500 mg voxelotor is administered for 4 days.

Part B:
There will be 20 participants enrolled in Part B. Rosuvastatin is used as the probe substrate of choice for sample size estimation because robust information on the intrasubject variability is lacking at sub-clinical doses of metformin and frusemide. A previous study indicated an intrasubject coefficient of variation (intra CV%) of approximately 12.3% for rosuvastatin AUC_{0-t} and 21.3% for rosuvastatin C_{max}. Using the precision method and assuming the true GMR = 1, a sample size of 17 participants will provide the GMR of C_{max}, given alone versus given with voxelotor, to be within 80% and 125% of the true value, with 90% confidence. Thus, approximately 17 participants (adjusting for a potential 10% dropout rate, out of approximately 20 enrolled participants) will be sufficient to provide adequate insight into the potential effect of voxelotor on the PK of rosuvastatin.

3.6 Study Drug Administration

Eligible participants will receive the following treatments in fasted state:

Part A, Period 1:

- Treatment A: On Day 1, single oral doses of bupropion 150 mg, flurbiprofen 50 mg, omeprazole 20 mg, and midazolam 2 mg will be administered.
- Treatment B: On Day 4, a single oral dose of repaglinide 0.5 mg will be administered.

Part A, Period 2:

- Treatment C: On Day 1 to Day 13, oral doses of voxelotor 1500 mg will be administered daily for 13 days.
- Treatment D: On Day 2, a single oral dose of bupropion 150 mg will be administered immediately following voxelotor administration.
- Treatment E: On Day 4, single oral doses of flurbiprofen 50 mg, omeprazole 20 mg, and midazolam 2 mg will be administered immediately following voxelotor administration.
- Treatment F: On Day 6, a single oral dose of repaglinide 0.5 mg will be administered immediately following voxelotor administration.
- Treatment G: On Day 12, a single oral dose of bupropion 150 mg will be administered immediately following voxelotor administration.

Part B, Period 1:

- Treatment A: On Day 1, single oral doses of metformin hydrochloride 10 mg, furosemide 1 mg, and rosuvastatin 10 mg will be administered.

Part B, Period 2:

- Treatment B: On Day 1 to Day 3, oral doses of voxelotor 1500 mg will be administered daily for 3 days.
- Treatment C: On Day 4, single oral doses of metformin 10 mg, furosemide 1 mg and rosuvastatin 10 mg will be administered immediately following a single oral dose of voxelotor 1500 mg.
- Treatment D: On Day 5, a single oral dose of voxelotor 1500 mg will be administered.

Study treatments will be administered with approximately 240 mL (8 fluid ounces) of non-refrigerated, noncarbonated water following an overnight fast of at least 10 hours. No food will be allowed for at least 4 hours postdose. Water will be allowed as desired, except for 1 hour before and 2 hours following dosing.

3.7 Prior and Concomitant Medications

Prior medication will be defined as any medication with a stop date prior to the date of the first dose of study drug.
A concomitant medication is defined as any prescription medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) with a start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date on or after the date of the first dose of study drug in each part.

3.8 Drug Administration and Compliance

Investigational product will be administered by delegated and trained staff at the CRU. Details regarding dosing, including the dose administered and the date and time of dosing, will be recorded.

3.9 Pharmacokinetic Sampling Schedule

Whole blood and plasma PK samples will be collected at time points specified in the PK sampling schedule (Part A, Period 1: Table 3.1.2, Part A, Period 2: Table 3.1.4, Part B, Period 1: Table 3.2.2, and Part B, Period 2: Table 3.2.4). Blood sample collection, processing, and shipping details will be outlined in a separate study reference manual.
Part A

- Whole blood and plasma concentrations of voxelotor, and plasma concentrations of bupropion, 6- hydroxybupropion, repaglinide, flurbiprofen, omeprazole, 5-hydroxyomeprazole, midazolam, and 1-hydroxymidazolam will be determined using validated assays.

Part B

- Whole blood and plasma concentrations of voxelotor, and plasma concentrations of metformin, furosemide, rosuvastatin, and CP-I will be determined using validated assays.

3.10 Evaluation of Treatment Safety

3.10.1 Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of an investigational product, whether or not thought to be related to the investigational product. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the participant signs the ICF for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

A TEAE is defined as any event not present before exposure to study drug (voxelotor or cocktail drugs [probe substrates]) or any event already present that worsens in either intensity or frequency after exposure to study drug.

A SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/ birth defect.

