Pharmacokinetics of Voxelotor in Patients With Renal and Hepatic Impairment

Richard A. Preston, MD, FCP[1,2,3,4], Thomas Marbury, MD[5], Ganesh Balaratnam, MBChB BAO (NUI)[6], Michelle Green, PhD[7], Sandy Dixon, MS[8], Josh Lehrer-Graiwer, MD, Phil, FACC[8], and Carla Washington, PhD[8]

Abstract

Two open-label studies assessed the safety, tolerability, and pharmacokinetics of Oxbryta (voxelotor) in subjects with hepatic or renal impairment. Eight subjects with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2) and 8 healthy age-, sex-, and body mass index–matched controls were administered a single oral dose of voxelotor 900 mg. Seven patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment and healthy age-, sex-, and body mass index–matched controls (7:7:7:7) were administered a single oral dose of voxelotor 1500 mg, except those with severe hepatic impairment (600 mg). There was no apparent effect of renal function on the excretion of voxelotor based on comparable half-life values between subjects with severe renal impairment and healthy matched controls. Mean area under the concentration-time curve from time 0 to infinity (AUC$_{0\text{-inf}}$) values were lower by approximately 50% (plasma) and 25% (whole blood) in subjects with severe renal impairment compared with controls. Accordingly, dose adjustment is not required in patients with severe renal impairment. Voxelotor plasma and whole-blood exposures were slightly increased in subjects with mild and moderate hepatic impairment. Mean AUC$_{0\text{-inf}}$ values were approximately 9% to 18% higher compared with those of healthy matched controls. Dose adjustment is therefore not required in patients with mild or moderate hepatic impairment. Voxelotor mean AUC$_{0\text{-inf}}$ values were approximately 90% higher in subjects with severe hepatic impairment. A lower voxelotor dose (1000 mg) is recommended for patients with severe hepatic impairment. Voxelotor was well tolerated in all treatment groups.

Sickle cell disease (SCD) is a debilitating disease that afflicts approximately 100 000 people in the United States and millions worldwide.[1] SCD is an autosomal recessive disorder caused by a mutation in the β-chain of hemoglobin that leads to the production of sickle hemoglobin.[2] When deoxygenated, sickle hemoglobin polymerizes and deforms red blood cells (RBCs) into a sickle shape, leading to cell membrane damage and abnormalities.[3,4] These damaged RBCs block capillaries and undergo hemolysis, which can trigger downstream effects, including anemia, fatigue, tissue ischemia, painful vaso-occlusive crisis, vascular injury, reduced quality of life, significant end-organ damage, and early death.[4,5]

Oxbryta 1500-mg tablets taken once daily (voxelotor; previously called GBT440) is a first-in-class oral therapy approved for patients with SCD aged ≥12 years. Voxelotor modulates hemoglobin's affinity for oxygen, preventing sickling of RBCs, with potential interruption in the molecular pathogenesis of the disease. The most common adverse reactions (incidence >10%) include headache, diarrhea, abdominal pain, nausea, fatigue, rash, and pyrexia.[6]

The pharmacokinetics (PK) profile of voxelotor has been extensively characterized in healthy subjects.[7] Voxelotor is rapidly absorbed, with an oral bioavail-ability of >35% and a median time to reach maximum observed concentration (t$_{max}$) of 2 hours in plasma and 6 hours in whole blood. The drug binds to protein at 99.8% and has a long half-life (t$_{1/2}$). The t$_{1/2}$ of voxelotor is approximately 3 days in healthy subjects

[1]Clinical Pharmacology Research Unit, Division of Clinical Pharmacology, Department of Medicine, Miller School of Medicine, University of Miami, Miami, Florida, USA

[2]University of Miami Clinical and Translational Sciences Institute, Miami, Florida, USA

[3]Peggy and Harold Katz Drug Discovery Center, Miller School of Medicine, University of Miami, Miami, Florida, USA

[4]Jackson Memorial Hospital, Miami, Florida, USA

[5]Orlando Clinical Research Center, Orlando, Florida, USA

[6]MyoKardia, South San Francisco, California, USA

[7]Integrated Drug Development, Certara, Menlo Park, California, USA

[8]Global Blood Therapeutics, South San Francisco, California, USA

Corresponding Author:
Carla Washington, PhD, Global Blood Therapeutics, 181 Oyster Point Blvd, South San Francisco, CA 94080
Email: cbwassf@gmail.com

and 36 hours in patients with SCD. In healthy subjects, accumulation is approximately 6-fold, and in patients with SCD the accumulation is approximately 3.5-fold. In addition, it preferentially partitions into RBCs relative to plasma, which is consistent with a high specificity of binding to hemoglobin, thus maximizing the therapeutic index and potentially minimizing off-target toxicities.[6–9] The apparent volume of distribution after oral administration is estimated at 754 L in plasma, 15.9 L in whole blood, and 7.27 L in RBCs. Voxelotor exposure increases proportionally with dose for both single and multiple doses. Voxelotor concentrations decline mono-exponentially, with a terminal elimination phase for voxelotor in plasma, whole blood, and RBCs in a parallel manner and with approximate terminal elimination $t_{1/2}$ values of 98.0 hours in plasma, 66.3 hours in whole blood, and 65.8 hours in RBCs. In healthy subjects, a high-fat, high-calorie meal was shown to increase voxelotor area under the concentration-time curve (AUC) by 42% and maximum observed concentration (C_{max}) by 45% in whole blood, and to increase voxelotor AUC by 42% and C_{max} by 95% in plasma relative to those in a fasted state.

Voxelotor is extensively metabolized by phase I (oxidation and reduction) and phase II (glucuronidation) processes. Oxidation of voxelotor is mediated primarily by cytochrome P450 (CYP) enzyme CYP3A4, with minor contribution from CYP2C19, CYP2B6, and CYP2C9.[6] Based on results from the human absorption, metabolism, and excretion study, unchanged voxelotor was the most abundant circulating radioactive component in blood, accounting for 97.5% of the total radioactivity in the blood samples. Three circulating metabolites were tentatively identified in whole blood and accounted for 2.5% of the total radioactivity in the blood samples. Voxelotor and metabolites are primarily excreted in feces (62.6%) and urine (35.4%) after oral administration. Approximately two-thirds of the administered dose is excreted as metabolites into urine and feces, and one-third is excreted as unchanged drug in the feces, presumably as unabsorbed drug. Approximately 0.08% of voxelotor is excreted unchanged in the urine. GBT440 glucuronidation and reduction-glucuronidation products, which are phase II metabolites, were the most abundant metabolites in urine, accounting for a combined 9.22% of the dose.[10] As the major route of voxelotor elimination is via metabolism,[6] it is important to evaluate the impact of both renal and hepatic impairment on the plasma and the whole-blood PK of voxelotor.

Considering that impaired renal and hepatic function may alter voxelotor exposure, studies were conducted to assess the safety and PK of voxelotor in patients with varying degrees of renal or hepatic function and to determine whether dosage adjustments were needed in these populations.

Methods

This investigation was conducted as 2 separate phase 1 open-label clinical trials. One study was conducted in patients with severe renal impairment, and the other was conducted in patients with varying degrees of hepatic function. The Western Institutional Review Board (Puyallup, Washington) and IntegReview Institutional Review Board (Austin, Texas) approved both protocols and their amendments. The trials were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice, according to the International Conference on Harmonization Tripartite Guideline. Participants provided written informed consent before participating in the study. Both studies were conducted in accordance with US Food and Drug Administration guidance documents dated March 2010 (impaired renal function) and May 2003 (impaired hepatic function).[11,12]

Study 1: Effect of Severe Renal Impairment (ClinicalTrials.gov Identifier: NCT03161015)

*Study Population and Selection of Participants.* This was a nonrandomized, open-label, parallel-group, phase 1 study to characterize the PK and safety of a single oral dose of voxelotor in subjects with normal renal function and severe renal impairment.

