CLINICAL STUDY PROTOCOL

Title	**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**
Brief Title/Acronym	Voxelotor CYP and Transporter Cocktail Interaction Study
Active Substance	Voxelotor
Study Phase	I
IND Number	121,691
Agency Product Number	EMEA/H/C/004869
Marketing Authorization Holder	Global Blood Therapeutics Netherlands B.V. Strawinskylaan 3051 1077ZX Amsterdam The Netherlands
Sponsor	Global Blood Therapeutics, Inc.; a wholly owned subsidiary of Pfizer 181 Oyster Point Blvd, South San Francisco, CA 94080 United States of America
Sponsor Contact	PPD Global Blood Therapeutics, Inc. 181 Oyster Point Blvd. South San Francisco, CA 94080 United States of America Email: PPD
Protocol Amendment 1	02 March 2023
Original Protocol	10 June 2022

CONFIDENTIALITY STATEMENT

The information in this protocol is strictly confidential and is available for review to Investigator, study center personnel, the ethics committee, and health authorities. It will not be disclosed to third parties without written authorization from the Sponsor, except to obtain informed consent from persons receiving study treatment. Once the protocol is signed, its terms are binding for all parties.

STATEMENT OF APPROVAL AND COMPLIANCE

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

Protocol Amendment 1 02 March 2023

SPONSOR APPROVAL

The signature of the Sponsor representative below represents that the above-referenced clinical trial is being conducted under FDA IND Number 121,691 voxelotor for the treatment of sickle cell disease. This IND application is held by the Sponsor. The protocol is being conducted in accordance with ICH GCP and all applicable federal, state, and local regulations governing the conduct of this research, including DHHS 45 CFR Part 46, FDA 21 CFR Parts 50, 54, 56, 312, and 812. The Sponsor will provide the Investigator with all information including safety information pertinent to the conduct of the study.

Sponsor Representative (Print):	**Clark Brown, MD, PhD**
Title:	Executive Director, Global Clinical Lead, Rare Diseases
Signature:	PPD
Date:	02 March 2023

INVESTIGATOR APPROVAL

The signature of the Investigator below constitutes approval of this protocol as written and reflects the Investigator's commitment to conduct the study in accordance with the protocol, the applicable laws and regulations and in compliance with ICH GCP guidelines and the Declaration of Helsinki.

Principal Investigator (Print):	**Cassandra Key, MD**
Title:	Principle Investigator
Signature:	PPD
Date:	02 March 2023

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
ADL	activities of daily living
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_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
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_t corrected for molecular weight
BMI	body mass index
BP	blood pressure
$C_{(2hr)}$	observed concentration at 2 hours
CFR	Code of Federal Regulations
C_{last}	last measurable concentration
CL_{cr}	creatinine clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed concentration
COVID-19	coronavirus disease 2019
CP-I	coproporphyrin I
$C_{predose}$	predose plasma concentration
CRU	clinical research unit
CV%	percent coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DHHS	Department of Health and Human Services
ECG	electrocardiogram
EMA	European Medicines Agency
eCRF	electronic case report form
ET	early termination
FDA	(United States) Food and Drug Administration

Abbreviation or Term	Definition
FSH	follicle-stimulating hormone
GBT440	voxelotor
GCP	Good Clinical Practice
GM	geometric mean
GMR	geometric mean ration
HAV	hepatitis A virus
Hb-O_2	hemoglobin-oxygen
HbS	sickle hemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MATE1	multi-drug and toxin extrusion protein 1
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OAT3	organic anion transporter
OATP1B1	organic anion transporting polypeptide 1B1
OTC	over-the-counter
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PR (interval)	interval measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by electrocardiogram
PT	prothrombin time
PTT	partial thromboplastin time

Abbreviation or Term	Definition
QRS (interval)	the interval between the Q wave and the S wave in the heart's electrical cycle as measured by electrocardiogram; principal deflection in the electrocardiogram
QT (interval)	a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by electrocardiogram
QTcF (interval)	QT interval corrected for heart rate using Fridericia's formula
RR (interval)	the time elapsed between 2 consecutive R waves as measured by electrocardiogram
SAE	serious adverse event
SCD	sickle cell disease
SD	standard deviation
SoA	schedule of assessments
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal elimination half-life
t_{max}	time at which the maximum plasma concentration was observed
λ_z	apparent terminal elimination rate constant

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Study Number: GBT440-0122

Active Substance: Voxelotor

Study Title: 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

Brief Title: Voxelotor CYP and Transporter Cocktail Interaction Study

Study Rationale:

This study is comprised of 2 parts, Parts A and B.

Part A is designed to determine whether voxelotor alters the plasma concentration profiles of the probe substrates for cytochrome P450s (CYPs) including CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4. In vitro data suggest that voxelotor may inhibit CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 or induce CYP2B6.

Part B is designed to determine whether voxelotor alters the plasma concentration profiles of the probe substrates for transporters including multi-drug and toxin extrusion protein 1 (MATE1), organic anion transporter 3 (OAT3), and organic anion transporting polypeptide 1B1 (OATP1B1). Furthermore, the study will assess the effect of voxelotor on plasma concentrations of coproporphyrin I (CP-I), a biomarker for OATP1B1 activity. In vitro data suggest that voxelotor may inhibit these transporters and could potentially cause drug-drug interactions (DDIs).

The evaluation of the effects of these CYPs and transporters is relevant to the full characterization of the DDI potential of voxelotor.

Number of Study Centers, Countries, and Regions:

One site in the United States of America, North America

Objectives and Endpoints:

Objectives
Primary Part A
• To evaluate the effect of multiple doses of voxelotor on the plasma pharmacokinetics (PK) of a single dose of bupropion, repaglinide, flurbiprofen, omeprazole, and midazolam, which are probe substrates for CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4, respectively
Exploratory Part A
• To evaluate the effect of voxelotor on midazolam and 1-hydroxymidazolam PK stratified by CYP3A5 genotype
Safety Part A
• To evaluate the safety and tolerability of voxelotor when administered in combination with bupropion, repaglinide, flurbiprofen, omeprazole, and midazolam to healthy participants

Primary Part B
• 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 MATE1, OAT3, and OATP1B1, respectively
Exploratory Part B
• To evaluate the effect of voxelotor on CP-I as a biomarker of OATP1B1 transport
Safety Part B
• To evaluate the safety and tolerability of voxelotor when administered in combination with metformin, furosemide, and rosuvastatin to healthy participants
Endpoints
Primary PK Part A
• 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
Secondary PK Part A
• 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
Exploratory PK Part A
• 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
Primary PK Part B
• C_{max}, AUC_t, and AUC_{inf} for metformin, furosemide, and rosuvastatin
Secondary PK Part B
• t_{max} and $t_{½}$ for metformin, furosemide, and rosuvastatin in plasma

Exploratory PK Part B
• 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
Safety Part A and Part B
• Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Results of clinical laboratory tests, physical examination findings, and vital signs

Overall Study Design:

Part A

This is an open-label, fixed-sequence, 2-period evaluation of 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. Approximately 26 healthy participants (at least 20% African Americans) will be enrolled and will be stratified by CYP3A5 expresser status (approximately 50% expressors). Treatment administration will be performed when participants are in a fasted state.

Part A, Period 1: All participants will receive the following treatments:

- 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.

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.

Part A, Period 2: All participants will receive the following treatments:

- 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.

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. Subjects 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.

A study schema is provided in Figure 1.

Part B

This is an open-label, fixed-sequence, 2-period evaluation of the effect of concomitant administration of voxelotor on metformin (a MATE1 probe substrate), furosemide (an OAT3 probe substrate), and rosuvastatin (an OATP1B1 probe substrate) plasma concentrations, as well as CP-I (an OATP1B1 biomarker) plasma concentrations. Approximately 20 healthy participants (at least 20% African Americans) will be enrolled. Treatment administration will be performed when participants are in a fasted state.

Part B, Period 1: All participants will receive the following treatment:

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

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.

Part B, Period 2: All participants will receive the following treatments:

- 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.

Participants will be admitted into the CRU on Day -1 and will remain resident in the CRU until discharge on Day 7 of Period 2. Subjects will return to the CRU for a Follow-up visit on Day 18 (± 1 day).

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

A study schema is provided in Figure 2.

Test Product, Dose, Route of Administration, and Duration of Treatment:

In Part A, the study drugs are oral doses of voxelotor 1500 mg (Period 2 [Days 1-13]) and oral doses of the following cocktail drugs (probe substrates):

- bupropion 150 mg: Period 1 (Day 1) and Period 2 (Days 2 and 12)
- flurbiprofen 50 mg, omeprazole 20 mg, and midazolam 2 mg: Period 1 (Day 1) and Period 2 (Day 4)
- repaglinide 0.5 mg: Period 1 (Day 4) and Period 2 (Day 6)

In Part B of this protocol, the study drugs are oral doses of voxelotor 1500 mg (Period 2 [Days 1-5]) and oral doses of the following cocktail drugs (probe substrates):

- metformin 10 mg, furosemide 1 mg, and rosuvastatin 10 mg: Period 1 (Day 1) and Period 2 (Day 4)

Duration of Study Participation:

For Part A, participant involvement is expected to last approximately 81 days, including a 33-day screening period and a 48-day on study period (consisting of 2 treatment periods, a washout period lasting 7 to 14 days, and the Follow-up visit).