Participants will be monitored throughout the study for AEs, from the time informed consent is obtained through Follow-up visit (Day 28 [Part A, Period 2] or Day 18 [Part B, Period 2]). The following details will be collected: description of the AE, onset date/time, stop date/time, severity (Grade 1- Mild, Grade 2 - Moderate, Grade 3 – Severe, Grade 4 - Life-threatening and Grade 5 -Fatal), relationship to study treatments, action taken with study drug, seriousness, duration and outcome.

Potential events of drug-induced liver injury (DILI) will be reported as SAEs. Potential events of DILI will be defined as meeting all of the following criteria:

- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN)
- Total bilirubin > 2 × ULN without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of laboratory value increases (eg, acute viral hepatitis; alcoholic and autoimmune hepatitis; hepatobiliary disorders; nonalcoholic steatohepatitis; cardiovascular causes; concomitant treatments)

3.10.2 Clinical Laboratory Assessments

Samples for hematology, serum chemistry, coagulation and urinalysis assessments will be collected as specified in the study schedule tables: Table 3.1.1 for Part A: Period 1, Table 3.1.3 for Part A: Period 2, Table 3.2.1 for Part B: Period 1 and Table 3.2.3 for Period 2.

The hematology, serum chemistry and other parameters that will be assessed are presented below:

Table 3-3 Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis**
Hematocrit Hemoglobin Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Platelet count (estimate not acceptable) Red blood cell count White blood cell count including differential count (percent and absolute): • Neutrophils • Lymphocytes • Monocytes • Basophils • Eosinophils	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Total bilirubin (direct and indirect) Lactate dehydrogenase [a] Total protein Blood urea nitrogen Creatinine Creatine phosphokinase [a] Calcium Phosphorou Sodium Potassium Magnesium Bicarbonat e Chloride Glucose [a]	Specific gravity Ketones pH Protein Blood Glucose Bilirubin Urobilinogen Nitrite Leukocytes Microscopic examination of sediment, if clinically indicated
Coagulation Prothrombin time Partial thromboplastin time International normalized ratio		

a. Fasting (8 hours) required at screening only

The following additional tests will be performed:

- Urine drugs of abuse (at a minimum, cocaine, cannabinoids, amphetamines, methylenedioxymethamphetamine, methamphetamines, opiates, methadone, barbiturates, and phencyclidine).
- Cotinine screen (urine)
- Alcohol test (urine)
- Serology tests (ie, HIV-1 and HIV-2 antibodies, HAV antibody, HBsAg, and HCV antibody, and any confirmatory tests performed at the discretion of the Investigator)
- Creatinine clearance (CL_{cr}); calculated using the Cockcroft-Gault formula: CL_{cr} (mL/min) = ([140-age (years)] × weight [kg] × [0.85 for female participants])/ (72 × serum creatinine [mg/dL])
- Pregnancy test (females only)
- Follicle stimulating hormone (FSH) (females only; as needed to confirm postmenopausal status)
- COVID-19 test
- CYP2C9 Genotyping (Part A only)
- CYP2C19 Genotyping (Part A only)
- CYP3A5 Genotyping (Part A only)
- SLCO1B1 genotyping (Part B only)

3.10.3 Vital Signs

Vital sign assessments will include oral temperature (°C), heart rate, respiratory rate (breaths per minute) and blood pressure (mmHg) will be collected at timepoints presented in Study Schedule tables: Table 3.1.1 for Part A: Period 1, Table 3.1.3 for Part A: Period 2, Table 3.2.1 for Part B: Period 1 and Table 3.2.3 for Part B: Period 2.

Blood pressure and heart rate measurements are measured after the participant has been resting quietly in a position for at least 5 minutes.

Any clinically significant abnormal vital sign assessment requires at least 1 repeat measurement. Further repeat vitals or additional vital signs may be performed at the discretion of the investigator.

Vital signs abnormalities that are (1) considered clinically significant initially and on confirmation, (2) requires a participant to be discontinued from the study, (3) requires a participant to receive treatment, or (4) requires a change or discontinuation from the study drug (if applicable) will be recorded as AEs.

3.10.4 Electrocardiograms

12-lead ECG(s) will be obtained using an Electrocardiogram (ECG) machine that automatically calculates the heart rate and measures at a minimum RR, PR, QRS, QT, and QTcF intervals at timepoints presented in Study Schedule tables: Table 3.1.1 for Part A: Period 1, Table 3.1.3 for Part A: Period 2, Table 3.2.1 for Part B: Period 1 and Table 3.2.3 for Period 2.

