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ORIGINAL RESEARCH ARTICLE

Single-Dose Pharmacokinetics of Milvexian in Participants with Mild or Moderate Hepatic Impairment Compared with Healthy Participants

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Abstract

Background Patients with hepatic impairment receiving antithrombotic agents metabolized primarily through the liver can be at risk for bleeding. Milvexian (BMS-986177/JNJ-70033093) is a small-molecule, active-site inhibitor of activated Factor XI (FXIa). Modulation of FXI may provide systemic anticoagulation without increased risk of clinically significant bleeding.

Objective This open-label study evaluated the effects of mild or moderate hepatic impairment on the pharmacokinetics of milvexian to assess their impact on safety and dosing.

Methods Single doses of milvexian 60 mg were administered to participants with mild hepatic impairment ($n = 9$), moderate hepatic impairment ($n = 8$), and normal hepatic function ($n = 9$). Healthy participants were matched to participants with hepatic impairment by body weight, age, and sex. Analysis of variance was performed on natural log-transformed milvexian exposure parameters, with hepatic function group as a fixed effect.

Results Single doses of milvexian 60 mg were generally well tolerated, with no serious adverse events (AEs), bleeding AEs, or discontinuations due to AEs. Geometric mean ratios (90% confidence interval) for total milvexian maximum observed plasma concentration and area under the plasma concentration–time curve from time zero extrapolated to infinite time were 1.180 (0.735–1.895) and 1.168 (0.725–1.882), respectively, for mild hepatic impairment versus normal hepatic function and 1.140 (0.699–1.857) and 0.996 (0.609–1.628), respectively, for moderate hepatic impairment versus normal hepatic function. Across groups, milvexian exposure–related increases were observed for activated partial thromboplastin time.

Conclusion Milvexian was well tolerated in participants with normal, mildly impaired, and moderately impaired hepatic function. Observed pharmacokinetic changes suggest it is unlikely that dose adjustments will be necessary in patients with mild or moderate hepatic impairment. Clinical Trial RegistrationClinicaltrials.gov identifier: NCT02982707.

1 Introduction

Vascular and thromboembolic diseases, including ischemic heart disease and stroke, remain the leading causes of death and disability worldwide [1, 2]. Although current antithrombotic therapies can reduce the risk of serious adverse vascular and thromboembolic events in high-risk patients with cardiovascular disease, these therapies are also associated with an increased risk of major bleeding [3]. Thus, new therapies are needed that can provide a better risk–benefit balance than currently available treatments.

The physiologic processes that control clot formation and dissolution are known as the coagulation cascade. These complex series of pathways are regulated by serine proteases and activation factors to maintain a balance of thrombosis and hemostasis. However, if imbalances develop within the coagulation cascade, elevated levels of serum proteases can contribute to pathologic venous and/or arterial thrombosis [4–7].

Scientific evidence accumulated to date from genetic, epidemiologic, preclinical, and clinical studies suggests that inhibition of the coagulation cascade protease Factor XI (FXI) is a promising novel therapeutic target. Specifically, individuals with inherited FXI deficiency have been shown to have a decreased risk for adverse cardiovascular events and venous thromboembolism, with very low rates of

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Key Points

This open-label study evaluated the effects of mild or moderate hepatic impairment on the pharmacokinetics of milvexian (BMS-986177/JNJ-70033093), a small-molecule, active-site inhibitor of activated Factor XI, to assess their impact on safety and dosing.

Results demonstrated that milvexian 60 mg was well tolerated in participants with normal hepatic function and in those with mild or moderate hepatic impairment after a single dose.

Observed pharmacokinetic changes suggest it is unlikely that dose adjustments will be necessary in patients with mild or moderate hepatic impairment.

spontaneous bleeding events [8–13]. In contrast, individuals with elevated plasma FXI levels have been shown to be at increased risk for venous thrombosis [14]. Additionally, in patients with a history of or high risk for cardiovascular disease, elevated levels of FXI are associated with an increased risk for stroke, transient ischemic attack, and myocardial infarction [15–17]. Taken together, these data indicate that modulation of FXI function may provide a novel mechanism for systemic anticoagulation without increasing the risk of clinically significant bleeding in a variety of conditions where patients are predisposed to a high risk of thrombotic or bleeding events.

Milvexian (BMS-986177/JNJ-70033093) is a potent small molecule that inhibits the active form of FXI (FXIa) with high affinity and selectivity. Milvexian is one of the first oral FXIa inhibitors being developed to prevent thrombotic events in multiple patient populations. Results from preclinical studies using animal models of arterial and venous thrombosis have shown that milvexian has antithrombotic activity while preserving hemostasis [18].

It is known that hepatic impairment alters the pharmacokinetics of several anticoagulants that target the coagulation cascade, including the activated Factor X (FXa) inhibitors rivaroxaban, apixaban, and edoxaban and the thrombin inhibitor dabigatran. The disposition of these drugs in patients with hepatic impairment can be impacted by altered metabolism in the liver as well as decreased synthesis of coagulation factors, which can increase bleeding risk [6, 19].