For Part B, participant involvement is expected to last approximately 68 days, including a 33-day screening period and a 35-day on study period (consisting of 2 treatment periods, a washout period lasting 7 to 14 days, and the Follow-up visit).

Number of Study Participants:

Part A: Approximately 26 healthy male or female participants (at least 20% African Americans will be enrolled in this part). Participants will be stratified by CYP3A5 expresser status (approximately 50% expressors)

Part B: Approximately 20 healthy male or female participants (at least 20% African Americans will be enrolled in this part).

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

Participant Selection Criteria:

Inclusion Criteria:

Participants must meet all inclusion criteria to be eligible for study participation.

1. Males or females ≥ 18 and ≤ 55 years of age inclusive, at the time of signing the informed consent.
2. No clinically significant findings as assessed by review of medical and surgical history, vital signs assessments, 12-lead electrocardiograms (ECG), physical examination, and clinical laboratory evaluations conducted at screening and day of admission. A single repeat measurement/test may be performed to confirm eligibility based upon initial vital signs, ECG, or clinical laboratory tests abnormalities.
3. Body mass Index (BMI) ≥ 18.0 and ≤ 30.0 kg/m^2, and body weight ≥ 50 kg at screening and Period 1 Day -1.

$$BMI = \text{weight (kg)}/(\text{height [m]})^2$$

4. Females of childbearing potential must agree to use a highly effective method of contraception or practice abstinence from 2 weeks prior to study start through 30 days after the last dose of study drug. A highly effective method of contraception is defined as one that results in a low documented failure rate when used consistently and correctly such as: condom plus use of an intrauterine device; intrauterine system or hormonal method of contraception (oral, injected, implanted, or transdermal) for their female partner; or sexual abstinence. Males must be surgically sterilized, or agree to practice true abstinence, or use acceptable contraception if sexually active with a female partner of childbearing potential, throughout the study, and for at least 30 days after the last dose of study drug.
5. Males must agree not to donate sperm during the study and for 30 days following last dose of study drug.
6. Participants must be able to communicate effectively in English with the study personnel.
7. Participants must be nonsmokers, defined as having abstained from tobacco- or nicotine-containing products (eg, cigarettes, chewing tobacco, snuff, nicotine patches, and electronic cigarettes) in the 6 months prior to screening.
8. Capable of providing signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.

Exclusion Criteria:

Participants meeting any of the following exclusion criteria will not be eligible for study enrollment:

1. Positive pregnancy test or is lactating.
2. History or presence of clinically significant allergic diseases (except for untreated, asymptomatic, seasonal allergies) at time of screening in the opinion of the Investigator.

3. History or presence of conditions which, in the opinion of the Investigator, are known to interfere with the absorption, distribution, metabolism, or excretion of drugs, such as previous surgery on the gastrointestinal tract (including removal of parts of the stomach, bowel, liver, or pancreas). Participants who have a history of cholecystectomy and appendectomy are eligible for enrollment.
4. History of surgery or major trauma within 12 weeks of screening, or surgery planned during the study.
5. Any signs and/or symptoms of acute illness at screening or Day -1.
6. Abnormal ECG in any of the single ECGs collected at screening or Day -1, including QTcF > 430 msec for males and > 450 msec for females, or any cardiac rhythm other than sinus rhythm that is interpreted by the Investigator to be clinically significant. A single repeat measurement may be performed to re-evaluate ECG abnormalities (ie, to confirm that a participant is eligible). All the single ECGs must be not clinically significant to qualify for enrollment into the study.
7. Known personal or family history of congenital long QT syndrome or known family history of sudden death.
8. Resting bradycardia (HR < 45 bpm) or resting tachycardia (HR > 100 bpm) at screening or Day -1. A single repeat measurement may be performed to re-evaluate vital signs abnormalities (ie, to confirm that a participant is ineligible). Each of the readings must be not clinically significant to qualify for enrollment into the study.
9. Hypertension, defined as resting (supine) systolic blood pressure (BP) > 140 mmHg or resting diastolic BP > 90 mmHg at screening or Day -1. A single repeat measurement may be performed to re-evaluate vital signs abnormalities (ie, to confirm that a participant is eligible). Each of the readings must be not clinically significant to qualify for enrollment into the study.
10. History of alcohol abuse, illicit drug use, significant mental illness, or physical dependence to any opioid.
11. Use of prescription medications (with the exception of contraception), any over the counter drugs including herbal preparations including St. John's wort or dietary supplements, or any drugs that induce or inhibit study drug specific CYP450(s) within 14 days or 5 half-lives, whichever is longer, prior to Day -1, or requires continuing use during study participation.
12. Consumption of more than 400 mg of caffeine (approximately 4 cups of coffee) per day or is unwilling to abstain from consumption of caffeine- or xanthine-containing products (eg, tea, coffee, chocolate, cola, etc.) from 48 hours prior to Day -1 until the end of the study (Follow-up visit).
13. Unwilling to abstain from alcohol 48 hours prior to Day -1 until the end of the study (Follow-up visit).
14. Consumption of Seville oranges and/or Seville orange juice, grapefruit and/or grapefruit juice within 14 days prior to Day -1 and is unwilling to abstain from consumption of Seville oranges and/or Seville orange juice, grapefruit and/or grapefruit juice until the end of the study (Follow-up visit).
15. Unwilling to abstain from any strenuous physical exercise (such as weight training or aerobics) from 72 hours prior to Day -1 until the final PK sample is collected in the study. Participants are permitted to exercise following the screening visit until 72 hours prior to Day-1.
16. Has participated in another clinical trial of an investigational drug (or medical device) within 30 days or 5 half-lives, whichever is longer, prior to screening, or is currently participating in another trial of an investigational drug (or medical device).
17. Prior exposure to voxelotor/Oxbryta® within the past month.

18. Clinically significant anemia, or has donated blood or blood components exceeding 400 mL within 90 days prior to screening.
19. Positive urine test for drugs of abuse, alcohol, or cotinine at screening or Day -1.
20. Positive screen for human immunodeficiency virus 1 (HIV-1) and HIV -2 antibodies, hepatitis A virus antibody, hepatitis B surface antigen, or hepatitis C virus antibody.
21. Positive COVID-19 test at admit to CRU.
22. Poor venous access as determined by the Investigator or study staff.
23. Involved in the planning or conduct of this study.
24. Any other condition or prior therapy that, in the Investigator's opinion, would confound or interfere with the evaluation of safety, tolerability, or PK of the study drug, interfere with study compliance, or preclude informed consent.

Part A only

25. History or presence of contraindication to the use of midazolam including but not limited to hypersensitivity to benzodiazepines or formulation ingredients, acute narrow-angle glaucoma, myasthenia gravis, severe respiratory insufficiency, or sleep apnea syndrome.
26. Poor CYP2C9 or CYP2C19 metabolizer (determined at screening or available historical data).
27. Participant has an allergy or sensitivity to voxelotor, bupropion, repaglinide, flurbiprofen, omeprazole, or midazolam.

Part B only

28. History of statin-induced myopathy or serious hypersensitivity reaction to other 3-hydroxy-3-methylglutaryl coenzyme A, reductase inhibitors (statins).
29. Heterozygous or homozygous variant allele carriers of SLCO1B1 (c.521T>C, rs4149056), encoding the hepatic uptake transporter OATP1B1, resulting in decreased transport activity.
30. Participant has an allergy or sensitivity to voxelotor, metformin, furosemide, or rosuvastatin.

Criteria for Evaluation:

Pharmacokinetics:

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.
- Plasma PK samples following dosing of flurbiprofen, omeprazole, and midazolam will be collected predose and at approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose during Part A, Period 1 on Day 1 and during Period 2 on Day 4.
- Plasma PK samples following dosing of bupropion will be collected predose and at approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose during Part A, Period 1 on Day 1 and during Period 2 on Days 2 and 12.
- Plasma PK samples following dosing of repaglinide will be collected predose and at approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose during Part A, Period 1 on Day 4 and during Period 2 on Day 6.

- Whole blood and plasma concentrations of voxelotor will be measured. Whole blood and plasma samples will be collected during Part A, Period 2 only on the following days:
  - Days 2-7 and Days 12-13: predose
  - Days 2, 4, 6, and 12: 2 hours postdose

Part B

- Plasma concentrations of metformin, furosemide, and rosuvastatin will be measured. Plasma PK samples will be collected predose and at approximately 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, and 48 hours postdose starting on Day 1 (Part B, Period 1) and Day 4 (Part B, Period 2). Additionally, PK samples of rosuvastatin will be collected up to 72 hours postdose on Day 1 (Part B, Period 1) and on Day 4 (Part B, Period 2).
- Whole blood and plasma concentrations of voxelotor will be measured. Whole blood and plasma samples will be collected during Part B, Period 2 only on the following days:
  - Days 4, 5, and 6: predose
  - Day 4: 2 hours postdose
- Plasma concentrations of CP-I will be measured. Samples will be collected predose and at approximately 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose on Day 1 (Part B, Period 1) and Day 4 (Part B, Period 2).

Part A and B Safety:

Participants will be monitored for adverse events (AE) from the time the informed consent is signed through Follow-up visit (Day 28 [Part A, Period 2] or Day 18 [Part B, Period 2]). Severity of AEs will be determined based on the Common Terminology Criteria for Adverse Events, Version 5.0.