Participants must be resting quietly in a supine position or in the most recumbent position possible for at least 5 minutes before the ECG is obtained.

Electrocardiogram assessment may include automated interpretation of the tracings (eg, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T-wave, and U-wave abnormalities). The Investigator

or designee is responsible for reviewing and over-reading the ECG interpretation, for assessing whether the ECG machine interpretation findings are accurate, appropriate, normal or abnormal, and for providing corrected interpretations as appropriate.

Any abnormal ECGs will be assessed for clinical significance. Additional ECGs may be obtained if clinically indicated and must be obtained if readings are abnormal and clinically significant or thought to be in error (e.g., lead placement error, movement artifact, etc.).

Any ECG that is considered and confirmed clinically significant and requires the participant to be discontinued from the study, requires the participant to receive treatment, or requires a change or discontinuation of the study drug (if applicable), will be recorded as an AE.

3.10.5 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded, and abnormal findings will be carefully documented in the participant's electronic case report form (eCRF). Physical examinations after the screening visit may be targeted, focusing on specific organ systems and abnormalities related to AEs and screening for drug toxicities.

An abnormal physical examination finding that is considered clinically significant and requires the participant to be discontinued from the study, requires the participant to receive treatment, or requires a change or discontinuation of the study drug (if applicable), will be recorded as an AE.

3.10.6 Oxygen Saturation (Part A only)

Oxygen saturation will be measured by pulse oximetry.

Oxygen saturation abnormalities during the on-study period (ie, following dose administration) that (1) are considered clinically significant initially and on confirmation, (2) require a participant to be discontinued from the study, (3) require a participant to receive treatment, or (4) require a change or discontinuation from the study drug (if applicable) will be recorded as AEs.

3.11 Protocol Deviation Reporting

Procedural deviations found by the clinical research associate (CRA) during monitoring visits and data deviations captured on the CRF and found through programming and examining the database will be listed by participant.

4. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

All analyses specified in this SAP are consistent with the final study protocol (final study protocol (original version, dated 10 June 2022). Any changes in this analysis provided or any additional analysis performed will be documented in the CSR.

5. QUALITY CONTROL AND QUALITY ASSURANCE METHODS FOR DATA ANALYSIS

CRF will be monitored and processed according to the ICON Study Specific Procedure (SSP) DM-35070067.01 Data Management Plan (DMP). The DMP describes CRF data processing, edit checks, data query management, medical dictionary coding, SAE reconciliation, data transfers, and data quality review through database lock or any necessary reopening of the database. After database lock, the data will be retrieved from the database using SAS Grid/ SAS Linux - SAS® 9.4.

6. PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic variables will be calculated from the plasma concentration data for the probe substrates and their metabolites using noncompartmental methods (Phoenix™ WinNonlin®, Version 8.0.0 or later; Certara LP, Princeton, New Jersey, USA) and actual sampling times.

Table 6-1. Pharmacokinetic Parameters

The following PK parameters will be determined for Part A:

Parameter	Description
C_{max}	Maximum observed plasma concentration.
t_{max}	The time that C_{max} was observed.
AUC_t	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; calculated using the linear/log trapezoid rule.
AUC_{inf}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity; calculated as AUClast + Clast/λz, where Clast is the last measurable concentration.
AUC%extrap	The percentage of AUC obtained by extrapolation is calculated as follows: $AUC\%extrap = 100 \text{ x } \frac{\text{Clast}/\lambda z}{\text{AUC}\infty}$
AUC_t M/P	Ratio of metabolite to parent AUCt corrected for molecular weight for 6-hydroxybupropion/ bupropion, 5-hydroxyomeprazole/omeprazole, and 1-hydroxymidazolam/midazolam.
$t_{1/2}$	Terminal elimination half-life; calculated as $\ln(2)/\lambda_z$.
$C_{predose}$	Predose plasma concentration (Voxelotor only).
$C_{(2hr)}$	Observed concentration at 2 hours (Voxelotor only)

Molecular Weights

Parent	Parent Molecular Weight	Metabolite	Metabolite Molecular Weight
midazolam	325.8	1-hydroxymidazolam	341.8
bupropion	239.7	6-hydroxybupropion	255.7
omeprazole	345.4	5-hydroxyomeprazole	361.4

The following PK parameters will be determined for Part B:

Parameter	Description
C_{max}	Maximum observed plasma concentration.
$C_{predose}$	Predose plasma concentration (CP-I and Voxelotor only).