Eligible female participants of nonchildbearing potential and male participants aged ≥18 and ≤80 years with a body mass index (BMI) ≥18 and ≤40 kg/m^2 and body weight of ≥50 kg were enrolled in this trial. Eligible subjects with normal renal function (healthy subjects) were included if they had an estimated glomerular filtration rate (eGFR) ≥90 mL/min/ 1.73 m^2, based on the Modification of Diet in Renal Disease equation or creatinine clearance (CrCl), as determined by a 24-hour urine collection, and were in good general health based on medical history, physical examination, vital signs, laboratory evaluations, and electrocardiogram (ECG). Subjects with normal renal function were matched to patients with severe renal impairment based on age, BMI, and sex. Subjects with severe renal impairment, as defined by an eGFR <30 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease equation, were required to be medically stable based on medical history, physical examination, vital signs, laboratory evaluations, and ECGs, with no current or prior history of hemodialysis, and stable renal function for at least 1 month before dosing. Subjects were excluded from the study if they had a diet or drug or substance use/abuse

A Study Design 1: Effect of Severe Renal Impairment
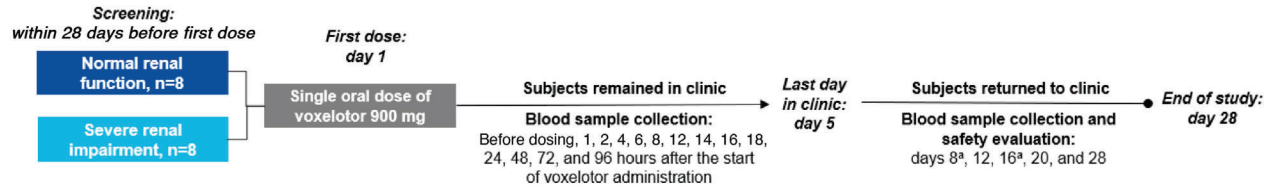
B Study Design 2: Effect of Mild, Moderate, or Severe Hepatic Impairment
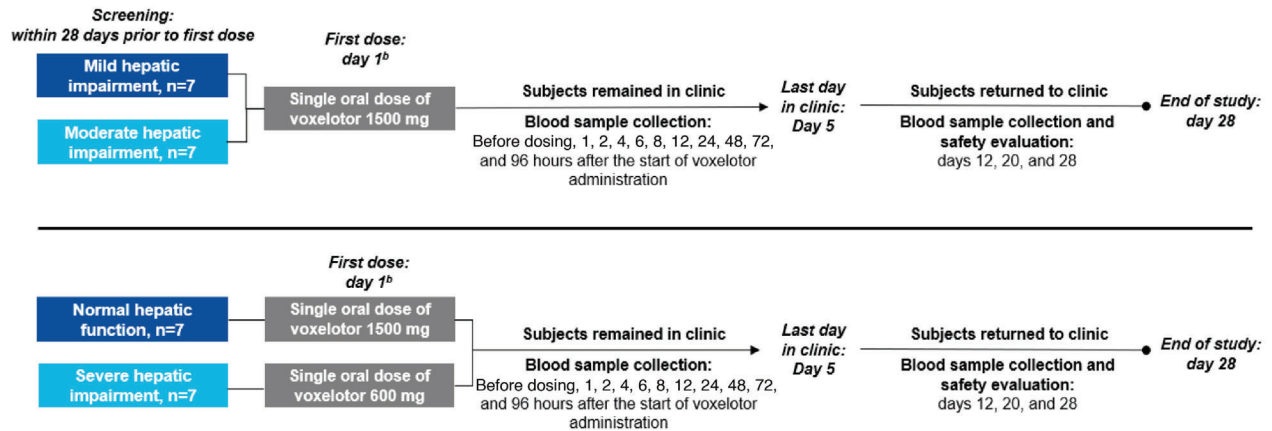
Figure 1. (A) Study design 1: effect of severe renal impairment; (B) study design 2: effect of mild, moderate, or severe hepatic impairment. [a] No safety evaluations were completed on days 8 and 16. [b] Subjects with mild and moderate hepatic impairment were enrolled first. Once at least 4 subjects in each of these groups completed sample collection through day 5, whole-blood and plasma GBT440 PK analysis was performed and compared to historical PK data in healthy subjects to determine whether a dose adjustment was needed for subjects with severe hepatic impairment. Subjects with normal hepatic function were enrolled last, once at least 4 subjects with severe hepatic impairment were enrolled. Study design 1: a phase 1, nonrandomized, open-label, parallel-group study to compare the pharmacokinetics and safety of a single oral dose of voxelotor in subjects with impaired renal function to healthy subjects (A). Study design 2: a phase 1, open-label study to characterize the pharmacokinetics and safety of a single oral dose of voxelotor in subjects with hepatic impairment (B).

that could interfere with accurate study results, or if they had donated blood/plasma within 56 days or participated in another clinical study within 30 days, or 5 half-lives, whichever is longer, before screening. All prescription or nonprescription medications that were strong inhibitors or inducers of CYP enzymes were prohibited for at least 14 days before dosing and for 28 days throughout the study.

Blood Sample Collection. Screening of subjects occurred within 28 days before dosing. On day 1, subjects with normal renal function (n = 8) and subjects with severe renal impairment (n = 8) received a single oral dose of voxelotor 900 mg (3 × 300-mg capsules) with approximately 240 mL of water after an overnight fast. The 900-mg dose of voxelotor was selected for this study, as it was expected to be within the upper range of the therapeutic dose and was well tolerated in healthy subjects. Participants remained in the clinic through day 5 and returned to the clinic on days 8, 12, 16, 20, and 28 for blood sampling and days 12, 20, and 28 for safety evaluations. Furthermore, blood collection for

whole-blood and plasma voxelotor PK determination were also collected at the following times: before dosing and 1, 2, 4, 6, 8, 12, 14, 16, 18, 24, 48, 72, and 96 hours after the start of voxelotor administration (Figure 1A). Blood samples were also collected for determination of voxelotor plasma protein binding.

Study 2: Effect of Mild, Moderate, or Severe Hepatic Impairment (ClinicalTrials.gov Identifier: NCT03114540)

Study Population and Selection of Participants. This was a multicenter, open-label, parallel-group phase 1 study to characterize the PK and safety of a single oral dose of voxelotor in subjects with hepatic impairment.

Eligible female participants of nonchildbearing potential and male participants aged ≥18 and ≤75 years, a BMI ≥18 and ≤38 kg/m^2 for healthy subjects and 18 and 40 kg/m^2 for subjects with severe hepatic impairment, and body weight of ≥50 kg were enrolled in this trial. Eligible subjects with normal hepatic function were in good general health based on medical history,

physical examination, vital signs, laboratory evaluations, and ECG. Subjects with normal hepatic function were excluded if they had any signs and/or symptoms of acute illness or had a known history of porphyria, Gilbert's syndrome, or alcoholism; personal or family history of long QT syndrome; ECG QT Fridericia's correction formula >470 milliseconds for men or >480 milliseconds for women; active liver disease; unexplained elevated liver enzymes; resting bradycardia or tachycardia; untreated hypertension; and an estimated CrCl of <60 mL/min, calculated using the Cockcroft-Gault equation, at baseline. Subjects with normal hepatic function were matched to patients with mild, moderate, and severe hepatic impairment with similar demographics such as age, BMI, and sex. The degree of hepatic impairment was categorized using the Child-Pugh system and in accordance with the guidelines of the Food and Drug Administration.[12,13] Subjects with hepatic impairment had chronic (>6 months), stable, mild (Child-Pugh A [5 or 6 points]), moderate (Child–Pugh B [7-9 points]), or severe (Child–Pugh C [10-15 points]) liver disease of cryptogenic, posthepatic hepatitis B or hepatitis C virus origin. Stable hepatic impairment was defined as no clinically significant change in disease status within the past 60 days. Subjects were excluded if they had an expected survival period of <12 months, history of liver transplantation or suspected hepatocellular carcinoma, severe ascites, active severe hepatic encephalopathy (grade ≥3), acute liver disease (caused by infection or drug toxicity), biliary liver cirrhosis, elevated liver enzyme (aspartate aminotransferase/alanine aminotransferase >5 upper limit of normal), resting bradycardia or tachycardia, untreated hypertension, ECG Fridericia's correction formula >470 milliseconds for men or >480 milliseconds for women, personal or family history of long QT syndrome, or an estimated CrCl of <60 mL/min at baseline, calculated using the Cockcroft-Gault equation. Subjects were excluded if they had a diet, drug, or substance use/abuse that could interfere with accurate study results or donated blood/plasma within 90 days or participated in another clinical study within 30 days, or 5 half-lives, whichever is longer, before screening. No concomitant medications (prescription, over-the-counter, or herbal, including any drugs that induced study drug–specific CYP enzymes) were administered during the study to subjects with normal hepatic function unless they were prescribed by the investigator for treatment of specific clinical events, such as adverse events (AEs). No strong inhibitors or inducers of CYP enzymes were administered to subjects with hepatic impairment.