Safety assessments also include physical examinations, vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature), oxygen saturation (Part A only), clinical laboratory evaluations (hematology, coagulation, serum chemistry, and urinalysis), pregnancy tests as appropriate, and concomitant medications.

Statistical Methods:

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 furosemide. A previous study indicated an intrasubject coefficient of variation (intraCV%) 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 (geometric mean ratio) = 1, a sample

size of 17 subjects 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 subjects (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.

Pharmacokinetic Analysis:

Whole blood and plasma concentrations of voxelotor (whole blood applicable only for voxelotor) and 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 nonmissing observations, arithmetic mean, standard deviation (SD), percent coefficient of variation (CV%), geometric mean (GM), geometric CV%, median, minimum, and maximum values at each sampling time.

Part A

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 mean, GM, SD, CV%, geometric CV%, median, and range. Whole blood and plasma PK parameters will be listed for voxelotor.

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

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 as a fixed effect and participant as a random effect. Point estimates and 90% confidence intervals for treatment differences (probe substrate alone versus probe substrate administered with voxelotor) on the log scale will be exponentiated to obtain estimates for GM ratios on the original scale. For bupropion, both Day 2 and Day 12 in Period 2 will be compared separately to Period 1 data.

Part B

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 mean, GM, SD, CV%, geometric CV%, median, and range. Whole blood and plasma PK parameters will be listed for voxelotor.

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 as a fixed effect and participant as a random effect. Point estimates and 90% confidence intervals for treatment differences (probe substrate alone versus probe substrate administered with voxelotor) on the log scale will be exponentiated to obtain estimates for GM ratios on the original scale.

Safety Analysis Part A and Part B

Demographics (age, sex, ethnicity, and race) and baseline characteristics (height, weight, and BMI) will be summarized by part and overall. Medical history will be provided in a data listing.

All safety data will be presented in listings by part. Descriptive summaries will be provided for AEs, clinical laboratory tests (hematology, serum chemistry, and coagulation), and vital signs (heart rate, blood pressure, respiratory rate, and oral temperature). Urinalysis laboratory tests, concomitant medications, and physical examinations will be presented in data listings only.

The number and percentage of participants reporting any treatment-emergent AE will be tabulated by

system organ class and preferred term (coded using Medical Dictionary for Regulatory Activities). Treatment-emergent AEs will be further classified by severity and relationship to treatment.

1.2. Study Schema

Figure 1: Part A Study Schema

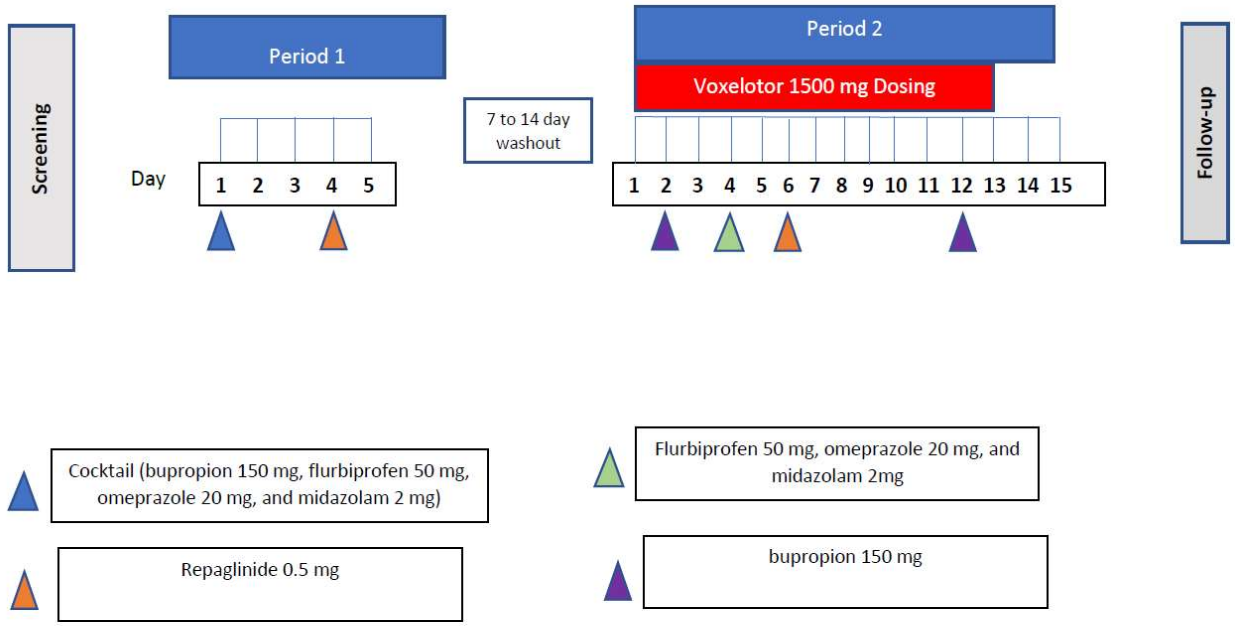
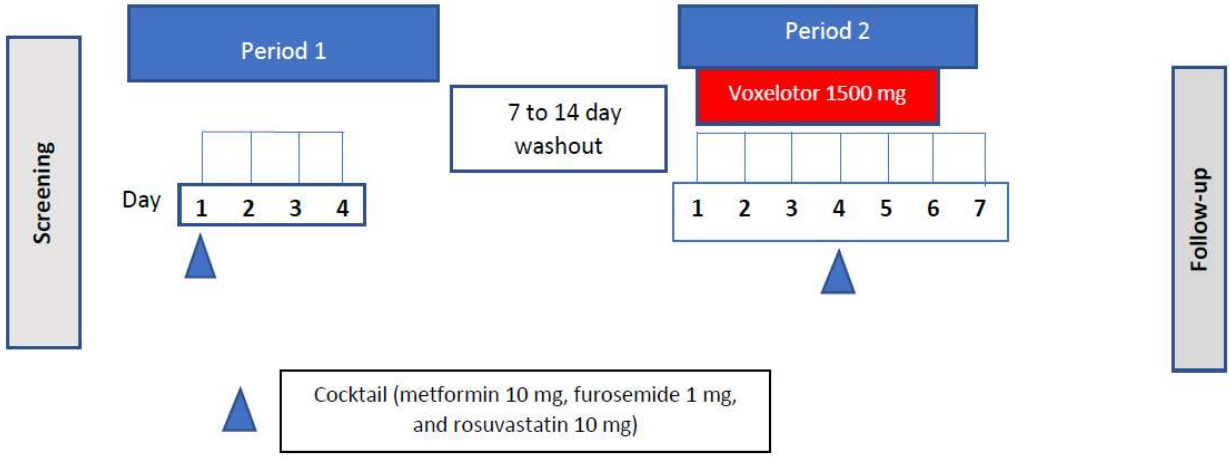


Figure 2: Part B Study Schema



1.3. Schedules of Assessments and Procedures

Table 1: Schedule of Assessments – Part A, 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				
Flurbiprofen, Omeprazole, 5-hydroxyomeprazole, Midazolam, and 1-hydroxymidazolam PK Sampling (Plasma) [l]			X	X	X		
Bupropion, 6-hydroxybupropion 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 2.
d. Oxygen saturation will be measured by pulse oximetry prior to and following cocktail administration as outlined in Table 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.
j. 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)]).
k. Participants must remain upright or semi-recumbent (head of bed > 45 degrees) for 4 hours postdose on days of probe substrate administration.
l. 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 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 2: Schedule of Study Procedures - Part A, 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 Flurbiprofen, Omeprazole, Midazolam Dose [a] -PK Sampling Timepoints [d]	Time Relative to Bupropion [a] -PK Sampling Timepoints [e]	Time Relative to Repaglinide Dose [a] -PK Sampling Timepoints [f]
1	0, 4	0, 0.5, 1, 1.5, 2, 3, 4	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12	
2	24		24	24	
3	48		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 flurbiprofen, omeprazole, 5-hydroxyomeprazole, midazolam, and 1-hydroxymidazolam 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 bupropion and 6-hydroxybupropion 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.
f. 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: Schedule of Assessments - Part A, 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			
Bupropion Administration [g, h]			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 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 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 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 4: Schedule of Study Procedures - Part A, 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 5: Schedule of Assessments - Part B, 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	
Cocktail Administration [j]			X			

Assessment	Screening (Day -35 to Day -2)	Part B, Period 1				
		Day -1 Admission	Day 1	Day 2	Day 3	Day 4 / Discharge
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 6.
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 6.

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 6: Schedule of Study Procedures - Part B, 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 7: Schedule of Assessments - Part B, 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
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 8.
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 8.
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 8.

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 8: Schedule of Study Procedures - Part B, 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.

2. INTRODUCTION

Voxelotor (formerly known as GBT440) is a small molecule inhibitor of HbS polymerization, which allosterically modifies Hb-O_2 affinity and is being developed by the Sponsor for the treatment of SCD.

Voxelotor increases Hb-O_2 affinity and stabilizes hemoglobin in the oxyhemoglobin state, thereby inhibiting the underlying mechanism of disease in SCD: the polymerization of HbS in red blood cells (Oksenberg et al, 2016). By addressing this underlying mechanism of SCD, voxelotor constitutes a disease-modifying therapy, improving anemia, and reducing hemolysis, and has the potential to reduce the end-organ damage resulting from hemolytic anemia.