Parameter	Description
$C_{(2hr)}$	Observed concentration at 2 hours (Voxelotor only)
t_{max}	The time that C_{max} was observed.
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to 24 hours (CP-I only).
AUC_t	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; calculated using the linear/log trapezoid rule.
AUC_{inf}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity; calculated as $AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last measurable concentration.
AUC%extrap	The percentage of AUC obtained by extrapolation is calculated as follows: $AUC\%extrap = 100 \text{ x } \frac{\text{Clast}/\lambda z}{\text{AUC}\infty}$
$t_{1/2}$	Terminal elimination half-life; calculated as $\ln(2)/\lambda_z$ (metformin, furosemide, and rosuvastatin).

Only data points that describe the terminal elimination log-linear decline will be used in the regression equation for calculation of λ_z; C_{max} and any data point in the distribution phase are not included in the calculation. A minimum of 3 points will be used for determination of λ_z. A general rule of adjusted $R^2 \geq 0.80$ will be considered as acceptable for calculation of λ_z. If adjusted R^2 falls below 0.80, then λ_z will be reported as Not Determined (ND) and that participant's λ_z, $t_{1/2}$, and AUC_{inf} will reported in the appropriate listings but will be flagged and excluded from descriptive summaries and statistical analysis. If the extrapolated AUC_{inf} is more than 20%, then AUC_{inf}, will be listed but flagged and excluded from descriptive summaries and statistical analysis.

6.1 Treatment of Outliers

Individual plasma (and whole blood for voxeletor) concentration-time points, if considered anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of the available documentation. Any such exclusion will be discussed with the Sponsor's Clinical Pharmacologist and clearly described in the CSR.

Entire individual treatment profiles for any participant may be excluded following review of the available documentation and discussion with the Sponsor. However, analysis results, with and without the excluded profiles, may be presented in the CSR. Any such exclusion will be clearly listed in the CSR along with justification for exclusion.

Any anomalous concentration values observed at predose will be identified and discussed in the CSR. Participants who experience emesis during the course of the study will be excluded from the PK summaries and statistical analysis if vomiting occurs at or before 2 times median T_{max} of the probe substrates from the current treatment or voxeletor (when dosed in combination with the probe substrates).

6.2 Non-Quantifiable Concentrations

All concentration values reported as no results (not collected or ND) values will be treated as missing. For the calculation of concentration summaries and plotting mean concentration time profiles, all concentrations below the quantifiable limit (BLQ) will be treated as zero. For calculating PK parameters, BLQ values will be treated as zero prior to the first measurable concentration. After the first measurable concentration, subsequent BLQ values will be treated as missing.

7. STATISTICAL METHODS

7.1 General

All statistical analyses will be conducted following the principles specified in the International Council for Harmonization (ICH) Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

All statistical analyses will be performed using the statistical software SAS Grid/ SAS Linux - SAS®, Version 9.4 or newer and any exceptions will be detailed in the CSR.

All continuous data will be listed with the same precision as presented in the database. All safety and demographic analyses will be performed for each part of the study. Part, Subject Number, Period, treatment and visit will be used to sort data listings. Both observed values and change-from-baseline values for each participant will be given where applicable.

Unless otherwise noted, continuous variables will be summarized using number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum; categorical variables will be summarized using the frequency count and the percentage of participants in each category.

In the data listings, study day relative to first dose of study drug may be presented. Study day for each part relative to first dose will be calculated as: event date – first dose date (+ 1 if event date ≥ first dose date).

Baseline will be the latest available measurement (scheduled or unscheduled assessment) prior to the study drug administration in each period in the study for each part.

The change from baseline to any subsequent post-baseline visit will be calculated as the absolute difference between that post-Baseline visit's value and the Baseline visit value, as below:

Change from baseline = Post-baseline value – baseline value

For safety summaries, the unscheduled and repeat assessments will not be summarized; however, will be included in the data listing.

7.2 Handling of Dropouts or Missing Data

All attempts will be made to collect all data per protocol. No imputation will be performed for missing values except for AE and concomitant medication start and stop date, and laboratory data as mentioned below. Missing concentrations will be handled as per Section 6.2.

If the character result is reported for quantitative laboratory parameter then for summary and analysis it will be changed as follows into numerical value –

a) If less than '<' sign is used then the value will be reduced by 1 point from the last precision digit

b) If greater than '>' sign is used then 1 point will be added to the last precision digit.