Screening of subjects occurred within 28 days before dosing. On day 1, subjects were enrolled in a ratio of 7:7:7:7 subjects per hepatic function group (normal hepatic function and mild, moderate, and severe hepatic impairment). Subjects with mild and moderate hepatic impairment were enrolled first in parallel, and then subjects with severe hepatic impairment and normal hepatic function were enrolled in parallel. Eligible subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment received a single oral dose of voxelotor 1500 mg (5 × 300-mg capsules) (Figure 1B). The 1500-mg dose was selected for this study to support voxelotor dosing in ongoing programs. To determine whether a dose adjustment was needed before dosing subjects in the severe hepatic impairment group, an interim analysis was conducted after a minimum of 4 subjects in the mild and 4 subjects in the moderate hepatic impairment groups completed the in-house portion of the study. In this interim analysis, the AE profiles and whole-blood and plasma PK parameters were compared with historical data from the GBT440-001 PK study in healthy subjects to determine whether there was an increase in exposure and whether a dose adjustment was needed.[7] A lower single oral dose of voxelotor 600 mg (2 × 300-mg capsules) was administered to the subjects with severe hepatic impairment based on the observation of diarrhea (mild treatment-emergent AE) occurring in 5 of 7 subjects (71.4%) with moderate hepatic impairment and due to the potential for substantially higher voxelotor exposures in subjects with severe hepatic impairment.

Blood Sample Collection. All subjects received the investigational drug with approximately 240 mL of water after an overnight fast. Participants remained in the clinic through day 5 and returned to the clinic on days 12, 20, and 28 for blood sampling and safety evaluations. Similar to study 1, blood collection for whole-blood and plasma voxelotor PK determination were collected at the following times: before dosing and 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours after the start of voxelotor administration. Blood samples were also collected for determination of voxelotor plasma protein binding.

Bioanalytical Methods

Blood samples were collected in K_2–ethylenediaminetetraacetic acid tubes and inverted several times to mix the blood and anticoagulant. Whole-blood samples were stored frozen at −20°C until analysis. For plasma collection, tubes were stored in an ice bath, then centrifuged for 10 minutes at 1600 × g in a refrigerated centrifuge set at 4°C to harvest plasma. Plasma samples were frozen at −20°C until analysis. Human K_2–ethylenediaminetetraacetic acid whole-blood, plasma, and mixed matrix (for free

fraction determination) concentrations of voxelotor were analyzed using liquid chromatography coupled to tandem mass spectrometry methods validated with respect to accuracy, precision, linearity, sensitivity, and specificity at Bioanalytical Sciences Inc. (Austin, Texas). The analytical range in whole blood (lower limit to upper limit of quantification) was 120 to 300 000 ng/mL, based on the analysis of 50.0 μL of human whole blood. The analytical range in plasma (lower limit to upper limit of quantification) was 6.00 to 15 000 ng/mL, based on the analysis of 50.0 μL of plasma. The analytical range in mixed matrix (lower limit to upper limit of quantification) was 0.100 to 25.0 ng/mL, based on the analysis of 100.0 μL of human mixed matrix. Human whole blood, plasma, or mixed matrix containing voxelotor and the internal standard, GBT1592 (GBT440-D$_7$), were extracted using liquid-liquid extraction and analyzed by an API 4000 liquid chromatography coupled to tandem mass spectrometry (Sciex, Framingham, Massachusetts) equipped with a high-performance liquid chromatography column. Selective detection of voxelotor and the internal standard was performed in multiple reaction monitoring and positive ionization modes by monitoring transitions of m/z 338.1 → 158.1 and m/z 345.1 → 159.1, respectively. Quantitation was performed using a weighted $1/\chi^2$ linear least-squares regression analysis generated from calibration standards.

Pharmacokinetic Analyses

PK parameters of voxelotor were calculated from the whole-blood and plasma concentrations of voxelotor via noncompartmental analysis (Phoenix WinNonlin, version 6.3; Pharsight Corporation, Mountain View, California) using actual sampling times. The following whole-blood and plasma PK parameters were determined for voxelotor: AUC from time 0 to the last quantifiable concentration (AUC$_{0-t}$), AUC from time 0 extrapolated to infinity (AUC$_{0-inf}$), C$_{max}$, t$_{max}$, terminal elimination rate constant (k$_{el}$), terminal elimination t$_{1/2}$, apparent oral clearance (CL/F), and apparent volume of distribution during the terminal elimination phase after oral voxelotor administration (V$_z$/F). Protein binding was assessed by determining the fraction of voxelotor unbound (Fu) at the 4-hour collection time point. The following PK parameters were calculated for the unbound voxelotor in plasma: Fu, AUC$_{0-inf,u}$, C$_{max,u}$, CL$_u$/F, and V$_{z,u}$/F.

Statistical Analyses

All voxelotor whole-blood and plasma (including unbound fraction) PK concentrations and PK parameter descriptive statistics were generated using SAS version 9.3 (SAS Institute, Cary, North Carolina). Geometric mean ratios (GMRs) and the corresponding 90% confidence intervals of AUC$_{0-t}$, AUC$_{0-inf}$, and C$_{max}$ between subject groups were assessed. The sample sizes selected for these studies were selected in accordance with Food and Drug Administration guidance documents dated March 2010 (impaired renal function) and May 2003 (impaired hepatic function).[11,12]

In the renal impairment study, the analysis was performed on the ln-transformed AUC and C$_{max}$ for voxelotor in plasma and whole blood. The model included subjects with severe renal impairment and healthy matched controls with normal renal function containing a factor for renal group, and sex, age, and BMI as covariates. The presence of an effect of renal impairment on voxelotor PK was concluded if the GMR of AUC$_{0-t}$ and AUC$_{0-inf}$ for subjects with severe renal impairment and matched subjects with normal renal function increased by >50%.

In the hepatic impairment study, a linear mixed-effect model was fitted to the log-transformed values of whole-blood and plasma C$_{max}$, AUC$_t$, and AUC$_{inf}$. The model included a hepatic impairment group as a fixed effect with age and weight as covariates. Point estimates and 90% confidence intervals for hepatic function group differences (mild, moderate, and severe hepatically impaired subjects vs the normal hepatic function subjects) on the log scale were exponentiated to obtain estimates for GMR on the original scale.

Safety Assessments

In both studies, safety was assessed by clinical laboratory tests (hematology profile, serum chemistry, and urinalysis), physical examinations, vital signs, 12-lead ECGs, serum pregnancy tests (female subjects), and review of concomitant medications performed at screening. Hematology and chemistry labs were assessed before study drug administration and repeated the day after. Vital signs were monitored during study drug administration. AEs and concomitant medications were monitored and documented throughout the study.

Results

Study 1: Effect of Severe Renal Impairment

Demographics. A total of 16 subjects were enrolled and completed the study, including 8 subjects with severe renal impairment and 8 healthy subjects. All subjects received a single dose of oral voxelotor 900 mg. Data from all 16 subjects were included in PK and safety analyses. Study groups were well matched for sex, age, and BMI, as shown in the key demographic and baseline characteristics (Table 1). All participants with renal impairment were taking concomitant medication.