On 25 November 2019, accelerated approval the US FDA was granted for voxelotor, now known by the trade name Oxbryta® for the treatment of adolescents and adults with SCD 12 years of age and older. On 17 December 2021, accelerated approval was expanded to pediatric patients down to 4 years of age. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Oxbryta also received marketing authorization valid throughout the European Union on 14 February 2022 for the treatment of hemolytic anemia due to SCD in adults and pediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide. This study is being conducted at the request of the EMA.

The recommended dosage of Oxbryta® is 1500 mg (three 500 mg film-coated tablets) taken orally once daily (Oxbryta, EMA Prescribing Information)

2.1. Background

Voxelotor is currently being investigated for the treatment of SCD.

2.2. Summary of Findings to Date

2.2.1. Nonclinical Experience

The nonclinical safety pharmacology, PK, metabolism, and toxicity are summarized in the Voxelotor Investigator's Brochure (Version 9.0, 17 December 2021).

2.2.2. Clinical Experience

As of 05 November 2021, approximately 1083 participants (of which 264 were pediatric participants) have received single or multiple doses of voxelotor in 30 clinical development studies (10 studies in SCD, 2 studies in IPF, 17 clinical pharmacology studies, and 1 study of healthy participants under hypoxic conditions).

Voxelotor has been well tolerated over a range of doses administered to healthy participants (up to 1800 mg) for up to 15 days, and participants with SCD (up to 1500 mg) for up to 18 months. The safety data have not shown clinically significant findings in 12-lead ECGs, vital sign measurements, or safety laboratory values. There were no deaths and no treatment related SAEs or severe AEs reported in healthy participants.

The most common treatment emergent AEs in healthy participants, observed in ≥ 10% of participants, included Grade 1 or 2 headache and gastrointestinal events (including diarrhea, abdominal pain, and gastroenteritis) and dizziness. All events of diarrhea and abdominal pain were Grade 1.

For additional information on voxelotor clinical trials in healthy participants and patients refer to the Voxelotor Investigator's Brochure (Version 9.0, 17 December 2021; Sections 5 and 6).

2.3. Benefit/Risk Assessment

Voxelotor is an EMA and FDA approved drug with an established safety profile and therefore the potential risks to healthy participants are minimal.

More detailed information about the known and expected benefits and risks and expected AEs of voxelotor may be found in the Voxelotor Investigator's Brochure (Version 9.0, 17 December 2021).

2.4. Study Rationale

2.4.1. Rationale for Study Design

2.4.1.1. Part A

Part A is designed to determine whether voxelotor alters the plasma concentration profiles of the probe substrates for CYPs including CYP2B6, CYP2C9, CYP2C8, CYP2C19, and CYP3A4. In vitro data suggest that voxelotor may inhibit a number of CYP enzymes. Voxelotor is approved for the treatment of SCD and evaluation of the effects of induction or inhibition of CYPs is relevant to the full description of the DDI potential of voxelotor.

2.4.1.2. Part B

Part B is designed to determine whether voxelotor alters the plasma concentration profiles of MATE1, OAT3, and OATP1B1 probe substrates. Furthermore, this part will assess the effect of voxelotor on plasma concentrations of CP-I, a biomarker for OATP1B1 activity. In vitro data suggest that voxelotor may inhibit these transporters and could potentially cause DDIs. Voxelotor is approved for the treatment of SCD and evaluation of the effects of inhibition of transporters may be relevant to the full description of the DDI potential of voxelotor.

2.4.2. Dose Rationale

2.4.2.1. Part A

To determine the likelihood of observing an effect of voxelotor on selected CYPs at therapeutic exposures, the highest approved dose of voxelotor (1500 mg) will be dosed orally daily for 14 days. Maximum CYP inhibition by voxelotor is likely to occur within 2 to 4 days and expected plasma voxelotor exposures are approximately 14 – 18 µg/mL by Day 4 (GBT440-0115), which is equivalent to plasma C_{max} exposures observed in patients with SCD (Savic et al, 2022). The induction of CYP2B6 by voxelotor will likely take longer; thus voxelotor will be dosed to steady-state for 13 days.

Single doses of CYP probe substrates, bupropion 150 mg (CYP2B6), flurbiprofen 50 mg (CYP2C9), omeprazole 20 mg (CYP2C19), midazolam 2 mg (CYP3A4), and repaglinide 0.25 mg (CYP2C8) were selected based on a previously conducted modified Geneva cocktail study (Dai et al, 2021). However, since repaglinide 0.25 mg is not commercially available in the United States or the European Union, after consultation with EMA, it was decided to administer repaglinide at 0.5 mg. Since repaglinide is administered at least 48 hours after probe substrates for other CYP pathways, it is unlikely that this higher dose would interfere with the PK of other substrates. In vitro data suggest that voxelotor may inhibit and induce CYP2B6, so the effect of voxelotor on the CYP2B6 probe substrate, bupropion 150 mg will be assessed on Day 2 and Day 12. Co-administration of voxelotor and bupropion on Day 2 was selected to assess voxelotor's potential to inhibit CYP2B6 because no induction is expected to be present. Co-administration of voxelotor and bupropion on Day 12 was selected to assess whether voxelotor has the potential to induce CYP2B6. The assessment of voxelotor's potential impact on the CYP2C8 probe substrate, repaglinide, is separated from the other CYP probe substrates by 3 days (Period 1) and 2 days (Period 2) to avoid the potential for drug interaction between repaglinide and the other probe substrates. The doses of these probe substrates have been shown to be clinically tolerable and result in exposures from which PK parameters can be reliably calculated.

2.4.2.2. Part B

To determine the likelihood of observing an inhibitory effect of voxelotor on selected transporters at therapeutic exposures, the highest approved dose of voxelotor (1500 mg) used in SCD clinical studies will be dosed orally daily for 5 days. This voxelotor dosing regimen is expected to result in target plasma voxelotor exposures of approximately 14 – 18 µg/mL by Day 4 (GBT440-0115), which is equivalent to plasma C_{max} exposures observed in patients with SCD (Savic et al, 2022). Single doses of the transporter probe substrates, metformin hydrochloride 10 mg (MATE1), furosemide 1 mg (OAT3), and rosuvastatin 10 mg (OAT1B1) are based on results from an optimized and validated cocktail study (Stopfer et al, 2018a; Wiebe et al, 2020). Doses of metformin (10 mg) and furosemide (1 mg) are lower than the typical clinical or therapeutic doses due to the potential for a drug interaction with metformin and/or furosemide with rosuvastatin (Stopfer et al, 2018b). The lower doses of metformin and furosemide have been shown to not increase rosuvastatin PK exposures and are suitable for assessing the potential for drug interactions with voxelotor.

3. OBJECTIVES

Table 9: Study Objectives

Objectives
Primary Part A
• 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
Exploratory Part A
• To evaluate the effect of voxelotor on midazolam and 1-hydroxymidazolam PK stratified by CYP3A5 genotype
Safety Part A
• To evaluate the safety and tolerability of voxelotor when administered in combination with bupropion, repaglinide, flurbiprofen, omeprazole, and midazolam to healthy participants
Primary Part B
• 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 MATE1, OAT3, and OATP1B1, respectively
Exploratory Part B
• To evaluate the effect of voxelotor on CP-I as a biomarker of OATP1B1 transport
Safety Part B
• To evaluate the safety and tolerability of voxelotor when administered in combination with metformin, furosemide, and rosuvastatin to healthy participants

4. STUDY DESIGN

4.1. Overall Design

4.1.1. Part A

This is an open-label, fixed-sequence, 2-period evaluation of 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. Figure 1 summarizes the design of Part A. Approximately 26 healthy participants (at least 20% African Americans) will be enrolled and will be stratified by CYP3A5 expresser status (approximately 50% expressors). Treatment administration will be performed when participants are in a fasted state.

Part A, Period 1: All participants will receive the following treatments:

- 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.

Participants will be admitted to the 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.

Part A, Period 2: All participants will receive the following treatments:

- 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.

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. Subjects will return to the CRU for a Follow-up visit on Day 28 (± 1 day).

For Part A, participant involvement is expected to last approximately 81 days.

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

4.1.2. Part B

This is an open-label, fixed-sequence, 2-period evaluation of the effect of concomitant administration of voxelotor on metformin (a MATE1 probe substrate), furosemide (an OAT3 probe substrate), and rosuvastatin (an OATP1B1 probe substrate) plasma concentrations, as well CP-I (an OATP1B1 biomarker) plasma concentrations. Figure 2 summarizes the design of the study. Approximately 20 healthy participants (at least 20% African Americans) will be enrolled. Treatment administration will be performed when participants are in a fasted state.

Part B, Period 1: All participants will receive the following treatment:

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

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 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.

Part B, Period 2: All participants will receive the following treatments:

- 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.

Participants will be admitted into the CRU on Day -1 and will remain resident in the CRU until discharge on Day 7 of Period 2. Subjects will return to the CRU for a Follow-up visit on Day 18 (± 1 day).

For Part B, participant involvement is expected to last approximately 68 days.

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

4.2. Scientific Rationale for Study Design

Refer to Section 2.4.1.