Milvexian is predominantly metabolized by cytochrome P450 (CYP)-3A4, with minor contributions from CYP3A5. In animal studies, excretion of milvexian occurred mainly through metabolism (~ 40–50% of the administered dose) and direct biliary excretion (~ 30% of the dose). The study reported herein investigated the pharmacokinetics, pharmacodynamics, safety, and tolerability of milvexian in participants with hepatic impairment to inform appropriate dosing strategies in this population based on available guidance from the US FDA and the European Medicines Agency, among others [20–22]. A recently completed phase II study showed that milvexian was effective for the prevention of venous thromboembolism and was associated with a low risk of bleeding in patients undergoing knee arthroplasty [23]. A second, ongoing, phase II study is evaluating the potential of milvexian to prevent secondary ischemic stroke in patients receiving aspirin and clopidogrel [24]. Investigating hepatic impairment, which encompasses decreased metabolism in addition to changes in protein binding and is typical of many disease states in older populations with cardiovascular conditions, provided important information on dosing of milvexian.

2 Methods

2.1 Study Design

This open-label, parallel-group, nonrandomized study was conducted at three clinical sites in the USA from 7 March 2018 to 28 September 2018. Key study objectives were to evaluate the pharmacokinetics, safety, and tolerability of a single oral dose of milvexian 60 mg in participants with normal hepatic function, mild (Child–Pugh class A) hepatic impairment, and moderate (Child–Pugh class B) hepatic impairment (Fig. 1) [25]. Healthy participants were matched to participants with hepatic impairment in each Child–Pugh class by body weight, age, and sex. Selection of the 60 mg dose was based on in vivo preclinical pharmacology data from the rabbit electric arterial thrombosis model, differences in the affinity of milvexian for rabbit and human FXIa, and modeling results, as described in the Dose Selection Considerations section [18].

Participants were screened for eligibility within 28 days prior to study drug administration. Eligible participants were admitted to the clinical facility the morning prior to dosing (day −1). On day 1, participants received a single oral dose of milvexian 60 mg in the fasted state. Participants remained at the clinical facility, and serial pharmacokinetic samples were collected for up to 72 h after study drug administration for healthy participants and for up to 96 h for participants with hepatic impairment.

2.2 Participants

Eligible participants included men and women of non-childbearing potential, with an age range of 18–70 years and a body mass index of 20–38 kg/m^2. Participants were assigned to one of three groups: normal hepatic function or mild (Child–Pugh class A) or moderate (Child–Pugh class B) hepatic impairment. Participants with normal hepatic function were matched to each of the hepatic impairment groups with regards to body weight, age, and sex. Healthy participants were required to have normal renal function at screening (estimated glomerular filtration rate [eGFR] > 80 mL/min/1.73 m^2 and absence of proteinuria). Participants with hepatic impairment were required to have eGFR > 60 mL/min/1.73 m^2, to have stable hepatic impairment (i.e., no clinically significant change in disease status within 6 months prior to screening), and to be on a stable dose of medication and/or treatment regimen for 60 days prior to administration of study medication.

Participants with normal hepatic function were excluded if they had any significant chronic medical illness, used tobacco- or nicotine-containing products within 6 months prior to administration of study drug, or abused drugs or alcohol within 6 months of study drug administration.

Study participants were prohibited from using strong or moderate CYP3A inhibitors within 2 weeks of enrollment and strong or moderate CYP3A inducers within 4 weeks of enrollment and from consuming grapefruit-containing products from 7 days prior to dosing until study discharge, alcohol-containing beverages from 3 days prior to day −1 until study discharge, and caffeine-containing products from 3 days prior to dosing until study discharge. Healthy participants were not permitted to consume tobacco- or nicotine-containing products throughout the study. All participants were required to fast from 8 h prior to until 4 h after study drug administration.

2.3 Study Assessments

2.3.1 Safety

Safety and tolerability were evaluated based on medical review of adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation, as well as changes in clinical laboratory parameters, 12-lead electrocardiogram (ECG) measures, vital signs, and physical examination findings. Information on non-SAEs was collected from study initiation until discharge. AEs and medical history were coded according to the *Medical Dictionary for Regulatory Activities* version 20.1.

2.3.2 Pharmacokinetics

Blood samples for pharmacokinetic assessments were collected at time 0 (predose) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 72 h after dosing for all study participants. Another blood sample was collected at 96 h after dosing for participants with hepatic impairment. Blood samples were also collected at 3 and 24 h for assessment of protein binding.

Plasma samples were analyzed for milvexian concentration using a validated liquid chromatography tandem mass spectrometry (LC–MS/MS) assay. Plasma protein was measured using a partially validated equilibrium dialysis LC–MS/MS assay. Both LC–MS/MS assays had a lower limit of quantification of 1.00 ng/mL and an upper limit of quantification of 1000 ng/mL.