Table 1. Voxelotor Key Demographic and Baseline Characteristics of Subjects With Severe Renal Impairment and Matching Healthy Subjects With Normal Renal Function (Study 1)

Characteristics	Normal Renal Function (n = 8)	Severe Renal Impairment (n = 8)
Sex, n (%)		
Female	4 (50)	4 (50)
Male	4 (50)	4 (50)
Age, y, mean (SD)	60.6 (5.8)	62.5 (7.1)
Race, n (%)		
Black or African American; White	1 (13); 7 (88)	2 (25); 6 (75)
Weight, kg, mean (SD)	84.7 (10.4)	82.2 (15.0)
BMI, kg/m^2, mean (SD)	30.3 (1.7)	31.9 (5.0)
Serum creatinine (53.0-123.8 μmol/L),[a] mean (SD)	56.0 (10.6)	393.8 (158.4)
CrCl (61-500 mL/min),[a] mean (SD)	134.8 (28.8)	12.5 (7.8)
Albumin (30-57 g/L),[a] mean (SD)	44.8 (2.7)	41.8 (4.6)
Hb (female, 11.8-16.0 g/dL; male, 13-17 g/dL),[a] mean (SD)	13.5 (1.4)	10.9 (1.4)
Hct (female, 0.34-0.47 v/v; male, 0.39-0.51 v/v),[a] mean (SD)	0.41 (0.04)	0.34 (0.04)

BMI, body mass index; CrCl, creatinine clearance; Hb, hemoglobin; Hct, hematocrit.

[a] Normal laboratory reference ranges varied across the study sites. The listed normal laboratory reference ranges include the minimum and maximum normal values across study sites.

Amlodipine, furosemide, simvastatin, and sodium bicarbonate were the most frequently used drugs, with 4 of 8 participants (50%) reporting use of amlodipine and 3 of 8 participants (38%) reporting use of furosemide, simvastatin, sodium bicarbonate, allopurinol, and ferrous sulfate. Subjects with severe renal impairment had mean CrCl of 12.5 mL/min and lower hemoglobin and hematocrit levels compared with those of the healthy matched control subjects.

Pharmacokinetics. Voxelotor plasma and whole-blood concentration-time profiles are shown in Figure 2A and 2E, and plasma PK parameters are shown in Table 2. Mean plasma voxelotor exposures were approximately 50% lower in subjects with severe renal impairment compared with those of their matched healthy controls. GMRs for voxelotor AUC_{0-inf} and C_{max} were approximately 50% and 44% lower, respectively, in subjects with severe renal impairment compared with healthy controls. In contrast, mean terminal elimination $t_{1/2}$ values were comparable between subjects with severe renal impairment (mean ± SD = 63 hours ± 11) and healthy controls (mean ± SD = 73 hours ± 12). Median plasma voxelotor t_{max} values were comparable between subjects with severe renal impairment and healthy controls, with median values of 5.0 and 4.0 hours, respectively, and individual minimum and maximum values ranging from 2.0 to

24 hours in both groups. Mean plasma voxelotor CL/F values were approximately 2 times higher in subjects with severe renal impairment than in healthy controls. There was no apparent effect of renal function on the excretion of voxelotor based on similar postpeak mean plasma voxelotor concentration decline rates between both groups (Figure 2A, 2B). Fu varies in renal disease, making interpretation based on total plasma concentration more problematic. Unbound plasma voxelotor PK parameters are shown in Table 2. As expected, the Fu of voxelotor was higher in subjects with severe renal impairment (∼0.83%) compared with that in healthy controls (∼0.38%), leading to comparatively higher unbound voxelotor exposures in those with severe renal impairment. $AUC_{0-inf,u}$ and $C_{max,u}$ values were approximately 18% to 25% higher in healthy controls. Mean CL_u/F and $V_{z,u}/F$ values were 16% and 28% lower in subjects with severe renal impairment than in healthy controls, respectively. However, the individual values (data not shown) show that unbound voxelotor plasma concentrations were comparable between those with severe renal impairment and healthy subjects. Therefore, there seems to be no effect of renal function on the excretion of voxelotor based on comparable unbound plasma CL values and the similar postpeak mean unbound plasma voxelotor concentration decline rates between both groups (Figure 2C, 2D).

Mean plasma voxelotor PK parameters were lower in severe renal impairment subjects (lower eGFR) compared with healthy controls (higher eGFR); however, no clear trend was observed between unbound plasma voxelotor PK parameters in severe renal impairment subjects and healthy controls. In addition, there was no apparent relationship between voxelotor exposures to eGFR for the total or unbound plasma PK parameters.

Mean plasma voxelotor V_z/F values were approximately 1.5-fold higher in those with severe renal impairment (mean ± SD = 774.8 L ± 254.3) than in healthy controls (mean ± SD = 502.2 L ± 181.0). There was no apparent effect of renal function on the excretion of voxelotor based on the comparable plasma voxelotor $t_{1/2}$ and CL_u/F values between the 2 groups; however, plasma voxelotor AUC_{0-inf} and C_{max} values were reduced by approximately 50% in severe renal impairment subjects compared with those in the healthy controls.

Similarly to plasma voxelotor exposures, mean whole-blood voxelotor exposures were lower in subjects with severe renal impairment compared with healthy control subjects but to a lesser degree: AUC_{0-inf} and C_{max} values were approximately 21% and 14% lower, respectively (Table 2), and postpeak mean whole-blood voxelotor concentration decline rates were comparable between both groups and seemed to decline in a
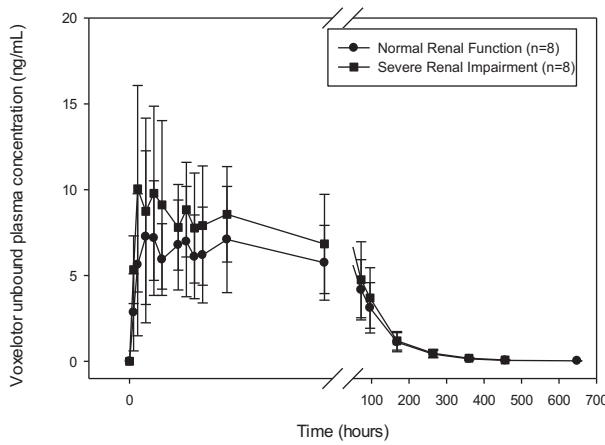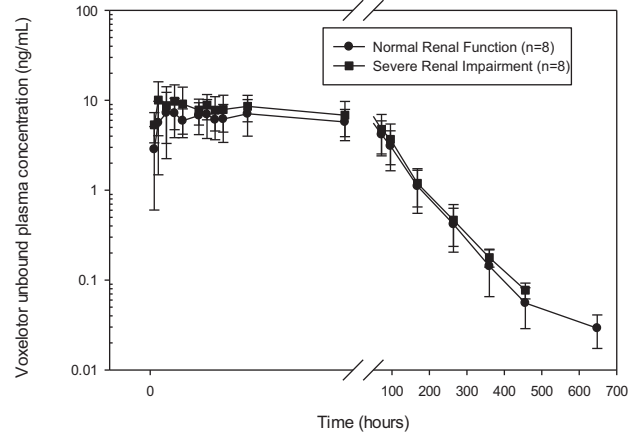
A Plasma (Linear Scale)
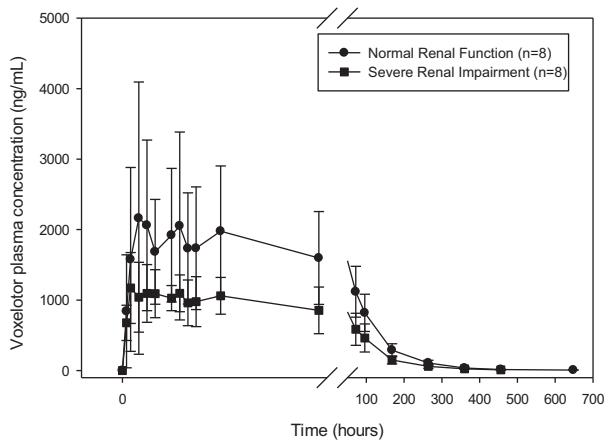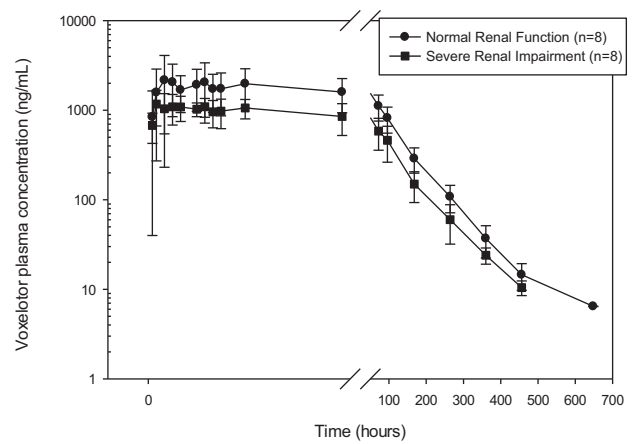
B Plasma (Semi-log Scale)