4.3. Dose Justification

Refer to Section 2.4.2.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study has completed all study procedures up to and including the Follow-up visit, as specified in the SoA (refer to Section 1.3).

A participant is considered to have completed the study if they have completed all periods of the study in their part, including the Follow-up.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants must meet all inclusion criteria to be eligible for study participation.

1. Males or females ≥ 18 and ≤ 55 years of age inclusive, at the time of signing the informed consent.
2. No clinically significant findings as assessed by review of medical and surgical history, vital signs assessments, 12-lead ECGs, physical examination, and clinical laboratory evaluations conducted at screening and day of admission. A single repeat measurement/test may be performed to confirm eligibility based upon initial vital signs, ECG, or clinical laboratory tests abnormalities.
3. BMI ≥ 18.0 and ≤ 30.0 kg/m^2, and body weight ≥ 50 kg at screening and Period 1 Day -1.

$$\text{BMI} = \text{weight (kg)}/(\text{height [m]})^2$$

4. Females of childbearing potential must agree to use a highly effective method of contraception or practice abstinence from 2 weeks prior to study start through 30 days after the final dose of study drug. A highly effective method of contraception is defined as one that results in a low documented failure rate when used consistently and correctly such as: condom plus use of an intrauterine device; intrauterine system or hormonal method of contraception (oral, injected, implanted, or transdermal) for their female partner; or sexual abstinence. Males must be surgically sterilized, or agree to practice true abstinence, or use acceptable contraception if sexually active with a female partner of childbearing potential, throughout the study, and for at least 30 days after the last dose of study drug.
5. Males must agree not to donate sperm during the study and for 30 days following last dose of study drug.
6. Participants must be able to communicate effectively in English with the study personnel.
7. Participants must be nonsmokers, defined as having abstained from tobacco- or nicotine-containing products (eg, cigarettes, chewing tobacco, snuff, nicotine patches, and electronic cigarettes) in the 6 months prior to screening.
8. Capable of providing signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Participants meeting any of the following exclusion criteria will not be eligible for study enrollment:

1. Positive pregnancy test or is lactating.
2. History or presence of clinically significant allergic diseases (except for untreated, asymptomatic, seasonal allergies) at time of screening in the opinion of the Investigator.
3. History or presence of conditions which, in the opinion of the Investigator, are known to interfere with the absorption, distribution, metabolism, or excretion of drugs, such as previous surgery on the gastrointestinal tract (including removal of parts of the stomach, bowel, liver, or pancreas). Participants who have a history of cholecystectomy and appendectomy are eligible for enrollment.
4. History of surgery or major trauma within 12 weeks of screening, or surgery planned during the study.
5. Any signs and/or symptoms of acute illness at screening or Day -1.
6. Abnormal ECG in any of the single ECGs collected at screening or Day -1, including QTcF > 430 msec for males and > 450 msec for females, or any cardiac rhythm other than sinus rhythm that is interpreted by the Investigator to be clinically significant. A single repeat measurement may be performed to re-evaluate ECG abnormalities (ie, to confirm that a participant is eligible). All the single ECGs must be not clinically significant to qualify for enrollment into the study.
7. Known personal or family history of congenital long QT syndrome or known family history of sudden death.
8. Resting bradycardia (HR < 45 bpm) or resting tachycardia (HR > 100 bpm) at screening or Day -1. A single repeat measurement may be performed to re-evaluate vital signs abnormalities (ie, to confirm that a participant is ineligible). Each of the readings must be not clinically significant to qualify for enrollment into the study.
9. Hypertension, defined as resting (supine) systolic BP > 140 mmHg or resting diastolic BP > 90 mmHg at screening or Day -1. A single repeat measurement may be performed to re-evaluate vital signs abnormalities (ie, to confirm that a participant is eligible). Each of the readings must be not clinically significant to qualify for enrollment into the study.
10. History of alcohol abuse, illicit drug use, significant mental illness, or physical dependence to any opioid.
11. Use of prescription medications (with the exception of contraception), any OTC drugs including herbal preparations including St. John’s wort or dietary supplements, or any drugs that induce or inhibit study drug specific CYP450(s) within 14 days or 5 half-lives, whichever is longer, prior to Day -1, or requires continuing use during study participation.

12. Consumption of more than 400 mg of caffeine (approximately 4 cups of coffee) per day or is unwilling to abstain from consumption of caffeine- or xanthine-containing products (eg, tea, coffee, chocolate, cola, etc.) from 48 hours prior to Day -1 until the end of the study (Follow-up visit).
13. Unwilling to abstain from alcohol from 48 hours prior to Day -1 until the end of the study (Follow-up visit).
14. Consumption of Seville oranges and/or Seville orange juice, grapefruit and/or grapefruit juice within 14 days prior to Day -1 and is unwilling to abstain from consumption of Seville oranges and/or Seville orange juice, grapefruit and/or grapefruit juice until the end of the study (Follow-up visit).
15. Unwilling to abstain from any strenuous physical exercise (such as weight training or aerobics) from 72 hours prior to Day -1 until the final PK sample is collected in the study. Participants are permitted to exercise following the screening visit until 72 hours prior to Day -1.
16. Has participated in another clinical trial of an investigational drug (or medical device) within 30 days or 5 half-lives, whichever is longer, prior to screening, or is currently participating in another trial of an investigational drug (or medical device).
17. Prior exposure to voxelotor/Oxbryta within the past month.
18. Clinically significant anemia or has donated blood or blood components exceeding 400 mL within 90 days prior to screening.
19. Positive urine test for drugs of abuse, alcohol, or cotinine at screening or Day -1.
20. Positive screen for HIV-1 and HIV-2 antibodies, HAV antibody, HBsAg, or HCV antibody.
21. Positive COVID-19 test at admit to CRU.
22. Poor venous access as determined by the Investigator or study staff.
23. Involved in the planning or conduct of this study.
24. Any other condition or prior therapy that, in the Investigator's opinion, would confound or interfere with the evaluation of safety, tolerability, or PK of the study drug(s), interfere with study compliance, or preclude informed consent.

Part A only

25. History or presence of contraindication to the use of midazolam including but not limited to hypersensitivity to benzodiazepines or formulation ingredients, acute narrow-angle glaucoma, myasthenia gravis, severe respiratory insufficiency, or sleep apnea syndrome.
26. Poor CYP2C9 or CYP2C19 metabolizer (determined at screening or available historical data).
27. Participant has an allergy or sensitivity to voxelotor, bupropion, repaglinide, flurbiprofen, omeprazole, or midazolam.

Part B only

28. History of statin-induced myopathy or serious hypersensitivity reaction to other 3-hydroxy-3-methylglutaryl coenzyme A, reductase inhibitors (statins).
29. Heterozygous or homozygous variant allele carriers of SLCO1B1 (c.521T>C, rs4149056), encoding the hepatic uptake transporter OATP1B1, resulting in decreased transport activity
30. Participant has an allergy or sensitivity to voxelotor, metformin, furosemide, or rosuvastatin.

5.3. Lifestyle Considerations

5.3.1. Dietary

- Participants are not permitted to consume Seville oranges and/or Seville orange juice, grapefruit and/or grapefruit juice from 14 days prior to Day -1 of Period 1 until the end of the study (Follow-up visit). Participants must also refrain from the consumption of other fruit juices while in the clinic.
- Participants are not permitted to consume any food and drink from outside of the CRU while residing at the CRU.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants are not permitted to consume alcohol from 48 hours prior to Day -1 of Period 1 until the end of the study (Follow-up visit).
- Participants are not permitted to consume caffeine-containing food or beverages for 48 hours prior to Day -1 of Period 1 until the end of the study (Follow-up visit).

5.3.3. Activity

Strenuous activity (such as weight training or aerobics) is prohibited from 72 hours prior to Day -1 until the final PK sample is collected in the study.

5.4. Screen Failures

Participants who are discontinued from the study prior to study drug administration will be considered screen failures.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened as long as the participant was not discontinued from the study due to noncompliance with the protocol (ie, positive urine drugs of abuse screen, etc.). Rescreened participants should be assigned a new participant number for every screening/rescreening event.

Screen failure data will not be recorded in the eCRF.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatments Administered

Identity of voxelotor is presented in Table 10 and identity of cocktail drugs (probe substrates) is presented in Table 11.

Table 10: Study Treatments Administered

Treatment Name	Voxelotor
Excipients	All of the excipients used in the formulations are either compendial per Ph. Eur. or are composed of mixtures which are compendial per Ph. Eur. or accepted by E number or European Commission regulation.
Dose Formulation	Tablet
Unit Dose Strength	500 mg/tablet
Dosage Level	1500 mg
Route of Administration	Oral
Packaging and Labeling	Tablets are packaged in 150 cc white, high density polyethylene bottles. The bottles are closed with child-resistant polypropylene screw caps.
Storage Conditions	Controlled room temperature between 15°C and 25°C

Table 11: Cocktail Drugs Administered

Drug (Probe Substrate)	**Dose**
Part A	
bupropion	150 mg
flurbiprofen [a]	50 mg
omeprazole	20 mg
midazolam	2 mg
repaglinide	0.5 mg
Part B	
metformin	10 mg
furosemide	1 mg
rosuvastatin	10 mg

a. Flurbiprofen (50 mg) is manufactured by Delpharm L' Aigle and marketed in the United Kingdom. The marketing authorization holder is Mylan Products Ltd.