Eg: if lab parameter is reported as whole number >40 then it will be considered as 41, if the parameter is reported with 1 decimal precision <40.1 then it will be considered as 40.0 and if the lab parameter is reported to 2 decimal precision, <40.01 then for summary and analysis it will be treated as 40.00.

7.2.1 Handling of missing/ incomplete dates for Adverse Event

Imputation rules for missing or partial AE start date are defined below:

If only Day of Adverse Event start date is missing:

If the start date has month and year but day is missing, the first day of the month will be imputed

- If this date is earlier than the first dose date, then the first dose date will be used instead.
- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If Day and Month of Adverse Event start date are missing:

If the start date has year, but day and month are missing, the 1st of January will be imputed

- If this date is earlier than the first dose date, then the first dose date will be used instead.
- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If Year of Adverse Event start date is missing:

If the year of AE start is missing or AE start date is completely missing then imputation will not be done.

Missing or partial Adverse Event stop date:

a. If only Day is missing, the last day of the month will be assumed.
b. If Day and Month are both missing, the last day of the year will be assumed.
c. If Day, Month and year are all missing, 'Ongoing' status to stop date will be assigned.

If the AE end date (full or partial) is before the first dose date then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

7.2.2 Handling missing or partial Prior/Concomitant Medication Dates

Missing or partial medication start date:

a. If only Day is missing, the first day of the month will be assumed.
b. If Day and Month are both missing, the first day of the year will be assumed.
c. If Day, Month and Year are all missing, the day before the first dose date will be assumed.

Missing or partial medication stop date:

a. If only Day is missing, the last day of the month will be assumed.
b. If Day and Month are both missing, the last day of the year will be assumed.
c. If Day, Month and year are all missing, 'Ongoing' status to stop date will be assigned.

7.3 Multiple Comparisons and Multiplicity

Not applicable.

7.4 Adjustments for Covariates

Not applicable.

7.5 Multicenter Studies

This is a single-center study.

7.6 Examination of Subgroups

No subgroup analyses are planned.

7.7 Coding Dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0 or higher. Medications will be coded using the World Health Organization Drug Dictionary (WHO Global B3 format - Mar 2023). Medical procedures will be coded.

7.8 Analysis Populations

The following populations will be analyzed.

7.8.1 Enrolled Population

The Enrolled Population will include all participants who signed the informed consent form.

7.8.2 Safety Population

The Safety Population will include all participants who received any amount of study drug (voxelotor or cocktail drugs [probe substrates]).

7.8.3 Pharmacokinetic Full Population

The Pharmacokinetic Full Population will include all participants who received at least 1 dose of study drug (voxelotor or cocktail drugs [probe substrates]) and have at least 1 whole blood or plasma concentration data point.

7.8.4 Pharmacokinetic Evaluable Population

The Pharmacokinetic Evaluable Population will include all participants who received at least 1 dose of study drug (voxelotor or cocktail drugs [probe substrates]) and have a sufficient PK profile to derive at least 1 PK parameter.

7.9 Subject Accountability

Summaries of analysis populations and participant disposition will be presented by parts.

- Number of participants enrolled (Enrolled Population)
- Number and percent of participants who were dosed (Safety Population)
- Number and percent of participants who received all doses
- Number and percent of participants who completed the study

- Number and percent of participants who discontinued early from the study and reason for early discontinuation
- Number and percent of participants in the PK full and PK evaluable population.

Percentage will be based on Safety Population.

Participant disposition data, eligibility criteria satisfaction and consent information will be presented in listings for all participants enrolled in the study. Analysis populations and reason for exclusion will be presented for Safety Population.

7.10 Protocol Deviations

All protocol deviations will be listed using safety population.

7.11 Subject Demographics and Baseline Characteristics

Demographics (sex, age, ethnicity and race) and baseline characteristics (height, weight and BMI) will be listed and summarized by part and overall using safety population. Genotype, Phenotype results will be listed.

7.12 Medical and Surgical History

The medical and surgical history data will be coded using MedDRA, Version 26.0 or later and will be listed using safety population.

7.13 Measurements of Treatment Compliance

Individual participant listing will be provided for eCRF collected exposure data using safety population. Dosing data will be listed.

7.14 Pharmacokinetic Statistical Analysis

The PK Full population will be used for all concentration listings, summary statistics and plots for concentration vs. time. The PK Evaluable population will be used for the PK parameters, summary statistics and statistical analyses.