C Unbound Plasma (Linear Scale)

D Unbound Plasma (Semi-log Scale)

E Whole Blood (Linear Scale)

F Whole Blood (Semi-log Scale)

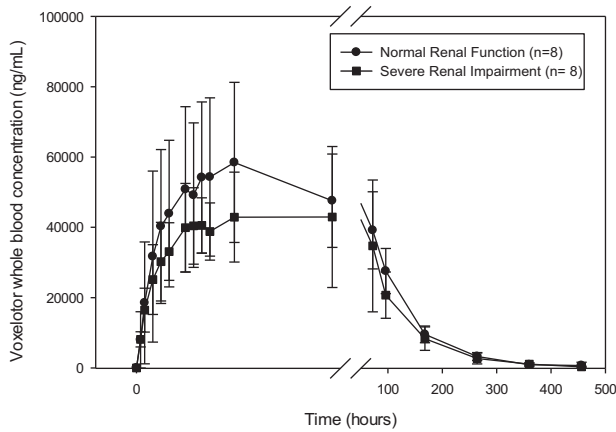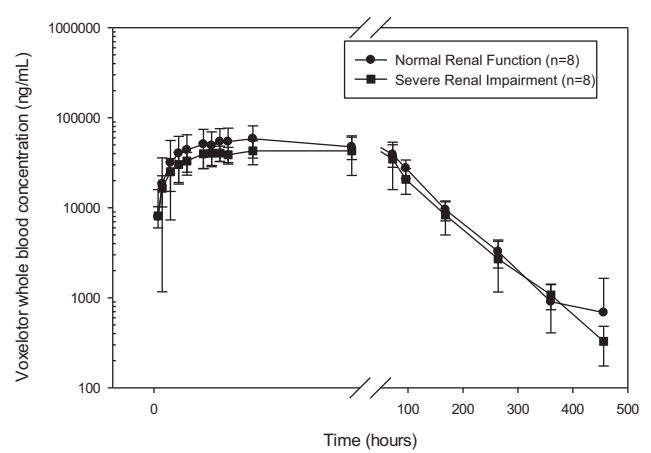**Figure 2.** (A) Plasma (linear scale); (B) plasma (semilog scale); (C) unbound plasma (linear scale); (D) unbound plasma (semilog scale); (E) whole blood (linear scale); (F) whole blood (semilog scale). Study 1: mean (±SD) plasma (A, B), unbound plasma (C, D), and whole-blood (E, F) voxelotor concentrations vs time in subjects with severe renal impairment and matching healthy subjects with normal renal function.

Table 2. Plasma, Unbound Plasma, and Whole-Blood Voxelotor Pharmacokinetic Parameters in Subjects With Severe Renal Impairment and Matching Healthy Subjects With Normal Renal Function (Study 1)

Pharmacokinetic Parameters[a]	Normal Renal Function (n = 8)	Severe Renal Impairment (n = 8)	GMR[c] % (90%CI)
Plasma			
C_{max}, µg/mL	2.33 (71.3)	1.32 (27.7)	56.41 (42.7-74.6)
t_{max}, h	4.0 (2.0, 24.0)	5.0 (2.0, 24.0)	
AUC_{0-t}, µg • h/mL	199.2 (34.3)	106.9 (40.1)	50.11 (37.5-67.0)
AUC_{0-inf}, µg • h/mL	200.4 (34.2)	108.1 (39.4)	50.49 (37.9-67.3)
V_z/F, L	502.2 ± 181.0	774.8 ± 254.3	
CL/F, L/h	4.71 ± 1.49	8.96 ± 4.28	
K_{el}, 1/h	0.0096 ± 0.0014	0.0114 ± 0.0025	
$t_{1/2}$, h	73.4 ± 11.5	63.1 ± 11.5	
Unbound plasma			
$C_{max,u}$, µg/mL	0.0084 (65.3)	0.0105 (45.6)	124.66[d]
$AUC_{0-inf,u}$, µg • h/mL	0.720 (44.1)	0.856 (43.0)	118.89[d]
$V_{z,u}/F$, L	142542 ± 62469	102616 ± 40656	
CL_u/F, L/h	1358.1 ± 646.6	1138.8 ± 536.0	
Fraction unbound[b]	0.0038 ± 0.0015	0.0083 ± 0.0025	
Whole blood			
C_{max}, µg/mL	57.4 (41.8)	49.3 (38.8)	83.6 (67.0-104.3)
t_{max}, h	18.0 (12.0, 24.0)	24.0 (14.0, 72.0)	
AUC_{0-t}, µg • h/mL	6170.4 (26.2)	4886.2 (41.2)	75.3 (57.9-98.0)
AUC_{0-inf}, µg • h/mL	6222.1 (26.6)	4925.6 (40.5)	75.4 (58.1-98.0)
CL/F, L/h	0.15 ± 0.04	0.20 ± 0.10	
V_z/F, L	12.2 ± 3.7	14.7 ± 5.1	
K_{el}, 1/h	0.013 ± 0.003	0.013 ± 0.002	
$t_{1/2}$, h	57.2 ± 11.7	54.0 ± 8.6	
Whole blood:plasma ratio, range	9 ± 2 to 46 ± 69	13 ± 3 to 61 ± 29	

AUC_{0-t}, area under the concentration-time curve from time 0 to the last quantifiable concentration; AUC_{0-inf}, AUC from time 0 extrapolated to infinity; CI, confidence interval; CL/F, apparent oral clearance; C_{max}, maximum observed concentration; GMR, geometric mean ratio (100 × severe/normal renal function); K_{el}, terminal elimination rate constant; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach C_{max}; V_z/F, apparent volume of distribution during the terminal elimination phase after oral voxelotor administration.

[a] Geometric means and geometric coefficient of variation are presented for AUC and C_{max}; t_{max} is presented as median (minimum, maximum). Otherwise, values are presented as mean ± SD.

[b] Result at 4 hours after dosing.

[c] Geometric least-squares means (LSMs) were calculated by exponentiating the LSMs from the analysis of covariance containing a factor for renal group, categorical covariate for sex, and continuous covariates of age and body mass index.

[d] CI was not calculated for GMR for $C_{max,u}$ and $AUC_{0-inf,u}$.

monophasic manner (Figure 2E, 2F). Mean whole-blood voxelotor CL/F and V_z/F values were approximately 33% and 25% higher in severe renal impairment subjects than in healthy controls, respectively. Mean whole-blood voxelotor $t_{1/2}$ values were comparable between severe renal impairment subjects (approximately 54 hours) and healthy controls (approximately 57 hours). Whole-blood voxelotor PK parameters were slightly lower in severe renal impairment subjects (lower eGFR) compared with healthy controls (higher eGFR). Whole-blood voxelotor exposure did not appear to correlate with eGFR.