Eligible participants will receive the following treatments:

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 nonrefrigerated, 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.

6.2. Preparation, Handling, Storage, and Accountability

Details regarding preparation of study drugs for administration are provided in the Study Reference Manual (provided separately).

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study drug.

Cocktail drugs (probe substrates) will be stored according to the package inserts.

Only participants enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A Drug Accountability Record will be used for the study drug. The record must be kept current and should contain the dates and quantities of study drug received, study number, lot or batch number(s), participants receiving study drug, the date and quantity of study drug dispensed and remaining, and the initials of the dispenser.

All study drug inventory forms must be made available for inspection by an authorized representative of the Sponsor or designee.

Further guidance and information for the final disposition of unused study drugs are provided in the Study Reference Manual.

6.3. Randomization and Blinding

This is an open-label study. Randomization and blinding are not applicable.

6.4. Study Treatment Compliance

When participants are dosed at the site, they will receive study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

If a participant misses a dose, the participant should resume normal dosing the next day.

6.5. Concomitant Therapy

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.

In the interests of participant safety and acceptable standards of medical care, the Investigator will be permitted to prescribe treatment(s) at their discretion. For all enrolled participants, all administered concomitant medications from signing the informed consent until 30 days after the participant's last dose of study drug, must be recorded in the participants' eCRF (medication, dose, treatment duration, and indication).

All reported prior and concomitant medications will be coded using the current version of the World Health Organization Drug Dictionary.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Restrictions Regarding Concomitant Medications

Participants must abstain from the use of prescription medications (with the exception of contraception), any OTC drugs including herbal preparations including St. John's wort or dietary supplements, or any drugs that induce or inhibit study drug specific CYP450(s) within 14 days or 5 half-lives, whichever is longer, prior to Day -1, or requires continuing use during study participation.

Other concomitant medications may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor.

Penicillin prophylaxis and vaccinations (including the COVID-19 vaccine) are allowed in accordance with standard of care.

6.5.1.1. Prohibited Concomitant Medications and Therapies

Treatment with any of the following is not allowed during the study:

- Prescription medications with the exception of oral contraceptive agents taken by women of child-bearing age
- OTC drugs (including herbal preparations and any dietary supplements)
- Drugs that induce or inhibit study drug specific CYP450(s)

6.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (eg, surgery/biopsy, physical therapy) or diagnostic assessment (eg, chest x-ray, blood gas measurement, bacterial cultures) performed between the time the participant is enrolled in the study and the Follow-up/ET Visit.

The use of concomitant therapies or procedures must be recorded on the participant's eCRF, according to instructions for eCRF completion. Adverse events related to administration of these therapies or procedures must be documented in the appropriate eCRF.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.9.

7.1. Early Discontinuation of the Study

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the incidence or severity of AEs in participants.

Participants will be informed that they are free to discontinue treatment or withdraw from the study at any time and for any reason. The Investigator must withdraw any participant from the study who requests to be withdrawn.

Participants who ask to leave the study early (withdraw consent) should be encouraged to undergo the tests and evaluations listed for the ET Visit (ie, ET is intended for participants who withdraw consent). If a participant withdraws before completing the study, the date and reason for withdrawal is to be documented on the eCRF.

A participant who withdraws from the study or is lost to follow-up will not be replaced.

7.2. Discontinuation of Study Treatment

Participants may discontinue study treatment for any of the following reasons:

- Adverse event
- Withdrawal of consent
- Discretion of the Investigator
- Participant is lost to follow-up
- Participant is noncompliant
- Pregnancy. Study drug must be discontinued immediately. Report the pregnancy according to the instructions in Section 8.4.7.

Participants who discontinue from study treatment will be encouraged to continue to participate in the study assessments, as applicable. Participants who are discontinued from study treatment due to pregnancy will also be discontinued from the study (Section 8.4.7). A participant may be discontinued from study treatment at any time at the discretion of the Investigator in accordance with his or her clinical judgment.

7.2.1. Discontinuation due to Adverse Events

Any participant who experiences an AE may be withdrawn at any time from the study at the discretion of the Investigator. Participants withdrawn from the study due to an AE, whether serious or nonserious, should be followed by the Investigator until the clinical outcome of the AE is determined (ie, the event has resolved or has stabilized). The details of AE(s) should be noted on the appropriate eCRFs. The Sponsor and Medical Monitor must be notified of the study participant discontinuation. If the AE is due to overdose of study treatment, the most recent

version of the voxelotor IB should be referred for further details on any specific actions to be taken.

7.2.2. Liver Chemistry Stopping Criteria

Participants will be monitored for signs of DILI. Study drug will be withheld in the event of potential DILI.

Potential events of DILI will be defined as meeting all of the following criteria (as specified in the FDA Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation, 2009):

- Alanine aminotransferase or aspartate aminotransferase > 3 × 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)

Potential events of DILI will be reported as SAEs (Section 8.4). All participants with potential DILI will be closely followed until abnormalities return to normal or baseline or until reasonable attempts to determine resolution of the event are exhausted.

7.3. Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at their own request or may be discontinued at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.

- At the time of discontinuing from the study, if possible, an ET visit should be conducted, as shown in the SoA Section 1.3. The SoA details the data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study treatment and the study at the time of discontinuation.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.4. Lost to Follow up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, a minimum of 2 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor/Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Demographic/Medical History

Demographic information (sex, age, race/ethnicity, and height) will be recorded.

Participants will be asked to provide a thorough medical history. Moreover, weight will also be measured on Day -1 in both periods of Parts A and B.

8.2. Pharmacokinetics

Whole blood and plasma PK samples will be collected at time points specified in the PK sampling schedule (Part A, Period 1: Table 2, Part A, Period 2: Table 4, Part B, Period 1: Table 6, and Part B, Period 2: Table 8). 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.

The following PK parameters will be determined for Part A:

C_{max}	Maximum observed plasma concentration (probe substrates only).
t_{max}	The time that C_{max} was observed (probe substrates 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 (probe substrates only).
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 (probe substrates only).
AUC_t M/P	Ratio of metabolite to parent AUC_t corrected for molecular weight for 6-hydroxybupropion/ bupropion, 5-hydroxyomeprazole/omeprazole, and 1-hydroxymidazolam/midazolam.
$t_{½}$	Terminal elimination half-life; calculated as $\ln(2)/\lambda_z$.

The following PK parameters will be determined for Part B:

C_{max}	Maximum observed plasma concentration.
$C_{predose}$	Predose plasma concentration (CP-I 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.
$t_{½}$	Terminal elimination half-life; calculated as $\ln(2)/\lambda_z$ (metformin, furosemide, and rosuvastatin).

Retained research samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examination

- 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.
- Physical examinations after the screening visit will be performed at the discretion of the Investigator and may be targeted, focusing on specific organ systems,

abnormalities identified on the screening examination, and abnormalities related to adverse events 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.

8.3.2. Vital Signs

- Oral temperature (°C), heart rate, respiratory rate (breaths per minute), and blood pressure will be assessed.
- Blood pressure and heart rate measurements will be assessed in a supine position with a completely automated device.
- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of heart rate, blood pressure measurement, oral temperature, and respiratory rate.
- Any clinically significant abnormal vital sign assessment requires at least one repeat measurement.
- A vital signs abnormality that is (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 an AE or SAE as applicable.

8.3.3. 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.

8.3.4. Electrocardiograms

- 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.
- 12-lead ECG(s) will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures at a minimum RR, PR, QRS, QT, and QTcF intervals.
- 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. In addition, any abnormal ECGs will be assessed for clinical significance.

- Additional ECGs may be obtained if clinically indicated and must be obtained if abnormal and clinically significant or thought to be an error (eg, lead placement error, movement artifact, etc.). Any additional relevant data obtained by the Investigator during the course of this study will be supplied to the Sponsor.

For any ECG that the Investigator considers clinically significant, the Investigator will:

- Repeat the ECG.
- Follow-up ECG(s) will be obtained if any significant abnormalities are detected after dose administration to document resolution and as clinically indicated.
- Record as an AE any ECG that is confirmed and the Investigator considers clinically significant, requires a participant to be discontinued from the study, requires a participant to receive treatment, or requires a change or discontinuation of the study drug (if applicable).

8.3.5. Clinical Laboratory Tests

See Table 12 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

- Protocol-specific requirements for the determination of participant eligibility are detailed in Section 5 of the protocol.
- It is the responsibility of the Investigator or designee to assess the clinical significance of all abnormal clinical laboratory values as defined by the applicable list of normal values on file (ie, local or central). All clinically significant laboratory value abnormalities should be recorded as AEs
- Additional and repeat laboratory safety testing for the evaluation of abnormal results and/or AEs during the study may be performed at the discretion of the Investigator or upon request of the Sponsor; it is preferred for the analyses to be conducted by the central laboratory unless medical need necessitates urgent results reporting. Repeat laboratory testing of abnormal potentially clinically significant or clinically significant results for the screening evaluation of the participant may be repeated at the discretion of the Investigator

Table 12: 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 Phosphorous Sodium Potassium Magnesium Bicarbonate 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

8.3.5.1. Other Tests

The following 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)

- 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**)

Tests for drugs of abuse and alcohol screens may not be repeated for eligibility at screening or Day -1.