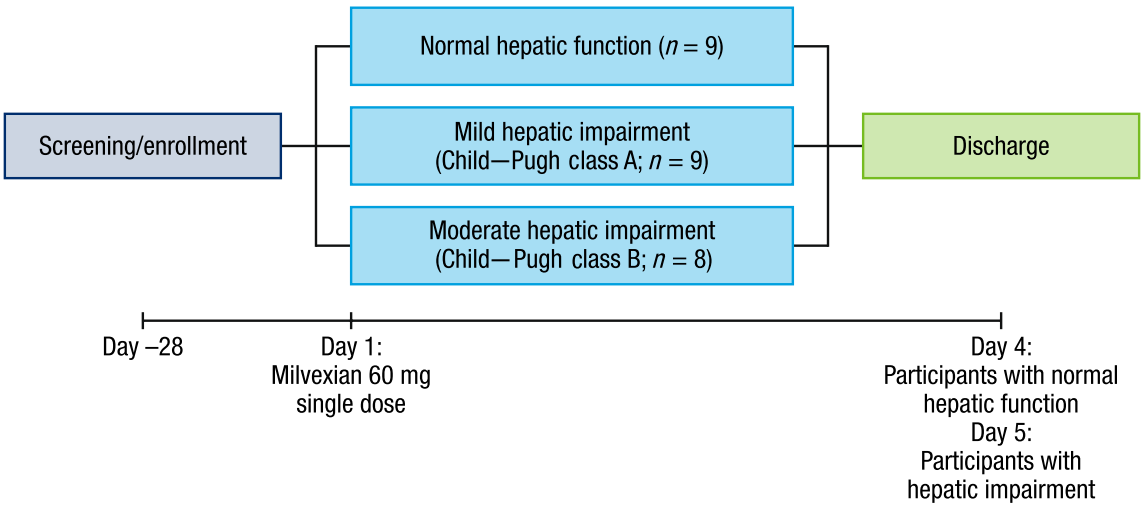

Fig 1 Study design

The single-dose pharmacokinetic properties of both total and unbound milvexian were derived from plasma concentration versus time data. Assessed parameters included fraction of unbound drug, maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration–time curve (AUC) from time zero to 72 h ($AUC_{(0–72\ h)}$), AUC from time zero to the time of last quantifiable concentration ($AUC_{(0–t)}$), AUC from time zero extrapolated to infinite time ($AUC_{(INF)}$), terminal plasma half-life ($t_{½}$), apparent total body clearance, and terminal phase apparent volume of distribution.

2.3.3 Pharmacodynamics

Blood samples for exploratory pharmacodynamic assessment of activated partial thromboplastin time (aPTT) and FXI clotting activity (FXIc) were collected at time 0 (predose) and at 0.5, 2, 3, 4, 8, 12, 24, 48, and 72 h after dosing for all study participants and at 96 h for participants with hepatic impairment. The pharmacodynamic parameters aPTT and FXIc were measured with validated assays at LabCorp Colorado Coagulation (Englewood, CO, USA). The assays were performed on a Siemens BCS®XP analyzer. The aPTT assay was performed using the Dade®Actin® FS reagent (Siemens Healthcare Diagnostics Inc). FXIc was measured with a modification of aPTT using the Dade®Actin® FS reagent. The activity of FXI in the study sample was derived from a calibration curve prepared using calibrators (Standard Human Plasma, Siemens Healthcare Diagnostics Inc.) with a range of known concentrations of human FXI. Briefly, the study sample to be tested was mixed with FXI-deficient plasma, the aPTT reagent was then added, and the mixture was incubated. Following incubation, calcium chloride was added to the mixture, the time to clot formation was compared with those of the calibrators, and the FXI activity level was interpolated.

The relationship between milvexian concentration and the mean change and mean percentage change from baseline in aPTT and FXIc over time were explored graphically. The baseline value was defined as the last nonmissing result collected prior to the first dose of study medication.

2.4 Pharmacokinetic and Statistical Analysis

The sample size for this study was not based on statistical power. Rather, the sample size was determined based on consideration of the precision of the estimate of geometric mean ratios (GMRs; 90% confidence interval [CI]) of C_{max} and AUC for milvexian in participants with hepatic impairment compared with participants with normal hepatic function, assuming an inter-participant coefficient of variation of 24% for C_{max} and 12% for AUC; these assumptions were based on results from previous studies [26].

Safety was assessed for all treated participants who received a dose of study drug. The pharmacokinetic population was defined as all participants who received milvexian and had any available concentration–time data. The evaluable pharmacokinetic population was defined as all participants who had adequate pharmacokinetic profiles. The pharmacodynamic population was defined as all participants who received one dose of study drug and had any available pharmacodynamic biomarker data.

Descriptive summaries were generated for categorical safety variables, including AEs, SAEs, deaths, AEs leading to discontinuation, and AEs of clinically significant bleeding. Results were summarized descriptively for 12-lead ECG parameters, vital signs, and clinical laboratory tests that were outside prespecified criteria.

All plasma pharmacokinetic data were summarized by hepatic function group and nominal collection time for total and unbound milvexian. An analysis of variance was performed on natural log-transformed values for C_{max}, $AUC_{(INF)}$, and $AUC_{(0–t)}$, with hepatic function group as a fixed effect. Point estimates and 90% CIs on the natural log scale for differences between least squares means of each hepatic impairment group and the healthy group were exponentiated to express the results as GMRs on the original scale. No adjustments were made for multiplicity.

Results for the exploratory pharmacodynamic biomarkers of aPTT and FXIc were summarized descriptively by group. Plots of mean (standard error) aPTT and FXIc values over time and plots of percentage change from baseline in aPTT and FXIc were generated.

Individual pharmacokinetic parameter values were calculated by noncompartmental methods using Phoenix™ WinNonlin® (Pharsight Corporation, Palo Alto, CA, USA; version 6.2 or higher) software with actual sampling times.

2.5 Dose Selection Considerations

At the time of designing this study, limited information was available on the pharmacokinetics of milvexian. The first in human (FIH) study was ongoing and had completed single doses up to 500 mg [26]. The goal of dose selection in this study was to identify a dose that would not exceed exposures that had been investigated in the FIH study. The anticipated exposures of the dose selected also needed to produce meaningful changes in the aPTT and FXIc based on data from the single ascending dose study. Further, the anticipated exposures also lie within the targets for antithrombotic efficacy derived from the rabbit preclinical thrombosis models. Therefore, Simcyp PBPK simulator v15 was employed using a minimal physiological based pharmacokinetic (PBPK) model developed for milvexian to estimate the potential increase in exposures when simulating varying degrees of hepatic impairment based on Child–Pugh scores.