Median whole-blood voxelotor t_{max} values were delayed by 6.0 hours in severe renal impairment subjects (24 hours) compared with healthy controls (18 hours). Furthermore, due to apparent drug partitioning into RBCs, blood:plasma ratios (ranging from approximately 13 ± 3 to 61 ± 29 in subjects with severe renal impairment and from 9 ± 2 to 46 ± 69 in healthy controls) show variability, as anemia is associated with renal impairment (Table 2). As expected, subjects with severe renal impairment had lower baseline hemoglobin and hematocrit levels compared with those of the healthy matched control subjects (Table 1).

Safety and Tolerability. In study 1, 2 subjects (25%) with severe renal impairment reported 3 mild AEs (grade 1), and all AEs resolved. Abdominal pain and headache were considered possibly or probably related to the study drug by the investigator; nasopharyngitis was deemed not related to the study drug. There were no deaths, serious AEs, or subject discontinuations due to AEs (Table 3).

Table 3. Summary of Treatment-Emergent Adverse Events[a] in Study 1 and Study 2 (Grade 1)

	Renal Impairment Status, n (%)		Hepatic Impairment Status, n (%)[b]			
	Normal (n = 8)	Severe (n = 8)	Normal (n = 7)	Mild (n = 7)	Moderate (n = 7)	Severe (n = 7)
Dose	Voxelotor 900 mg	Voxelotor 900 mg	Voxelotor 1500 mg	Voxelotor 1500 mg	Voxelotor 1500 mg	Voxelotor 600 mg
Patients with ≥1 event[c]	0	2 (25.0)	0	4 (57.1)	6 (85.7)	1 (14.3)
Gastrointestinal disorders						0
Diarrhea	0	0	0	2 (28.6)	5 (71.4)	0
Dyspepsia	0	0	0	2 (28.6)	0	0
Abdominal pain	0	1 (12.5)	0	0	0	0
Vomiting	0	0	0	0	1 (14.3)	0
Infections and infestations						
Nasopharyngitis	0	1 (12.5)	0	0	0	0
Influenza	0	0	0	0	1 (14.3)	0
Nervous system disorders						
Headache	0	1 (12.5)	0	1 (14.3)	0	0

AE, adverse event; MedDRA, *Medical Dictionary for Regulatory Activities;* TEAE, treatment-emergent adverse event.

[a] AEs are classified according to System Organ Class and Preferred Term of MedDRA Version 19.1.

[b] Subjects with multiple events in the same category are counted only once in that category for each hepatic impairment status. Subjects with events in >1 category are counted once in each of those categories for each hepatic impairment status. Number of subjects includes those reporting at least 1 event of type specified. For subjects with any TEAE, the number of subjects reporting at least 1 event of any type is represented.

[c] Includes organ systems with >1 TEAE report across both Study 1 and Study 2.

Study 2: Effect of Mild, Moderate, or Severe Hepatic Impairment

Demographics. A total of 29 subjects were dosed, and 28 subjects (97%) completed the study. The additional subject was dosed in error and discontinued from the study. Data from all 28 subjects were included in the safety analyses, and 27 subjects were included in the PK analysis (1 subject had all-plasma and whole-blood voxelotor concentrations below the limit of quantification, although they were dosed). Study groups were well matched for sex, age, and BMI, as presented in the key demographic and baseline characteristics (Table 4). All participants with hepatic impairment were taking medications before participation in the study. Furosemide (9/20; 45%) and spironolactone (7/20; 35%) were the most frequently used concomitant drugs.

Pharmacokinetics. The mean dose-adjusted plasma and whole-blood voxelotor concentration-time profiles were higher in subjects with severe hepatic impairment than in subjects with normal hepatic function. Subjects with mild and moderate hepatic impairment had similar voxelotor concentrations in whole blood to those in subjects with normal hepatic function (Table 5, Figure 3C, 3D). Voxelotor plasma PK parameters showed similar results (Table 5, Figure 3A, 3B).

In comparison with subjects with normal hepatic function, the plasma and whole-blood voxelotor AUC_{0-inf} exposures were approximately 9% to 21% higher and 14% to 15% higher in subjects with mild and moderate hepatic impairment, respectively. Plasma and whole-blood voxelotor AUC_{0-inf} exposures adjusted for dose were approximately 90% to 93% higher and 87% to 90% higher in subjects with severe hepatic impairment, respectively. In comparison with subjects with normal hepatic function, whole-blood C_{max} was 19%, 6%, and 39% higher and plasma C_{max} was 18%, 51%, and 45% higher in the mild, moderate, and severe hepatic impairment subjects, respectively. Due to preferential partitioning of voxelotor into RBCs (RBC:plasma ratio range, 67:1 to 111:1), plasma voxelotor exposures represent a small percentage of total voxelotor exposures.[7] Thus, the increase in plasma exposure (51%) was not considered clinically significant, and no safety concerns were observed in this group. The median t_{max} was similar for all hepatic function groups. Subjects with normal hepatic function and those with mild and moderate hepatic impairment had a similar mean $t_{1/2}$ and CL/F. In comparison, the $t_{1/2}$ was longer and the CL/F was lower in subjects with severe hepatic impairment compared with those with normal hepatic function. The Fu of voxelotor measured at the 4-hour time point was similar across all groups (Table 5), and the unbound parameters showed similar results to the bound parameters.

Safety and Tolerability. In study 2, 11 of 21 subjects (52.4%) with hepatic impairment reported 17 AEs, including 4 of 7 subjects (57.1%) with mild hepatic impairment, 6 of 7 subjects (85.7%) with moderate hepatic impairment, and 1 of 7 subjects (14.3%) with

Table 4. Voxelotor Key Demographic and Baseline Characteristics of Subjects With Hepatic Impairment and Matching Healthy Subjects With Normal Hepatic Function (Safety Population) (Study 2)

Characteristic	Normal Hepatic Function (n = 7)	Mild Hepatic Impairment (n = 7)	Moderate Hepatic Impairment (n = 7)	Severe Hepatic Impairment (n = 7)
Sex, n (%)				
Female	1 (14.3)	2 (28.6)	1 (14.3)	1 (14.3)
Male	6 (85.7)	5 (71.4)	6 (85.7)	6 (85.7)
Age, y, mean (SD)	54.3 (3.9)	56.4 (4.7)	60.3 (4.5)	55.4 (6.9)
Race, n (%)				
Black or African American	1 (14.3)	1 (14.3)	0	0
White	6 (85.7)	6 (85.7)	7 (100)	7 (100)
Weight, kg, mean (SD)	86.8 (10.5)	83.1 (28.3)	90.7 (14.3)	82.4 (10.5)
BMI, kg/m^2, mean (SD)	28.6 (1.7)	27.4 (6.2)	32.2 (3.3)	29.5 (6.4)
Encephalopathy grade, n (%)				
None	7 (100)	3 (42.9)	0	0
1	0	1 (14.3)	3 (42.9)	5 (71.4)
2	0	3 (42.9)	4 (57.1)	1 (14.3)
3	0	0	0	1 (14.3)
Ascites, n (%)				
Absent	7 (100)	5 (71.4)	0	0
Slight	0	2 (28.6)	5 (71.4)	0
Moderate	0	0	2 (28.6)	7 (100)
Albumin (30-57 g/L),[a] mean (SD)	43.0 (2.9)	44.1 (2.3)	42.0 (2.6)	31.0 (5.1)
Bilirubin (3.4-20.5 μmol/L),[a] mean (SD)	11.7 (4.0)	10.3 (5.0)	16.9 (6.0)	51.6 (29.0)
Prothrombin INR (0.8-1.3), mean (SD)	0.9 (0.1)	1.1 (0.1)	1.3 (0.3)	1.6 (0.5)

BMI, body mass index; INR, international normalized ratio; SD, standard deviation.
[a] Normal laboratory reference ranges varied across the study sites. The listed normal laboratory reference ranges include the minimum and maximum normal values across study sites.