8.3.6. Pregnancy Testing

Pregnancy tests will be performed on all female participants as indicated in the SoA (Section 1.3). A serum pregnancy test will be conducted at screening with urine pregnancy tests conducted thereafter as indicated in the SoA. If the Day-1 urine test is positive, a serum pregnancy test should be performed; if positive, the participant will be considered a screen failure.

8.4. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

8.4.1. Definition of Adverse Events

An 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 suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the Investigator or Sponsor, places the study participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered to be “unexpected” if it is not listed in the Reference Safety Information section of the current IB or is not listed at the specificity or severity that has been observed.

The Investigator will assess each AE for seriousness, severity, and relationship to investigational product.

8.4.2. Definition of Serious Adverse Events or Serious Suspected Adverse Reactions

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that, at any dose, in the view of either the Investigator or Sponsor, results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or disability (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the study participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

NOTE: Hospitalization planned prior to study enrollment (eg, for elective surgeries) is not considered to be an SAE. Any complications arising from a planned hospitalization may be considered an AE and should be reported as applicable. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

8.4.3. Severity of Adverse Events

Whenever possible, the severity of all AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0.

For AEs not adequately addressed in the NCI-CTCAE, Version 5.0, the criteria presented in Table 13 should be used.

Table 13: Grading for Adverse Events not Covered in the NCI-CTCAE

Severity	Description
Grade 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 – Moderate	Minimal, local, or noninvasive intervention indicated; limited age-appropriate instrumental ADL
Grade 3 – Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4 – Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5 – Fatal	Death

Abbreviations: ADL = activities of daily living; NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events.

To make sure that there is no confusion or misunderstanding between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (ie, mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (eg, severe headache). This is not the same as "serious", which is based on the study participant/event outcome or action criteria associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.4.4. Relationship to Investigational Product

The relationship of an AE to the study drug should be determined by the Investigator according to the following definitions:

NOT RELATED: Evidence exists that the AE has an etiology other than the study drug and/or the temporal relationship of the AE/SAE to the investigational product administration makes the relationship unlikely. If an SAE is not considered to be related to study drug, then an alternative explanation should be provided.

RELATED: A temporal relationship exists between the event onset and the administration of the study drug and makes a causal relationship possible or probable. It cannot be readily explained by the participant's clinical state or concomitant therapies and may appear, with some degree of certainty, to be related based on the known therapeutic and pharmacologic actions of the drug. Good clinical judgment should be used for determining causal assessment.

8.4.5. Adverse Event Reporting

8.4.5.1. General

All AEs will be recorded from the time the study participant signs the ICF form obtained through the Follow-up visit (Day 28 [Part A, Period 2] or Day 18 [Part B, Period 2]). All SAEs must be reported within 24 hours of AE awareness on the AE eCRF via the electronic data capture system. The Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring that documentation of the event is complete. Details of each reported AE must include at a minimum severity, relationship to study treatment, duration, and outcome. All (both serious and nonserious) AEs must be followed until they are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

Any participant who experiences an AE may be discontinued from study treatment at any time at the discretion of the Investigator. The Sponsor and the contract research organization Medical Monitors must be notified of the study participant discontinuation.

8.4.5.2. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event

should be recorded separately on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

8.4.5.3. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities will be recorded on the AE eCRF (eg, abnormalities that have clinical sequelae, require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, or further diagnostic investigation). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 × the upper limit of normal associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded on the eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia”.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless their severity, seriousness, or etiology changes.

8.4.6. Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting

All SAEs, regardless of causal attribution, must be reported by the Investigator or designee or site personnel within 24 hours of SAE awareness. The SAE will be reported by completing the paper SAE report forms and faxed or emailed to the Sponsor or designee.

The Sponsor or designee may request additional source documentation pertaining to the SAE from the investigational site. Follow-up reports must be submitted within 24 hours of awareness, and participant identifier information (eg, name, medical record number) must be redacted in the hospital discharge summaries, autopsy reports, and/or death certificates.

Follow-up SAE information must be submitted within 24 hours of awareness as additional information becomes available. All SAEs regardless of causal attribution must be followed to resolution or stabilization, or until reasonable attempts to determine resolution of the SAE are performed.

8.4.6.1. Reporting Suspected Unexpected Serious Adverse Reactions and Urgent Safety Issues

The Sponsor or designee is responsible for reporting SUSARs to regulatory agencies, competent authorities, IRBs/ECs, and the Investigator as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7 calendar days of the Sponsor’s or designee’s first knowledge of the event and follow-up information submitted within an additional 8 calendar days, or as otherwise required per local laws and regulations. All other SUSARs will be submitted within 15 calendar days of the Sponsor’s or designee’s first knowledge of the event. The Investigator is responsible for notifying the local IRBs of all SAEs that occur at his or her site as required by local regulations or IRB policies, if this responsibility resides with the site.

Investigators are required to report any urgent safety matters to the Sponsor or designee within 24 hours of awareness. The Sponsor or designee will inform regulatory authorities, IRBs, and Investigators, as applicable, of any events (eg, change to the safety profile of voxelotor, major safety findings that may place study participants at risk) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may adversely affect the safety of study participants.

8.4.7. Reporting Pregnancy

If a participant becomes pregnant while taking study drug, the study treatment will be immediately discontinued, and the pregnancy must be reported to the Sponsor or designee within 24 hours of awareness. The Investigator will discuss the risks and concerns of study drug exposure to a developing fetus and counsel the participant and/or pregnant partner (or ensure such counselling is provided).

Reported pregnancy of a participant or a participant's partner, while participating in this study, will be monitored for the full duration of the pregnancy and/or followed through a definitive outcome (ie, birth, or spontaneous or elective abortion).

An uncomplicated pregnancy will not be considered an AE or SAE. Pregnancy complications such as spontaneous abortion/miscarriage and congenital anomalies are considered SAEs and must be reported as described in Section 8.4.6. Note that an elective abortion is not considered an SAE. Pregnancy and pregnancy outcomes must be reported on a Pregnancy Notification Form or Pregnancy Outcome Form, respectively, and sent to the Sponsor or designee within 24 hours of the Investigator site personnel learning of the pregnancy or pregnancy outcome.

The child born to a female participant or partner of a male participant exposed to study drug may be followed for 3 months after delivery. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the Pregnancy Outcome Form and reported to the Sponsor or designee. Any congenital abnormalities in the offspring will be reported as an SAE and must be reported as described in Section 8.4.6.

Information regarding pregnancy testing (including definition of females of childbearing potential) is provided in Section 11. Highly effective means of contraception are listed in Appendix 1.

8.4.8. Reporting Overdose

If a participant takes more than the protocol-defined dose of study drug in a day and experiences a drug related AE, this will be reported as an overdose (AEs must be recorded on the AE eCRF) and a protocol deviation. However, if the participant did not experience any AEs, this will only be reported as a protocol deviation.

The Investigator will discuss the risks and concerns of investigational agent exposure with the participant. Participants are to be instructed to contact their study site immediately if an overdose of study drug is suspected. An overdose with associated AEs must be reported within 24 hours of the Investigator, designee, or site personnel learning of the overdose and reported to the Study Director/Medical Monitor. An overdose must be followed until any adverse effects are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

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

All AEs and SAEs will be collected from the signing of the ICF until the Follow-up visit (Day 28 [Part A, Period 2] or Day 18 [Part B, Period 2]) at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 8.4.6. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

8.4.10. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.11. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4).

8.5. Missed Assessments

Missed assessments should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the Investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

9. STATISTICAL CONSIDERATIONS

The statistical analysis will be conducted following the principles as specified in ICH Topic E9 (CPMP/ICH/363/96). All statistical analyses will be described in a separate statistical analysis plan. The statistical analysis plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

No formal hypotheses will be tested.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Table 14: Analysis Sets

Participant Analysis Set	Description
Pharmacokinetic Full Population	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.
Pharmacokinetic Evaluable Population	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.
Safety Population	All participants who received any amount of study drug (voxelotor or cocktail drugs [probe substrates]).

9.3. Statistical Analyses

9.3.1. General Considerations

Unless otherwise noted, continuous variables will be summarized by using the number of nonmissing observations, arithmetic mean, standard deviation, median, minimum, and maximum values as descriptive statistics; categorical variables will be summarized by using the frequency count and the percentage of study participants in each category as descriptive statistics. All safety and demographic analyses will be performed for each part of the study.

All analyses and tabulations will be performed by using SAS Version 9.4 or higher and PK parameters will be determined using WinNonlin Version 8.0.0 or higher.

9.3.1.1. Disposition

Among the study participants enrolled into the study, the number and percentage who complete the study and who prematurely discontinue from the study will be summarized. In addition, reasons leading to study discontinuation will be summarized. The number of study participants included in each analysis population (PK Full Population, PK Evaluable Population, and Safety Population) will also be presented.

