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ARTICLE

Pharmacokinetics, pharmacodynamics, and safety of asundexian in healthy Chinese and Japanese volunteers, and comparison with Caucasian data

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Abstract

There is an unmet clinical need for effective anticoagulant therapies for the management of thromboembolic diseases that are not associated with a relevant risk of bleeding. Asundexian (BAY 2433334) is an oral, direct, small-molecule inhibitor of activated factor XI (FXIa). Phase I data from healthy Caucasian male participants indicated predictable pharmacokinetic (PK) and pharmacodynamic (PD) profiles and no clinically relevant bleeding-related adverse events (AEs). Reported here are data from two phase I, randomized, placebo-controlled, single- and multiple-dose escalation studies of asundexian conducted in 60 healthy men: 24 Japanese and 36 Chinese. Baseline characteristics were comparable between the treatment groups. All treatment-emergent AEs were mild, with no serious AEs or AEs of special interest reported. Systemic exposure to asundexian increased dose proportionally after single or multiple dosing, with relatively low accumulation following multiple once-daily dosing in both Chinese and Japanese volunteers. Asundexian induced dose-dependent prolongation of activated partial thromboplastin time and inhibition of FXIa activity, with no effects on prothrombin time or FXI concentration in Japanese participants. There were no clinically relevant interethnic differences in PK profile across the Japanese, Chinese, and Caucasian (data from the previous phase I study) participants and no clinically relevant difference in PD response between Japanese and Caucasian participants.

Study highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Asundexian (BAY 2433334) is a novel, developmental, oral, small-molecule inhibitor of activated factor XI (FXIa). Its mode of action offers the potential for reduced thrombus formation without a substantially increased risk of bleeding. Multiple dosing of asundexian in healthy Caucasian volunteers was well tolerated in phase I studies, with predictable pharmacokinetic (PK) and pharmacodynamic (PD) profiles and no clinically relevant cytochrome P450 3A4 induction or inhibition.

WHAT QUESTION DID THIS STUDY ADDRESS?

What are the safety, PK, and PD profiles of asundexian in Chinese/Japanese populations, and are there differences to those in Caucasians?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The data from these studies demonstrated that multiple once-daily dosing of asundexian was well tolerated in healthy Japanese and Chinese individuals, with no clinically relevant bleeding, and showed predictable PK and PD profiles supporting once-daily dosing. A comparison of data from the Japanese and Chinese studies with those reported previously for Caucasian individuals identified no clinically relevant differences in PK and PD parameters.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Asundexian has the potential to be a valuable asset in the treatment of thromboembolic disorders, in which there is an unmet need for effective treatments that are not limited by an associated increased risk of bleeding. These data are consistent with earlier phase I findings in Caucasian individuals, and support further clinical development of asundexian in patients with thromboembolic disease, including those of Chinese/Japanese ethnicity.

INTRODUCTION

Thromboembolic diseases are a major cause of mortality and morbidity worldwide, causing or contributing to acute cardiovascular diseases including myocardial infarction and stroke.[1] Although anticoagulants are a cornerstone for the treatment of thromboembolic disorders, an unmet clinical need remains for anticoagulant therapies that effectively prevent thrombotic events without increasing the risk for clinically relevant bleeding.

Coagulation occurs via a cascade initiated by either the intrinsic pathway or the extrinsic pathway, which then converge into a common pathway. Clotting factors in the intrinsic pathway, such as factor XI (FXI) and activated FXI (FXIa), represent attractive therapeutic targets.[2,3] Published evidence indicates that reduced FXIa activity could provide antithrombotic benefits with minimal impact on bleeding risk, distinguishing FXIa inhibitors as promising candidates for safe anticoagulation.[3,4]

Asundexian (BAY 2433334) is an oral small-molecule FXIa inhibitor that has shown promising tolerability and predictable pharmacokinetic (PK) and pharmacodynamic (PD) profiles in phase I studies. In two phase I studies in healthy Caucasian participants, single and multiple dosing of asundexian was well tolerated, with no bleeding-related adverse events (AEs), and similar bleeding times were reported in participants who received a single dose of asundexian or placebo.[5,6] Exposure of asundexian increased dose proportionally over 25–100 mg once daily (OD), and the PK of asundexian appeared to be independent of time after multiple dosing. At steady state, 50%–72% accumulation (for area under the plasma concentration–time curve [AUC]) was observed for doses between 25 and 100 mg OD, with a mean terminal half-life of 15.8 to 17.8 h, supporting the use of OD dosing. Asundexian prolonged activated partial thromboplastin time (aPTT) and inhibited FXIa activity; both effects were dose-dependent.[5,6]

Herein, findings from two phase I studies that investigated the safety, PK, and PD profiles of asundexian after single and multiple OD dosing in healthy Japanese and Chinese participants are reported. We also present an interethnic evaluation of the PK and PD of asundexian across studies conducted in healthy Caucasian,[5] Japanese, and Chinese participants.