Plasma concentrations of all probe substrates (alone and probe substrate administered with voxelotor) will be listed and summarized by dosing regimen and nominal sampling time with the number of non-missing observations, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum values at each sampling time. Similarly, whole blood and plasma concentration of voxelotor will be presented and summarized.

The drug concentrations will be summarized descriptively by part, treatment, day and nominal time point in graphical formats (linear and semi-log scales). Overlay of individual concentration profiles over time will be provided for all probe substrates by part.

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by part, treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).
- Individual concentration-time (spaghetti) plots by part and treatment (on both linear and semi-log scales) against actual time postdose (there will be separate plot for each treatment per scale).
- Individual concentration-time plots by participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (containing all treatments) per scale].

- Spaghetti concentration-of Voxelotor time plots by participant (linear scale) against actual time postdose.

7.14.1 Part A Pharmacokinetic Analysis

Plasma PK parameters will be listed for bupropion, 6-hydroxybupropion, repaglinide, flurbiprofen, omeprazole, 5-hydroxyomeprazole, midazolam, and 1-hydroxymidazolam. Summary statistics of PK parameters (primary and secondary) will be presented for each treatment including arithmetic mean, geometric mean, SD, CV%, geometric CV%, median, and range.

In addition, C_{max}, AUC_t and AUC_{inf} of midazolam and 1-hydroxymidazolam with and without voxelotor will be summarized by CYP3A5 genotype (CYP2C9, CYP2C19, CYP3A5, SLCO1B1).t

To assess the effect of voxelotor on the PK of the probe substrates and their metabolites, a linear mixed effect model will be fitted to the log-transformed values of C_{max}, AUC_t and AUC_{inf}. The model will include treatment (probe substrate administered with voxelotor and probe substrate alone) as a fixed effect and participant as a random effect. Point estimates and 90% confidence intervals for treatment differences (probe substrate administered with voxelotor) vs. probe substrate alone on the log scale will be exponentiated to obtain estimates for GM ratios on the original scale.

For AUC_{inf}, AUC_t and C_{max}, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for AUC_{inf}, AUC_t and C_{max}, will be plotted by part, treatment and overlaid with geometric means.

For bupropion, both Day 2 and Day 12 in Period 2 will be compared separately to Period 1 data.

7.14.2 Part B Pharmacokinetic Analysis

Plasma PK parameters will be listed for metformin, furosemide, rosuvastatin, and CP-I. Summary statistics of PK parameters (primary and secondary) will be presented for each treatment including arithmetic mean, geometric mean, SD, CV%, geometric CV%, median and range.

To assess the effect of voxelotor on the PK of the probe substrates, a linear mixed effect model will be fitted to the log-transformed values of C_{max}, AUC_t and AUC_{inf}. The model will include treatment (probe substrate administered with voxelotor and probe substrate alone) as a fixed effect and participant as a random effect. Point estimates and 90% confidence intervals for treatment differences (probe substrate administered with voxelotor versus probe substrate alone) on the log scale will be exponentiated to obtain estimates for GM ratios on the original scale.
For AUC_{inf}, AUC_t and C_{max}, a listing of the individual participant ratios (Test/Reference) will be provided. Box and whisker plots for AUC_{inf}, AUC_t and C_{max}, will be plotted by part, treatment and overlaid with geometric means.

7.15 Safety Analyses

All Safety analyses will be presented using the Safety Population.

Tables will be presented by Part.

7.15.1 Adverse Events

All AE summaries will include TEAEs.

All AEs will be coded by primary system organ class (SOC) and preferred term (PT) according to the MedDRA Version 26.0 or higher and presented by participant in data listings.

The overall incidence of TEAEs (number and percentage of participant and number of events) will be summarized by parts and period (probe substrate alone, probe substrate administered with voxelotor and overall [as applicable]). It includes severity, relationship to study drug: either the investigational products or probe substrates of TEAE and SAEs, TEAEs leading to study or treatment discontinuation, life-threatening SAEs, and SAEs resulting in death.

The TEAEs will be summarized and tabulated at both the participant (n [%] of participants) and event (number of events) level:

- TEAEs by SOC and PT
- TEAEs by SOC, PT and maximum reported severity
- Non Serious TEAEs by SOC, PT and maximum reported severity
- TEAEs by SOC, PT and relationship to study drug (voxelotor or probe substrates).

For the incidence at the participant level by SOC and PT, if a participant experience more than 1 event within the same SOC and PT, only 1 occurrence will be included in the incidence.