Table 5. Plasma, Unbound Plasma, and Whole-Blood Voxelotor Pharmacokinetic Parameters in Subjects With Hepatic Impairment and Matching Subjects With Normal Hepatic Function (Study 2)

Pharmacokinetic Parameters[a]	Normal Hepatic Function (n = 7)	Mild Hepatic Impairment (n = 7)	Moderate Hepatic Impairment (n = 6)	Severe Hepatic Impairment[b] (n = 7)
Dose	Voxelotor 1500 mg	Voxelotor 1500 mg	Voxelotor 1500 mg	Voxelotor 600 mg
Plasma				
C_{max}, μg/mL	2.01 (23.3)	2.39 (39.1)	2.91 (17.9)	2.96 (31.1)
t_{max}, h	4.00 (2.00, 48.0)	4.00 (2.00, 24.0)	5.00 (2.00, 48.0)	4.00 (2.00, 24.0)
AUC_{0-t}, μg • h/mL	199 (21.2)	223 (20.0)	252 (25.3)	386 (30.4)
AUC_{0-inf}, μg • h/mL	200 (21.1)	224 (19.9)	244 (27.4)	393 (30.8)
CL/F, L/h	7.50 (26.0)	6.69 (24.4)	6.14 (28.7)	3.81 (25.5)
V_z/F, L	865 (20.2)	674 (31.4)	789 (24.3)	592 (26.6)
$t_{1/2}$, h	80.8 (13.0)	71.4 (17.8)	90.0 (14.0)	109 (16.3)
Unbound plasma				
$C_{max,u}$, μg/mL	0.0082 (29.5)	0.0593 (51.7)	0.0106 (50.4)	0.0062 (63.4)
$AUC_{0-inf,u}$, μg • h/mL	0.815 (23.1)	0.507 (25.1)	1.04 (42.6)	2.07 (97.9)
CL_u/F, L/h	0.0305 (39.1)	0.0151 (45.0)	0.0260 (24.3)	0.0200 (37.6)
Fraction unbound[c] (%)	0.407 (18.4)	0.226 (21.6)	0.364 (48.9)	0.525 (55.7)
Whole blood				
C_{max}, μg/mL	60.9 (22.4)	73.6 (32.8)	63.8 (17.4)	86.6 (33.6)
T_{max}, h	24.0 (24.0, 48.0)	24.0 (12.0, 48.0)	24.0 (24.0, 24.0)	24.0 (24.0, 72.0)
AUC_{0-t}, μg • h/mL	6953 (10.8)	8193 (29.2)	8324 (22.6)	13331 (23.3)
AUC_{0-inf}, μg • h/mL	6980 (10.9)	8230 (29.1)	8363 (22.8)	13636 (24.2)
CL/F, L/h	0.215 (11.1)	0.182 (32.4)	0.179 (23.9)	0.110 (26.1)
V_z/F, L	19.6 (16.4)	15.8 (31.0)	20.6 (18.5)	17.6 (22.0)
$t_{1/2}$, h	63.2 (17.5)	60.1 (60.7)	79.5 (18.7)	111 (19.1)

AUC_{0-t}, area under the concentration-time curve from time zero to the last quantifiable concentration; AUC_{0-inf}, AUC from time 0 extrapolated to infinity; CL/F, apparent oral clearance; C_{max}, maximum observed concentration; CV, coefficient of variation; GM, geometric mean; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach C_{max}; V_z/F, apparent volume of distribution during the terminal elimination phase after oral voxelotor administration.
[a] t_{max} is presented as median (minimum, maximum). $t_{1/2}$ is presented as mean (SD). Otherwise, values are presented as GMs and geometric CV%.
[b] For subjects with severe hepatic impairment, AUC and C_{max} were adjusted for dose.
[c] Result at 4 hours after dosing.

A Plasma (Linear Scale)
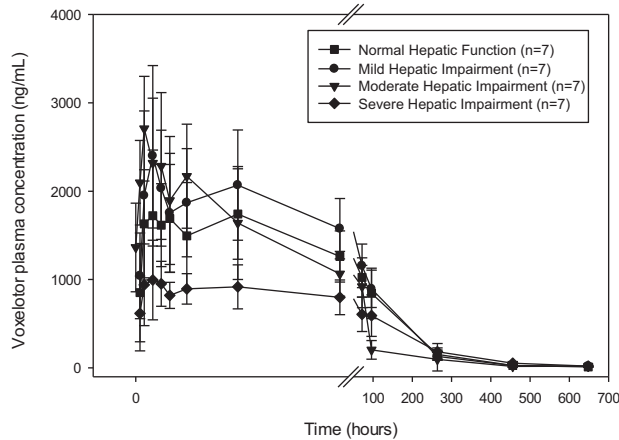
B Plasma (Semi-log Scale)
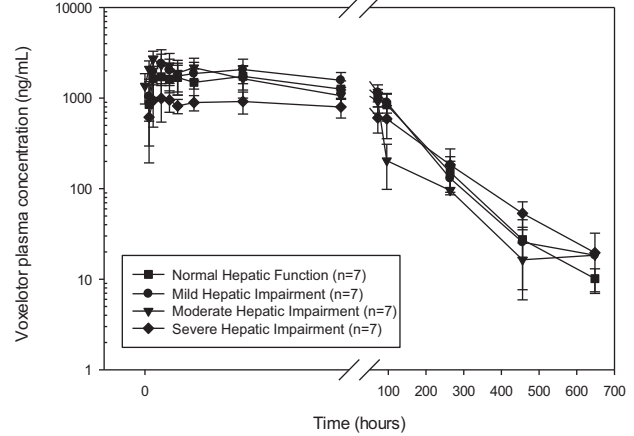
C Whole Blood (Linear Scale)
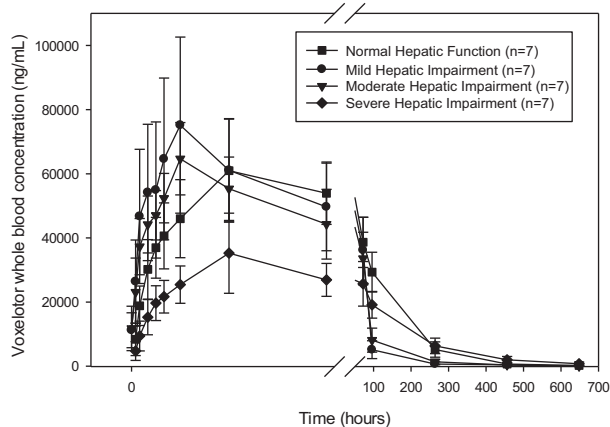
D Whole Blood (Semi-log Scale)
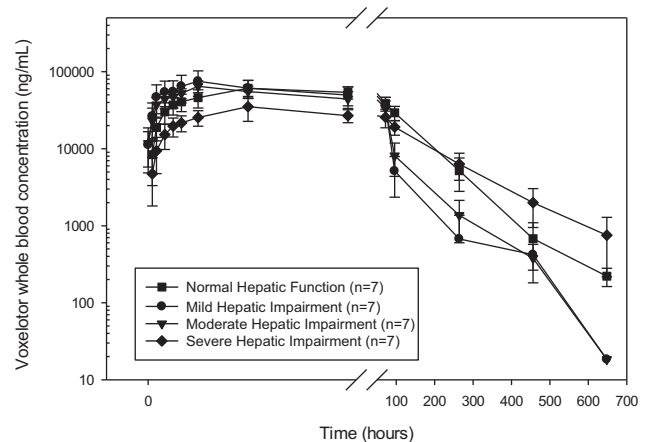
Figure 3. (A) Plasma (linear scale); (B) plasma (semilog scale), (C) whole blood (linear scale), (D) whole blood (semilog scale). Study 2: mean (±SD) plasma (A, B) and whole-blood (C, D) voxelotor concentrations versus time in subjects with hepatic impairment and matching subjects with normal hepatic function. For subjects with severe hepatic impairment, concentrations were adjusted for dose. Dose-adjusted concentration = (concentration/600 mg) × 1500 mg.

severe hepatic impairment. No AEs were reported in the subjects with normal hepatic function. The most common AE reported was 7 events of diarrhea in 7 subjects (25% of subjects), followed by 2 events of dyspepsia in 2 subjects (7.1% of subjects) (Table 3). All AEs resolved. Fifteen AEs were considered mild in intensity (grade 1), including diarrhea (7 events), dyspepsia (2 events), vomiting (1 event), sinus tachycardia (1 event), pyrexia (1 event), influenza (1 event), ligament sprain (1 event), and headache (1 event). Two nonrelated AEs (nephrolithiasis due to kidney stones and dyspnea due to worsening ascites) were considered moderate in intensity (grade 4). A total of 7 subjects (25.0%) reported 8 AEs that were considered possibly or probably related to the study drug by the investigator. These included 6 events of diarrhea, 1 event of dyspepsia, and 1 event of headache. Overall, liver enzymes generally remained within normal range in all treatment

groups. For some subjects, liver enzymes were out of normal range after treatment with voxelotor, but these instances were deemed not clinically significant.