METHODS

Study design

Two phase I, single-center, randomized, placebo-controlled, single- and multiple-dose escalation studies were conducted in healthy Japanese (study registration not required) and Chinese men (ChinaDrugTrials.org.cn: CTR20200336).

The objective of these studies was to investigate the safety, tolerability, PK, and PD (Japanese only) of single and multiple OD doses of asundexian.

Ethics statement

The Japanese study was approved by the institutional review board of Fukuoka Mirai Hospital. The Chinese study was approved by the independent biomedical research

ethics committee of Peking University First Hospital. Both studies were conducted according to the principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines on Good Clinical Practice. Participants provided written informed consent before study enrollment.

Participants

Healthy Japanese men aged 20–40 years with a body mass index (BMI) in the range ≥17.6 to ≤26.4 kg/m^2 and healthy Chinese men aged 18–45 years with a BMI within the range ≥19 to <28 kg/m^2 were eligible. Major exclusion criteria were a history of thrombophilia disorders or relevant bleeding; known coagulation disorders; known disorders with increased bleeding risk; positive fecal occult blood test; and an aPTT outside normal reference ranges. The full inclusion and exclusion criteria are shown in the Supplementary Methods S1.

Study treatment

In the Japanese study, participants were randomized (6:2) to receive a single dose followed by multiple OD dosing of asundexian (25, 50, or 100 mg) or placebo (Figure 1). A single dose of asundexian or placebo was administered on day 1, followed by OD treatment with asundexian or placebo for 5 days (days 4–8) after a 3-day wash-out. The Chinese study included three cohorts: asundexian 25, 50, and 100 mg. Participants in the asundexian 25 and 50 mg cohort were randomized (9:3) to receive a single dose of asundexian (25 mg or 50 mg) or placebo on day 1 (Figure 1); those in the asundexian 100 mg cohort were randomized (9:3) to receive a single dose of asundexian 100 mg or placebo on