Table 1 shows the predicted fold increase in C_{max} when evaluating severe, moderate, and mild hepatic impairment populations from the Simcyp simulator compared with healthy volunteers was 1.68, 1.57, and 1.21, respectively; when comparing AUC, the fold increase was 3.12, 2.23, and 1.29, respectively. Therefore, the dose selected in this study was chosen taking these simulations into account.

3 Results

3.1 Participants

A total of 26 participants entered the treatment period and completed the study, including nine participants with normal hepatic function, nine with mild hepatic impairment, and eight with moderate hepatic impairment. All 26 participants received a single dose of milvexian and were included in the safety, pharmacokinetic, and pharmacodynamic analysis populations. Baseline characteristics were generally similar between groups (Table 2).

3.2 Safety and Tolerability

Milvexian 60 mg was safe and well tolerated when administered as a single oral dose to participants with mild or moderate hepatic impairment and to participants with normal hepatic function. There were no deaths, SAEs, or treatment discontinuations due to AEs during the study. Overall, 2 of 26 participants (7.7%) reported a total of three AEs, including two events of headache and one event of fatigue. These AEs were considered mild or moderate in intensity, and all three events resolved within a few hours. All three AEs were assessed by study investigators as being related to milvexian.

There were no bleeding AEs or clinically meaningful abnormalities based on clinical laboratory results, 12-lead ECGs, vital signs, or physical examinations. Notably, there were no reports of drug-induced liver injury (defined as alanine or aspartate aminotransferase levels > 3 times the upper limit of normal [ULN]), total bilirubin > 2 times the ULN without initial findings of cholestasis, and no other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia. One participant in the moderate hepatic impairment group had consistently elevated aspartate aminotransferase > 3 times the ULN (range 72–136 U/L), alkaline phosphatase > 1.5 times the ULN (range 197–217 U/L), and total bilirubin > 2 times the ULN (range 90.6–164.2 µmol/L) before, during, and after treatment with milvexian. Aspartate aminotransferase, alkaline phosphatase, and total bilirubin ranges were 15–159 U/L, 48–224 U/L, and 5.1–164.2 µmol/L, respectively, among

Table 1 Predicted C_{max} and AUC fold changes in milvexian exposure in mild, moderate, and severe hepatic impairment relative to healthy volunteers

Hepatic impairment	C_{max} fold change to healthy volunteers	AUC fold change to healthy volunteers
Severe (Child–Pugh class C)	1.68	3.12
Moderate (Child–Pugh class B)	1.57	2.23
Mild (Child–Pugh class A)	1.21	1.29

AUC area under the plasma concentration–time curve, C_{max} maximum observed plasma concentration

Table 2 Baseline demographic characteristics

Characteristic	Hepatic function			Total ($N = 26$)
	Normal ($n = 9$)	Mild impairment ($n = 9$)	Moderate impairment ($n = 8$)	
Sex				
Female	4 (44.4)	4 (44.4)	3 (37.5)	11 (42.3)
Male	5 (55.6)	5 (55.6)	5 (62.5)	15 (57.7)
Age, years	52.6 ± 7.62	59.0 ± 6.22	56.3 ± 6.50	55.9 ± 7.09
Race				
White	6 (66.7)	8 (88.9)	7 (87.5)	21 (80.8)
Black or African American	3 (33.3)	0	1 (12.5)	4 (15.4)
Asian	0	1 (11.1)	0	1 (3.8)
Body mass index, kg/m^2	30.22 ± 4.42	32.41 ± 4.80	28.51 ± 3.82	30.45 ± 4.50

Data are presented as mean ± standard deviation or *n* (%)

all participants in the moderate impairment group and 10–159 U/L, 44–680 U/L, and 3.4–164.2 µmol/L, respectively, in the overall population before, during, and after treatment with milvexian.

3.3 Pharmacokinetics

Plasma concentration–time curves for total and unbound milvexian are shown in Fig. 2a and b, respectively. Pharmacokinetic parameters summarized in Table 3 indicate that, following administration of a single dose of 60 mg, milvexian was rapidly absorbed, with a median t_{max} of 2.00–4.00 h across hepatic function groups. Mean $t_{½}$ ranged from 11.9–15.0 h. There was no trend of prolonged elimination in participants with mild or moderate hepatic impairment compared with participants with normal hepatic function. Plasma protein binding for milvexian was moderate to high. The geometric mean fraction of unbound milvexian increased with the severity of hepatic impairment, at 7.75%, 8.52%, and 9.55% for participants with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment, respectively.

As shown in Fig. 3, the geometric mean exposure parameters (C_{max}, $AUC_{(INF)}$, and $AUC_{(0–t)}$) for total and unbound milvexian tended to be higher in participants with hepatic impairment than in those with normal hepatic function. However, individual values overlapped across the hepatic function groups, and the 90% CIs for GMRs were wide and all contained the unity of 1, suggesting no meaningful differences.