Discussion

Renal dysfunction is a common comorbidity in patients with SCD. In a retrospective analysis from 2007 to 2012, the annual rate of incidence of acute renal failure and chronic kidney disease was 2- to 3-fold higher in patients with SCD compared with those without SCD.[14] Liver dysfunction is estimated to have a prevalence of 10% in adults with SCD and is expected to increase in the older population.[15]

In 2 open-label clinical studies, we evaluated the safety, tolerability, and PK of voxelotor in subjects with various degrees of renal or hepatic insufficiency. The studies used a single-dose design, as voxelotor

demonstrated linear, dose-proportional PK in single- (dose range, 100-2800 mg) and multiple-dose (dose range: 300-900 mg) cohorts of healthy subjects.[7] Therefore, the results from the single-dose studies on voxelotor can be extrapolated to multiple-dose PK. Due to the preferential partitioning of voxelotor into RBCs, both whole-blood and plasma PK have been considered where appropriate in these studies. Because voxelotor binds to hemoglobin, whole-blood concentrations were used to determine efficacy, and plasma concentrations of voxelotor were considered relevant for safety assessments.

There was no apparent effect of renal function on the excretion of voxelotor based on comparable $t_{1/2}$ values between subjects with severe renal impairment and healthy matched control subjects. AUC_{0-t} and C_{max} values were lower by approximately 50% (plasma) and 25% (whole blood), respectively, in subjects with severe renal impairment compared with those in healthy matched control subjects. This is likely due to the lower hemoglobin/hematocrit levels observed in subjects with severe renal impairment compared with the healthy matched control subjects. A single oral dose of voxelotor 900 mg, administered under fasting conditions to subjects with severe renal impairment and to matched healthy controls, seemed to be safe and well tolerated. No specific dose adjustment is warranted for patients with impaired renal function, as the excretion of voxelotor is mainly nonrenal, and renal function was shown to have minor effects on voxelotor exposure. However, it is important to note that voxelotor has not been evaluated in patients with end-stage renal disease requiring dialysis.[6]

Whole-blood and plasma voxelotor exposures were 87% to 93% higher in subjects with severe hepatic impairment compared with subjects with normal hepatic function, whereas those in subjects with mild to moderate hepatic impairment were only 9% to 21% higher compared with those in subjects with normal hepatic function. Voxelotor was well tolerated at a dose of 1500 mg in subjects with normal hepatic function and mild and moderate hepatic impairment; it was also well tolerated at a dose of 600 mg in subjects with severe hepatic impairment. There was no apparent difference in the incidence or severity of AEs between subjects with severe hepatic impairment at 600-mg doses and other impairment groups. No dose adjustment was warranted in subjects with mild to moderate hepatic impairment. However, based on this increase in exposure in subjects with severe hepatic impairment, a dose adjustment to 1000 mg is recommended.[6] The dose recommendation is limited by the commercially available tablet strength (500 mg), and a further dose reduction to 500 mg daily would lead to considerable underexposure in patients with severe hepatic impair-

ment. In both studies, there were no deaths, serious AEs, or subject discontinuations due to AEs. AEs were mostly mild in severity. These safety and tolerability findings are consistent with those reported in voxelotor clinical trials.[7,16]

Conclusions

In summary, our results indicate that a dosage adjustment of voxelotor is not required in patients with severe renal impairment or in patients with mild or moderate hepatic impairment. A reduction in voxelotor dose to 1000 mg once daily is recommended for patients with severe hepatic impairment.[6] With this dose adjustment, whole-blood and plasma C_{max} values in patients with severe hepatic impairment are expected to be approximately 25% higher than those in patients with normal hepatic function treated at the Food and Drug Administration-approved dose of 1500 mg daily. Considering the broad safety margin for voxelotor, the dose of 1000 mg in patients with severe hepatic impairment is expected to provide a risk-benefit profile similar to that of the dose of 1500 mg in patients with normal hepatic function. PK parameters analyzed in this study are not expected to be different in patients with SCD. Therefore, voxelotor may be considered as a treatment option for patients with SCD with renal or hepatic impairment.

Conflicts of Interest

R.A.P. is an employee of Miller School of Medicine, University of Miami; he received research funding from Global Blood Therapeutics. T.M. is an employee and equity owner of Orlando Clinical Research Center. G.B. is a stockholder of Global Blood Therapeutics. M.G. is an employee of Certara. S.D. is an employee and stockholder of Global Blood Therapeutics. J.L.-G. is a former employee and former stockholder of Global Blood Therapeutics. C.W. is an employee and stockholder of Global Blood Therapeutics.

Data Accessibility Statement

Individual subject data from this clinical study are not available; Global Blood Therapeutics is currently developing a data sharing plan.

References

1. Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med.* 2010;38(4 suppl):S512-21.

2. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. *Nat Rev Dis Primers*. 2018;4:18010.

3. Bunn HF. Pathogenesis and treatment of sickle cell disease. *N Engl J Med*. 1997;337(11):762-769.

4. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. *N Engl J Med*. 2017;376(16):1561-1573.

5. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: A 4-decade observational study of 1056 patients. *Medicine (Baltimore)*. 2005;84(6):363-376.

6. Oxbryta. Prescribing information. South San Francisco, CA: Global Blood Therapeutics, Inc; 2019.

7. Hutchaleelaha A, Patel M, Washington C, et al. Pharmacokinetics and pharmacodynamics of voxelotor (GBT440) in healthy adults and patients with sickle cell disease. *Br J Clin Pharmacol*. 2019;85(6):1290-1302.

8. Howard J, Hemmaway CJ, Telfer P, et al. A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease. *Blood*. 2019;133(17):1865-1875

9. Oksenberg D, Dufu K, Patel MP, et al. GBT440 increases haemoglobin oxygen affinity, reduces sickling and prolongs RBC half-life in a murine model of sickle cell disease. *Br J Haematol*. 2016;175(1):141-153.

10. Rademacher P, Hutchaleelaha A, Washington C, Lehrer J, Ramos E. Absorption, metabolism and excretion of GBT440, a novel hemoglobin S (HbS) polymerization inhibitor for the treatment of sickle cell disease (SCD), in healthy male subjects. *Blood*. 2016;128(22):2487.

11. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry: pharmacokinetics in patients with impaired renal function–study design, data analysis, and impact on dosing and labeling (draft guidance). www.fda.gov/downloads/drugs/guidances/ucm204959.pdf. Published 2010. Accessed June 2, 2020.

12. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for industry: pharmacokinetics in patients with impaired hepatic function—study design, data analysis, and impact on dosing and labeling. https://www.fda.gov/media/71311/download. Published 2003. Accessed June 2, 2020.

13. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-649.

14. Yeruva SL, Paul Y, Oneal P, Nouraie M. Renal failure in sickle cell disease: prevalence, predictors of disease, mortality and effect on length of hospital stay. *Hemoglobin*. 2016;40(5):295-299.

15. Allali S, de Montalembert M, Brousse V, et al. Hepatobiliary complications in children with sickle cell disease: a retrospective review of medical records from 616 patients. *J Clin Med*. 2019;8(9):1481.

16. Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. *N Engl J Med*. 2019;381(6):509-519.