9.3.2. Part A Pharmacokinetic Endpoints

9.3.2.1. Primary Endpoint Analysis

- C_{max}, AUC_t, and AUC_{inf} for bupropion, repaglinide, flurbiprofen, omeprazole, and midazolam

9.3.2.2. Secondary Endpoints Analysis

- C_{max}, AUC_t, and AUC_{inf} for 6-hydroxybupropion, 5-hydroxyomeprazole, and 1-hydroxymidazolam
- t_{max} and $t_{½}$ for bupropion, 6-hydroxybupropion, repaglinide, flurbiprofen, omeprazole, 5-hydroxyomeprazole, midazolam, and 1-hydroxymidazolam in plasma. AUC_t M/P for bupropion, omeprazole, and midazolam

9.3.2.3. Exploratory Endpoint Analysis

- 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 (Days 2, 4, 6, and 12) for voxelotor in whole blood and plasma

9.3.3. Part B Pharmacokinetic Endpoints

9.3.3.1. Primary Endpoint Analysis

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

9.3.3.2. Secondary Endpoints Analysis

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

9.3.3.3. Exploratory Endpoints Analysis

- $C_{predose}$, C_{max}, t_{max}, and AUC_{0-24} for CP-I
- Predose (Days 4, 5, 6) and postdose observed concentration (Day 4) for voxelotor in whole blood and plasma

9.3.4. Part A and B Safety Endpoints Analysis

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

9.3.5. Pharmacokinetic Analysis

Whole blood and plasma concentrations of voxelotor (whole blood applicable only for voxelotor) and 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 nonmissing

observations, arithmetic mean, SD, CV%, GM, geometric CV%, median, minimum, and maximum values at each sampling time.

9.3.5.1. 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 mean, GM, SD, CV%, geometric CV%, median, and range. Whole blood and plasma PK parameters and will be listed for voxelotor.

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

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 as a fixed effect and participant as a random effect. Point estimates and 90% confidence intervals for treatment differences (probe substrate alone versus probe substrate administered with voxelotor) on the log scale will be exponentiated to obtain estimates for GM ratios on the original scale. For bupropion, both Day 2 and Day 12 in Period 2 will be compared separately to Period 1 data.

9.3.5.2. 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 mean, GM, SD, CV%, geometric CV%, median, and range. Whole blood and plasma PK parameters will be listed for voxelotor.

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 as a fixed effect and participant as a random effect. Point estimates and 90% confidence intervals for treatment differences (probe substrate alone versus probe substrate administered with voxelotor) on the log scale will be exponentiated to obtain estimates for GM ratios on the original scale.

9.3.6. Part A and Part B Safety Analyses

Demographics (age, sex, ethnicity, and race) and baseline characteristics (height, weight, and BMI) will be summarized by part and overall. Medical history will be provided in a data listing.

All safety data will be presented in listings by part. Descriptive summaries will be provided for AEs, clinical laboratory tests (hematology, serum chemistry, and coagulation), and vital signs (HR, BP, respiratory rate, and oral temperature). Urinalysis laboratory tests, concomitant medications, and physical examinations will be presented in data listings only.

The number and percentage of participants reporting any treatment-emergent AE will be tabulated by system organ class and preferred term (coded using Medical Dictionary for Regulatory Activities). Treatment-emergent AEs will be further classified by severity and relationship to treatment.

9.4. Interim Analysis

No interim analysis is planned for the primary endpoint.

9.5. Sample Size Determination

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 (intraCV%) 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 subjects 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 subjects (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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable local laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Financial Disclosure statements will be handled in a separate agreement apart from the protocol, kept on file and submitted as applicable with any subsequent license application.

10.1.3. Informed Consent Process

- The Investigator or their representative will explain the nature of the study, purpose and duration of the study, participation/termination conditions, and risks and benefits,

to the participant or their legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary.
- Prior to initiation of any study-related procedures, participants will sign and date the ICF that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB or study center.
- In the event of a pregnancy in the female partner of a male participant, a pregnancy consent form will be provided to allow the follow up of the pregnancy.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant [or their legally authorized representative] in their native language.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Committees Structure

Not applicable.

10.1.5. Dissemination of Clinical Study Data

- Participants' medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those noted in this protocol, is prohibited. Participant to any applicable authorization(s), all reports and communications relating to participants in this study will identify participants only by initials and number.
- Medical information resulting from a participant's participation in this study may be given to the participant's personal physician, other authorized parties, or to the appropriate medical personnel responsible for the participant's participation in this clinical study.
- Data generated in this study will be available for inspection on request by the FDA or other government regulatory agency auditors, the Sponsor, the Sponsor's Medical Monitor (or designee), and their designated representatives, the IRB/EC, and other authorized parties.
- All information concerning the study medication and the Sponsor's operations (such as patent applications, formulas, manufacturing processes, basic scientific data, or other information supplied by the Sponsor and not previously published) are considered confidential and shall remain the sole property of the Sponsor. The

Investigator agrees to use this information only in conducting this study and to not use it for other purposes without the Sponsor's prior written consent.

- The information developed in this clinical study will be used by the Sponsor in the clinical development of voxelotor and therefore, may be disclosed by the Sponsor as required, to authorized parties (including its corporate partners for the study drug, if any, and their designated representatives), other clinical Investigators, pharmaceutical companies, the FDA, and other government agencies.
- Any information, inventions, discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in the eCRF completion document.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

- Source documents (including copies of protocols, original reports of test results, investigational agent dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must retain a comprehensive and centralized filing system of all study-related source documents that is suitable for inspection by the Sponsor and representatives of regulatory authorities.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Study Documentation and Data Storage

10.1.8.1. Inspection of Records

- The Sponsor or designees will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, participant charts, study source documents, and other records relative to study conduct.
- The Investigator agrees to maintain a Regulatory Binder in a current, organized fashion; this Binder will contain documentation supportive of the protocol- and GCP-compliance of the study. The contents of the Binder will be organized according to the standards of ICH E6, Section 8 (Essential Documents). The Investigator agrees to make this Binder accessible to the monitor, auditor, and representatives of regulatory agencies and the IRB/EC.

10.1.8.2. Retention of Records

- All study records must be retained for at least 2 years after the last approval of a marketing application in the United States of America or an ICH region and until (1) there are no pending or contemplated marketing applications in the USA or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product under study.

- The Investigator/institution should retain participant identifiers for at least 15 years after the completion or discontinuation of study. Study participant files and other resource data must be kept for the maximum period of time permitted by the hospital, institution but not less than 15 years. These documents should be retained for a longer period, if required by the applicable regulatory requirements or by the Sponsor. The Sponsor must be notified with retention should the Investigator/institution are unable to continue with the maintenance of study participant files for the full 15 years. All study records must be stored in a secure and safe facility.
- The Investigators must retain protocols, amendments, IRB approvals, copies of the Form FDA 1572, signed and dated consent forms, medical records, eCRFs, drug accountability records, all correspondence and any other documents pertaining to the conduct of the study.
- If the Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor. The Investigator must notify the Sponsor immediately in the event of accidental loss or destruction of any protocol records

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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APPENDIX 1. CONTRACEPTIVE AND BARRIER GUIDANCE

Contraception Requirements

All female participants of childbearing potential (post-menarche) should avoid pregnancy, and all sexually active male participants should avoid fathering a child.

Female participants will not be considered of childbearing potential if they are surgically sterile (hysterectomy, bilateral salpingectomy, tubal ligation, or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by FSH test results).

Highly Effective Methods of Birth Control for Female Participants

Highly effective methods of birth control are defined as those that result in a low failure rate (ie, < 1% per year) when used consistently and correctly. Highly effective methods of birth control are as follows:

- Hormonal contraceptives:
  - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral; intravaginal; injected; implanted; or transdermal.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral; injectable; or implantable.
  - Hormonal contraception must be supplemented with a barrier method (preferably male condom).
- IUD.
- IUS.
- Bilateral tubal occlusion.
- Sexual abstinence:
  - Sexual abstinence is a highly effective method only if the participant is refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
- Male partner who has been vasectomized with confirmation of azoospermia (verbal confirmation is acceptable).

Highly Effective Methods of Birth Control for Male Participants with Female Partners Capable of Reproduction

- For male participants who are not surgically sterile with confirmed absence of sperm, condom plus effective contraception for their female partners (ie, established use of oral, injected, or implanted hormonal contraception, or an IUD or IUS) must be used.

- Vasectomy at least 3 months prior to Day -1 with confirmation of azoospermia (verbal confirmation is acceptable).

Contraception Guidance

Instructions for Female Participants of Childbearing Potential

For female participants of childbearing potential (post-menarche) who are sexually active, pregnancy should be avoided. Females must use a highly effective method of contraception consistently throughout the study and for at least 30 days after the last dose of study drug.

Female participants who become pregnant during the study will be withdrawn from the study.

Pregnancy reporting is described in Section 8.4.7.

Instructions for Male Participants Capable of Fathering a Child

No information is available about the effects that voxelotor may have on the development of the fetus in humans. Therefore, it is important that the partners of male participants do not become pregnant during the study and for a total period of 30 days after the male participant has received his last dose of voxelotor. Sperm donation should be avoided for this same period.

Males must be surgically sterilized, or agree to practice true abstinence, or agree to use acceptable contraception if sexually active with a female partner of childbearing potential, throughout the study, and for at least 30 days after the last dose of study drug.

APPENDIX 2. GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB allow, a blood and/or saliva sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for determination of factors that may impact absorption, metabolism, transport, and elimination of drugs such as probe substrates used in this study. Genotyping may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for CYP2C9 or CYP2C19 poor metabolizer status, or carrying SLCO1B1 (c.521T>C, rs4149056) variant allele, as well as CYP3A5 expresser status.
- The results of genotyping may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while the study continues but no longer than 10 years or other period as per local requirements.