3.4 Pharmacodynamic Biomarkers

3.4.1 aPTT

As shown in Fig. 4a, aPTT increased in an exposure-related manner following administration of single oral doses of milvexian 60 mg. Maximal mean percentage changes occurred at times close to t_{max}, which is consistent with known milvexian pharmacology. Maximal percentage increases from baseline in aPTT were approximately 90% in both the mild and the moderate hepatic impairment groups and approximately 76% in participants with normal hepatic function. Mean aPTT returned to baseline by 48 h in participants with mild hepatic impairment and normal hepatic function and approximately 72 h post-dose in participants with moderate hepatic impairment.

aPTT values increased as milvexian total and unbound plasma concentrations increased, with the exposure–response relationship appearing to be similar between the group with normal hepatic function and those with hepatic impairment (Fig. 5a).

3.4.2 FXIc

Exposure-related decreases were observed in mean FXIc following single-dose administration of milvexian, with maximal percentage decreases from baseline observed at approximately 4 h post-dose (Fig. 4b). The maximal mean percentage decrease in FXIc was approximately 37% in participants with mild hepatic impairment and 32% in participants with moderate hepatic impairment, compared with 30% in participants with normal hepatic function. FXIc returned to near-baseline values by 48 h post-dose in all hepatic function groups.

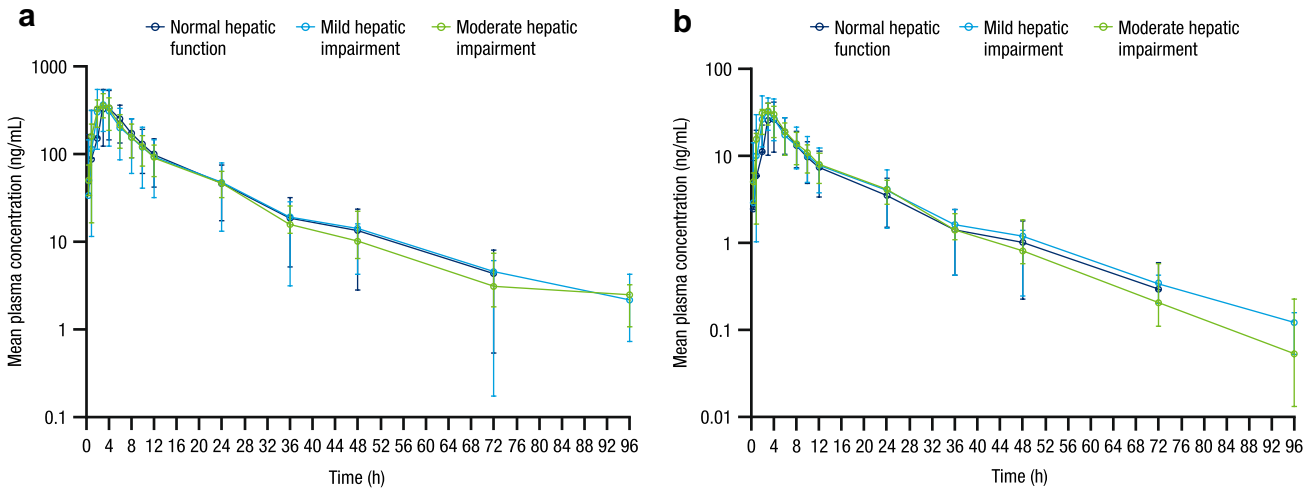

Fig 2 Mean (± standard deviation) plasma (**a**) total and (**b**) unbound milvexian concentration versus time profiles

Table 3 Milvexian pharmacokinetic parameters

Parameter[a]	Total			Unbound		
	Normal hepatic function ($n = 9$)	Mild hepatic impairment ($n = 9$)	Moderate hepatic impairment ($n = 8$)	Normal hepatic function ($n = 9$)	Mild hepatic impairment ($n = 9$)	Moderate hepatic impairment ($n = 8$)
Fraction unbound	NE	NE	NE	0.0775 (10.5)	0.0852 (8.6)	0.0955 (14.3)
C_{max}, ng/mL	318 (53.0)	375 (29.3)	362 (51.7)	24.6 (50.0)	31.9 (27.0)	34.6 (41.6)
t_{max}, h	4.00 (1.00; 6.00)	3.00 (2.00; 4.00)	2.00 (2.00; 4.00)	NE	NE	NE
$AUC_{(0–72\ h)}$, h·ng/mL	3148 (57.1)	3660 (36.4)	3166 (57.6)	244 (52.3)	312 (34.3)	302 (47.8)
$AUC_{(0–t)}$, h·ng/mL	3141 (57.3)	3699 (36.8)	3165 (58.1)	243 (52.5)	315 (34.7)	302 (48.4)
$AUC_{(INF)}$, h·ng/mL	3218 (57.1)	3758 (36.1)	3205 (57.9)	249 (52.6)	320 (33.9)	306 (48.0)
$t_{½}$, h	13.3 ± 3.43	15.0 ± 3.39	11.9 ± 4.83	NE	NE	NE
CLT/F, L/h	18.6 (90.6)	16.0 (27.4)	18.7 (69.6)	241 (79.4)	187 (26.9)	196 (58.8)
Vz/F, L	347 (99.6)	338 (29.4)	300 (45.4)	4472 (87.2)	3971 (31.6)	3140 (39.1)

AUC area under the plasma concentration–time curve, $AUC_{(0–72\ h)}$ AUC from time zero to 72 h, $AUC_{(0–t)}$ AUC from time zero to the time of last quantifiableconcentration, AUC (INF) AUC from time zero extrapolated to infinite time, CLT/F apparent total body clearance, C_{max}, maxmum observed plasma concentration, NE not estimated, $t_{½}$ terminal plasma half-life, t_{max} time to maximum observed plasma concentration, Vz/F terminal phase apparent volume of distribution

[a]Values are geometric mean (geometric coefficient of variation) for fraction unbound, C_{max}, AUCs, CLT/F, and Vz/F; arithmetic mean ± standard deviation for $t_{½}$; and median (minimum; maximum) for t_{max}

FXIc values decreased as milvexian total and unbound plasma concentration increased, with the exposure–response relationship appearing to be similar between the group with normal hepatic function and those with hepatic impairment (Fig. 5b).