For the incidence at the participant level by SOC, PT, and severity, if a participant experience more than 1 event within the same SOC and PT, only the most severe occurrence will be included in the incidence.

For the incidence at the participant level by SOC, PT, and relationship, if a participant experience more than 1 event within the same SOC and PT, only the closest occurrence will be included in the incidence.

Any SAEs, AEs with outcome of death and AEs resulting in discontinuation of study or study drug will be listed separately.

7.15.2 Clinical Laboratory Assessments

Observed values and change from baseline for each parameter of continuous clinical laboratory values (hematology, serum chemistry, urinalysis and coagulation) will be summarized by Part at each visit using descriptive statistics.

Shift from baseline to post-baseline laboratory findings based on normal range criteria will also be summarized by part.

A listing of all clinical laboratory data for each participant at each visit will be presented. Laboratory values outside the reference range will be flagged with ‘L’ for low and ‘H’ for

high in the data listings and clinical significance will also be indicated. A list of abnormal values will be presented.

7.15.3 Vital Signs

Observed and change from baseline vital signs values will be summarized by part at each visit and timepoint using safety population. Vital signs data will be listed by participant at each visit and timepoint with out of range values being flagged and clinical significance indicated.

7.15.4 Electrocardiograms

ECG data will be listed by part and participants at each visit and time point collected for Safety Population with clinically significant results indicated.

7.15.5 Physical Examinations

All physical examination findings will be presented in a participant listing for safety population.

An abnormal physical examination finding that is considered clinically significant and requires the participant to be discontinued from the study, requires the participant to receive treatment, or requires a change or discontinuation of the study drug (if applicable) will be recorded as an AE. Any physical examination findings documented as AEs will be included in the AE summaries.

7.15.6 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the WHO Global B3 format - Mar 2023 and classified according to anatomical therapeutic chemical code (ATC) levels 2 and 4. All prior and concomitant medications data will be listed for safety population.

Concomitant Procedures data will also be listed for safety population.

7.15.7 Oxygen Saturation

Pulse oximetry data will be listed for Part A for Safety Population.

7.16 Planned Interim Analysis

No interim analysis is planned for the primary endpoint.

7.17 General Conventions for Tables, Listings, and Figures

Tables and listings will be presented in landscape mode with minimum of 3/4” bound edge margin and 3/8” other margins on 8.5” x 11” paper.

Courier New font size of no less than 8 point will be used for tables and listings.

A source line will be included on the bottom of each page of all tables and listings. It will contain the SAS code program name and the run date and time.

Each variable is recorded to a specific number of decimal places. If the raw data is presented with varying precision, then the least precise value will be considered as the data precision.

For summary tables, unless otherwise specified, the number of decimal places provided in the tables and listings will be based on the accuracy of the least accurate value in the raw data as follows:

n	integer
nBLQ	integer
Arithmetic mean	1 decimal place more than the least accurate number in the raw data
SD	2 decimal places more than the least accurate number in the raw data
CV (%)/ GM CV (%)	integer
GM	1 decimal place more than the least accurate number in the raw data
Median	1 decimal place more than the least accurate number in the raw data
Minimum	same number of decimal places as raw data
Maximum	same number of decimal places as raw data
CI	same number of decimals as the associated statistic
Percentage	1 decimal place

The Table layouts are given below.

Only for section 14.1

Part A (N=xx)	Part B (N=xx)

Overall will be added for Demographic table

For PK Tables

By Part

Part A (or B)

Treatment A (N=xx)	Treatment B (N=xx)	Treatment C (N=xx)	…..

Footnote for description of treatments will be presented.

Note: PK tables will have analyte or metabolite as subtitle to table

For Safety Tables

By Part

Part as subtitle to table

Period 1 (N=xx)	Period 2 (N=xx)

Overall column will be presented for AE tables

The listing layouts are given below:

Part: A (or B)