4 Discussion

Hepatic impairment has been shown to alter the metabolism of several currently available anticoagulants, which may result in increased bleeding risk [19]. Therefore, it is important to fully characterize the safety and pharmacokinetic properties of potential new antithrombotic agents. The current study investigated the pharmacokinetics, pharmacodynamics, safety, and tolerability of the small-molecule, orally administered FXIa inhibitor milvexian in individuals with mild or moderate hepatic impairment compared with healthy participants with normal hepatic function. A key objective of this study was to provide data to inform milvexian dosing recommendations in patients with hepatic impairment. Data from this study are considered important to ensure the pharmacokinetic properties of milvexian complement the FXIa mechanism to provide a safe antithrombotic agent that can be used in a broad patient population.

Results of this study demonstrated that a single dose of milvexian 60 mg was safe and well tolerated in participants with mild (Child–Pugh class A) or moderate (Child–Pugh class B) hepatic impairment and in healthy participants with normal hepatic function. Across all hepatic function groups, a total of three AEs were observed in two participants (two events of headache and one event of fatigue), all of which were mild or moderate in intensity and resolved within a few hours.

The observed plasma concentration of milvexian over time showed that the drug was steadily absorbed, with a median t_{max} of 2.0–4.0 h, then eliminated with a mean terminal elimination $t_{½}$ of 11.9–15.0 h. There were slight increases in exposure to total milvexian (C_{max} and $AUC_{(INF)}$ both increased by up to 18%) and to unbound milvexian (C_{max} increased by up to 40% and $AUC_{(INF)}$ by up to 30%) in participants with mild or moderate hepatic impairment compared with normal hepatic function. There was a high degree of interparticipant variability, with wide and overlapping GMR 90% CIs across hepatic function groups, and there was no trend of prolonged elimination in participants with mild or moderate hepatic impairment compared with normal hepatic function.

Interestingly, the study showed that the total milvexian exposures were elevated in the mild hepatic impairment group compared with the moderate group, which is likely a reflection of the Child–Pugh scores that reflect multiple aspects of health and not just drug-metabolizing capacity in addition to the diversified elimination of milvexian. The Simcyp PBPK simulator predicted exposures in mild hepatic impairment close to the observed study results, whereas it overpredicted the moderate hepatic impairment.

Exploratory assessments of pharmacodynamic biomarkers showed that participants with and without hepatic impairment had rapid increases in aPTT (90 and 76%, respectively) and decreases in FXIc (32–37 and 30%, respectively) after receiving a single dose of milvexian 60 mg.

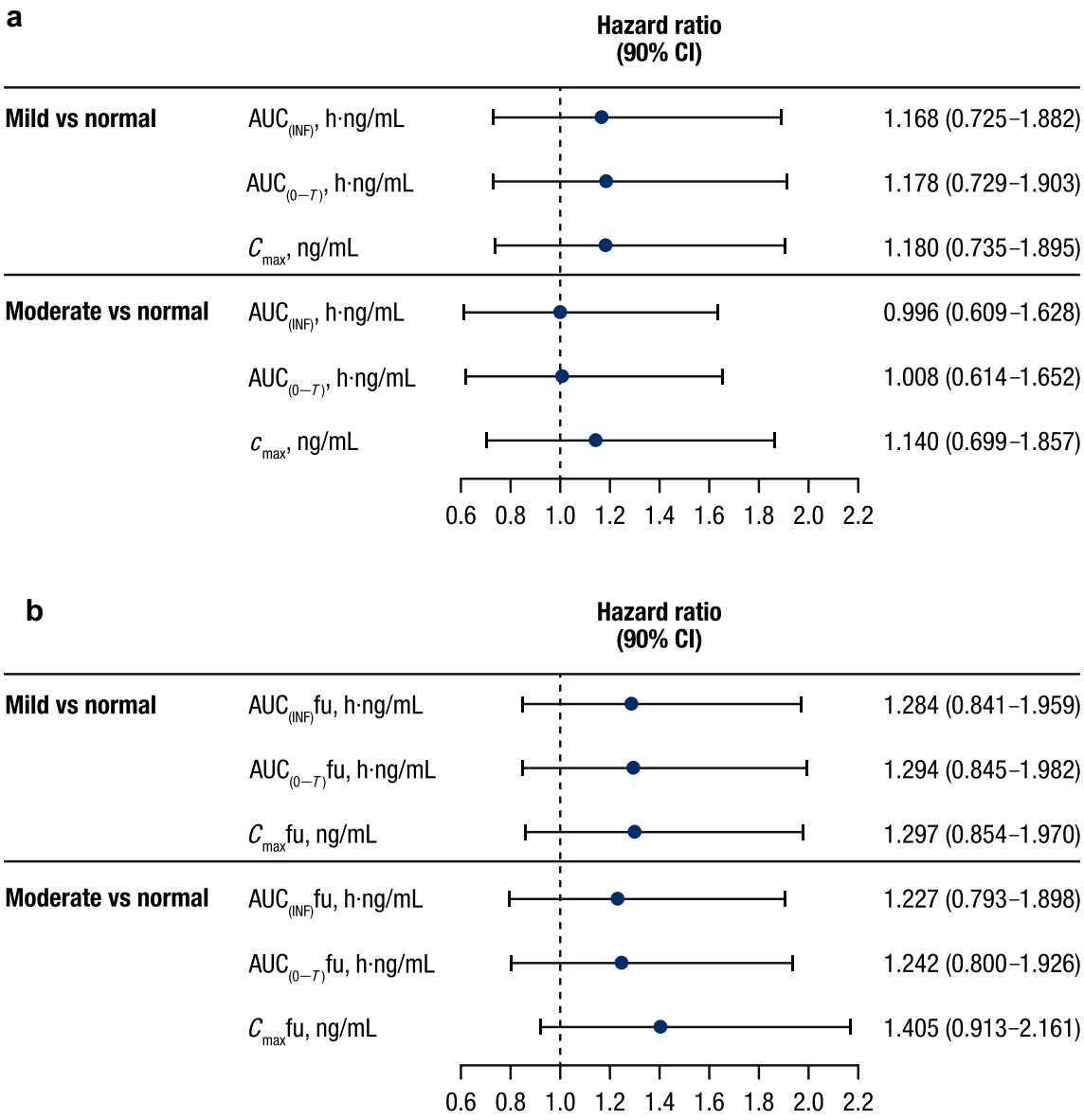

Fig 3 Effects of hepatic impairment on (**a**) total and (**b**) unbound milvexian pharmacokinetic properties. $AUC_{(0-t)}$ area under the plasma concentration–time curve from time zero to the time of last quantifiable concentration, $AUC_{(INF)}$ area under the plasma concentration–time curve from time zero extrapolated to infinite time, *CI* confidence interval, C_{max} maximum observed plasma concentration, *fu* fraction unbound

A good relationship was observed between aPTT and milvexian concentrations among all hepatic groups. When accounting for the protein binding, a more precise relationship between the unbound drug concentration of milvexian and key biomarkers aPTT and FXIc was observed. This is indicative of there being no additional changes to the mechanism of milvexian in participants with hepatic impairment beyond protein binding.

The increases in milvexian exposure observed in this study are comparable to FXa inhibitors, such as apixaban and rivaroxaban, that are primarily metabolized through the liver. In previous studies, rivaroxaban 10 mg increased the AUC 2.27-fold and apixaban 5 mg increased the AUC 1.09-fold in participants with moderate hepatic impairment [19]. In addition to altering the metabolism of FXIa and FXa inhibitors, severe liver disease can prolong aPTT, although the true bleeding risk for patients may not be as serious as the assay results suggest [19].

A limitation of this study is that safety data were obtained from a small sample of participants with mild or moderate hepatic impairment after only a single dose of milvexian. The wide CIs observed in the study were in part driven by

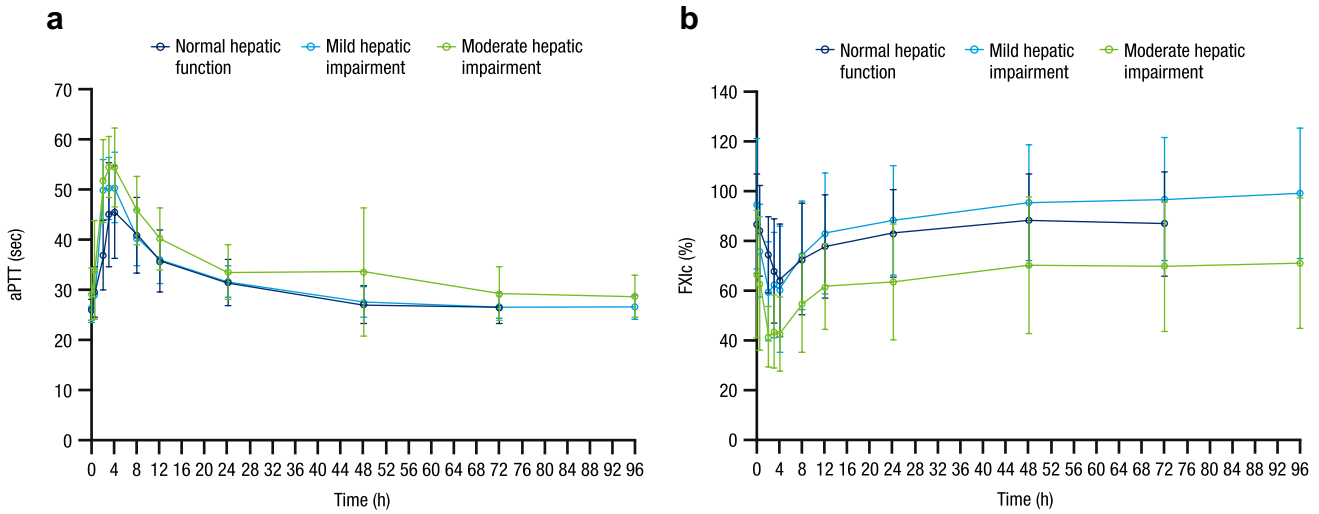

Fig 4 Mean (± standard deviation) (**a**) aPTT and (**b**) FXIc profile over time for milvexian. *aPTT* activated partial thromboplastin time, *FXIc* Factor XI clotting activity