Subject Number	xxxx	xxxx	xxxx
XXXX-XXXX			
XXXX-XXXX			
XXXX-XXXX			
XXXX-XXXX			

8. LIST OF TABLES, FIGURES, AND LISTINGS

Table/Figure Number	Table/Figure Name
Section 14.1	**Demographic and Participant Characteristics Data Summaries**
Table 14.1.1.1	Summary of Participant Disposition (Enrolled Population)
Table 14.1.2.1	Analysis Populations
Table 14.1.3.1	Demographic and Baseline Characteristics (Safety population)
Section 14.2	**Pharmacokinetic Data Summaries**
Table 14.2.1.1.1	Summary of Whole Blood and Plasma Voxelotor Cpredose and C(2hr) Concentrations – Part A (PK Full Population)
Table 14.2.1.1.2	Summary of Whole Blood and Plasma Voxelotor Cpredose and C(2hr) Concentrations – Part B (PK Full Population)
Table 14.2.1.2.1	Summary of Plasma Concentrations for Probe Substrates and Metabolites – Part A (PK Full Population) Note: for all analytes and metabolites Note: Present by analyte, treatment groups and study day/timepoints.
Table 14.2.1.2.2	Summary of Plasma Concentrations for Probe Substrates – Part B (PK Full Population) Note: Present by treatment groups and study day/timepoints.
Table 14.2.1.3.1	Summary of Plasma Pharmacokinetic Parameters for Probe Substrates and Metabolites - Part A (PK Evaluable Population) Note: Present by analyte, treatment groups
Table 14.2.1.3.2	Summary of Plasma Pharmacokinetic Parameters for Probe Substrates - Part B (PK Evaluable Population) Note: Present by analyte, treatment groups
Table 14.2.1.4.1	Summary of Plasma Pharmacokinetic Parameters of Midazolam and 1-hydroxymidazolam with and without Voxelotor by CYP3A5 Genotype - Part A (PK Evaluable Population) Note: Present by analyte
Table 14.2.2.1.1	Statistical Analysis of Effect of Voxelotor on the PK of the Probe Substrates and their Metabolites - Part A (PK Evaluable Population)
Table 14.2.2.1.2	Statistical Output for Effect of Voxelotor on the PK of the Probe Substrates and their Metabolites - Part A (PK Evaluable Population)
Table 14.2.2.2.1	Statistical Analysis of Effect of Voxelotor on the PK of the Probe Substrates - Part B (PK Evaluable Population)
Table 14.2.2.2.2	Statistical Output for Effect of Voxelotor on the PK of the Probe Substrates – Part B (PK Evaluable Population)
Figure 14.2.1.1.1	Mean (+/-SD) Plasma Concentrations of Probe Substrates and Metabolites - Time Profiles - Part A (PK Full Population) Note: Present both linear and semi-log
Figure 14.2.1.1.2	Mean (+/-SD) Plasma Concentrations of Probe Substrates - Time Profiles - Part B (PK Full Population) Note: Present both linear and semi-log

	Note: by Part
Listing 16.2.5.3	Individual Plasma Concentrations of Probe Substrates (PK Full Population) Note: Present for all Probe Substrates. By Part and treatment group
Figure 16.2.5.1	Individual Plasma Concentrations of Probe Substrates and Metabolites(PK Full Population) Note: For each participant, present the individual concentration in linear and semi-log scale by part and analyte.
Figure 16.2.5.2	Spaghetti Plot of Plasma Concentrations of Probe Substrates and Metabolites vs Time with Average Profile Overlaid (PK Full Population) Note: by part, treatment also separate probe substrate from metabolite
Figure 16.2.5.3	Spaghetti Plot of Whole Blood and Plasma Concentrations of Voxelotor Study day Profiles with Average Profile Overlaid (PK Full Population) Note: by part
Section 16.2.6	**Individual Pharmacokinetic Response Data**
Listing 16.2.6.1	Individual Probe Substrates Pharmacokinetic Parameters (PK Evaluable Population) Note: Present for each analyte and metabolite separately (as sub-title) by Part
Section 16.2.7	**Adverse Event Listings**
Listing 16.2.7	Adverse Events (Safety Population)
Section 16.2.8	**Individual Laboratory Measurements and additional Safety data by Subject**
Listing 16.2.8.1	Normal Ranges for Laboratory Data
Listing 16.2.8.2	Clinical Laboratory Data by Category (Safety Population) Note: All lab tests except Alcohol Screen, Urine drug screen, FSH and Pregnancy Tests to be included
Listing 16.2.8.3	Vital Signs (Safety Population)
Listing 16.2.8.4	12-lead Electrocardiogram Results (Safety Population)
Listing 16.2.8.5	Physical Examination (Safety Population)
Listing 16.2.8.6	Pulse Oximetry (Safety Population)
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Listing 16.2.8.8	Alcohol Test Result (Safety Population)
Listing 16.2.8.9	Urine Drug Screen Result (Safety Population)
Listing 16.2.8.10	SARS-CoV-2 Test (Safety Population)