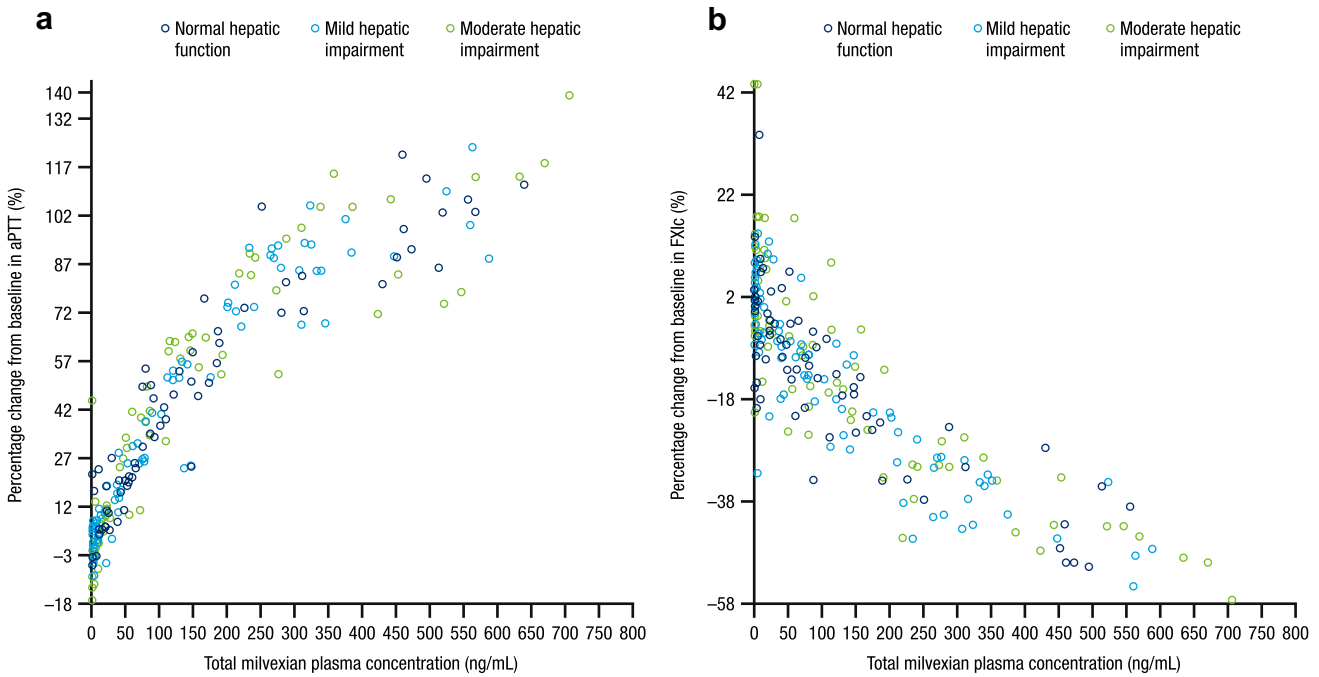

Fig 5 Percentage change from baseline in (**a**) aPTT and (**b**) FXIc versus plasma concentrations of milvexian. *aPTT* activated partial thromboplastin time, *FXIc* Factor XI clotting activity

the unexpected high variability observed in the group with normal hepatic function. Previous studies have demonstrated that the expected variability in pharmacokinetics of milvexian 60 mg is ~ 20%, whereas > 50% variability was observed in this study. This larger variability is likely due to the small sample size and thus the larger influence of a single participant on the pharmacokinetics. Additionally, participants with severe hepatic impairment were not included, as dose adjustment considerations cannot be directly made based on an observed increase in exposure alone. This is because synthesis of coagulation factors occurs in the liver, and patients with severe hepatic impairment may have deficiencies in multiple blood factors that cause coagulation disorders [27]. Additional, larger studies are needed to investigate the safety and efficacy of treatment with milvexian in broader populations of patients who may receive milvexian in routine

clinical care, including those with a wide range of hepatic function.

5 Conclusions

Milvexian 60 mg was well tolerated in participants with normal hepatic function and in those with mild or moderate hepatic impairment after a single dose. An important consideration from this study is that the accumulation of milvexian in hepatic impairment is not expected to be substantially changed relative to healthy volunteers when considering steady-state concentrations. Assuming no other changes are caused by hepatic impairment, except plasma protein binding as indicated in this study, the relationship between dose and pharmacodynamic response will not change. Further integration of data from the current study with phase II patient data through population pharmacokinetic and exposure–response analysis will enable investigation of whether dose adjustment of milvexian is necessary.

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Declarations

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Conflict of interest VP, GA, DL, ZW, SL, WC, AB, and BM are full-time employees of Bristol Myers Squibb. LZ is a full-time employee of Janssen Research & Development, LLC.

Availability of data and material The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

Code availability Not applicable.

Authors' contributions VP, GA, DL, ZW, LZ, SL, WC, AB, and BM contributed to the study design and concept, data analysis and review, data interpretation, and manuscript review.

Ethics approval This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and underlying EU Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50). Good clinical practice was followed, as defined by the International Council for Harmonisation. The study was registered with ClinicalTrials.gov (NCT02982707). The study protocol and all amendments were reviewed and approved by the Chesapeake Institutional Review Board, Columbia, MD, USA, according to specifications outlined in applicable regulations.

Consent to participate Prior to beginning the study, all participants provided written informed consent, including consent for any screening procedures conducted to establish participant eligibility for the study.

Consent for publication Not applicable.

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