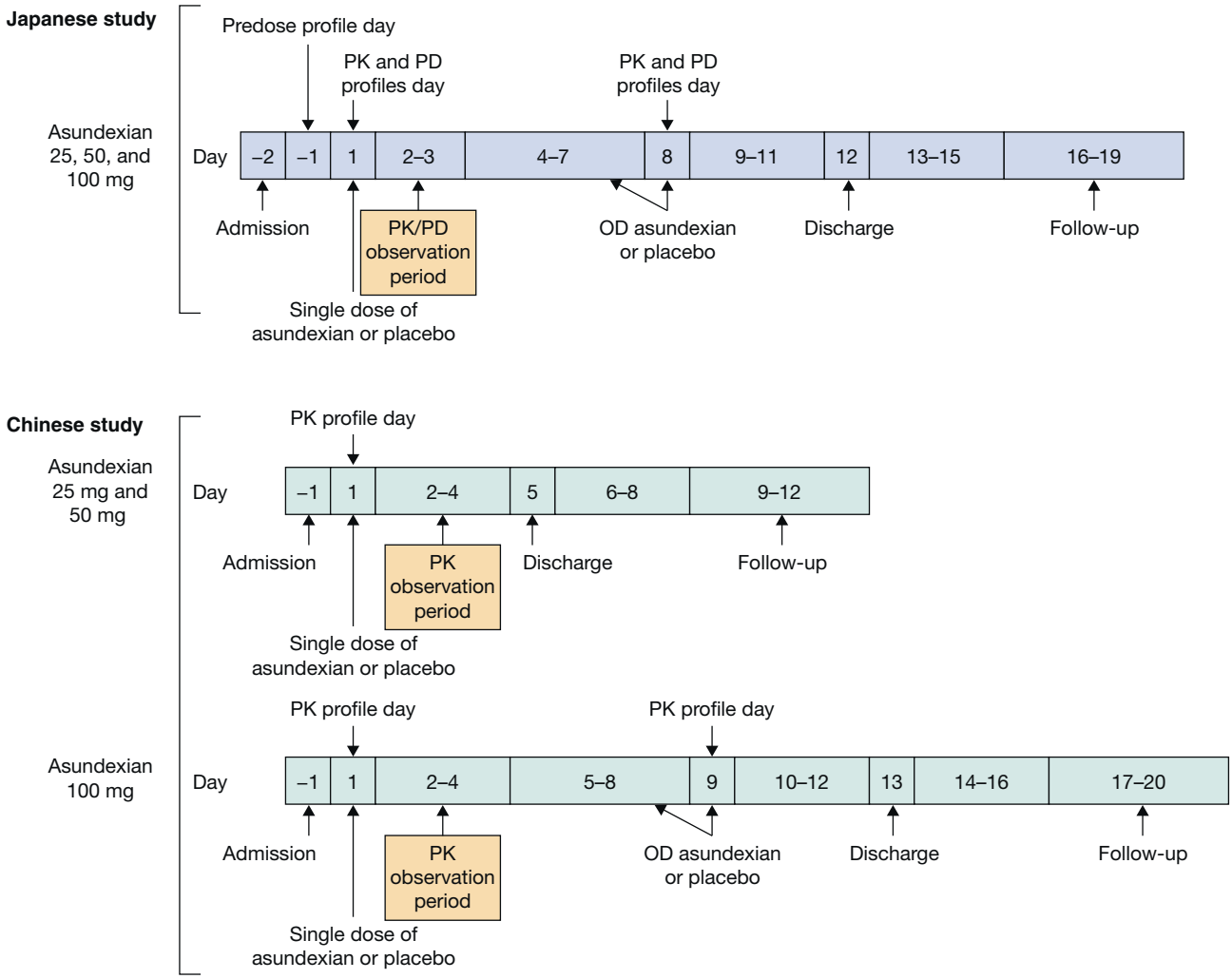

FIGURE 1 Overview of the study design in Japanese and Chinese participants. OD, once daily; PD, pharmacodynamic; PK, pharmacokinetic.

day 1, followed by OD asundexian 100 mg or placebo for 5 days (days 5–9) after a 4-day wash-out. Dose escalation occurred only after observing acceptable safety and tolerability profiles of the previous asundexian dose. On PK and PD profiling days, asundexian doses were administered after participants had fasted for at least 10 h.

Safety analyses

Safety and tolerability assessments included monitoring of AEs; physical examinations and monitoring of vital signs; 12-lead electrocardiograms (ECGs); and measurement of clinical laboratory variables. AEs were considered to be treatment-emergent if they started or worsened after the first application of the study intervention up to 7 days after the end of the study intervention. AEs of special interest (AESIs) were fatal bleeding or symptomatic bleeding in a critical area or organ, and/or symptomatic bleeding causing a clinically significant fall in hemoglobin level, hepatobiliary dysfunction, and (in the Japanese study only) pancreas disorders.

PK analyses

Blood samples were collected up to 72 h (Japanese) and 96 h (Chinese) after single dosing, and up to 96 h after the last study intervention in the multiple-dose phase in both studies (Figure S1). Bioanalysis was conducted in different laboratories for the Japanese and Chinese studies; cross-validation was carried out according to bioanalytical guidance to ensure data comparability.[7] Concentrations of asundexian and its major metabolite, M10, in plasma were measured by validated methods using high-pressure liquid chromatography–tandem mass spectrometry (LC–MS/MS). The details of bioanalytical methods for asundexian in plasma are provided in the Data S1. Urine samples were collected only in the Japanese study; concentrations of asundexian were measured using an exploratory LC–MS/MS method with abbreviated validation.

PK parameters were calculated by noncompartmental analysis (NCA) using WinNonlin (version 5.3; Certara, Princeton, NJ 08540, USA) in conjunction with the Automation Extension (version 2.90; Bayer AG, Leverkusen, Germany) in the Japanese study, and Phoenix WinNonlin (version 8.1; Certara) in conjunction with the NCA Tool plugin (release 1.0) in the Chinese study.

PK parameters of asundexian calculated after single and multiple dosing were as follows: area under the plasma concentration–time curve from zero to infinity after single dose and within the dosing interval for multiple dosing (AUC and $AUC_{(0-24)md}$); maximum plasma concentration (C_{max} and $C_{max,md}$); time to reach C_{max} and $C_{max,md}$, (t_{max} and $t_{max,md}$); half-life associated with the terminal slope ($t_{½}$ and $t_{½,md}$); renal clearance (CL_R) and percentage excreted into urine ($\%A_{E,ur}$) (100 mg dose in Japanese study only). AUC was calculated according to linear up log down trapezoidal rule. The apparent terminal rate constant (λz) was calculated by means of regression analysis of the terminal linear part of the curve in a semi-logarithmic scaled plot. For reliable calculation of the half-life, at least three data points (C_{max} excluded) were used. Additional parameters calculated after multiple dosing were the accumulation ratio for AUC (R_AAUC) calculated from $AUC_{(0-24)md}$ after multiple dosing and $AUC_{(0-24)}$ after single dosing; the accumulation ratio for C_{max} (R_AC_{max}) calculated from C_{max} after multiple dosing and single dosing; and the linearity factor of PK (R_{LIN}) after repeated administration of identical doses calculated as the ratio of $AUC_{(0-24)}$ after multiple dosing and AUC after single dosing. Dose-normalized key PK parameters of asundexian (day 1 [both studies]: C_{max} and AUC divided by dose (D), i.e. C_{max}/D and AUC/D; day 8 [Japanese study] and day 9 [Chinese study]: $C_{max,md}/D$ and $AUC_{(0-24)md}/D$) were also calculated. The metabolic ratio was calculated by the metabolite (M10) AUC to asundexian AUC with molecular weight adjusted.

PD analysis

Blood samples for PD analysis in the Japanese study were obtained as outlined in Figure S1. PD responses were assessed for aPTT, PT, FXIa activity, and FXI concentration, from baseline to 72 h after study intervention in the single-dose phase, and to 8 ~ 11 days after the last study intervention in the multiple-dose phase. PD response was measured using the same validated techniques as in the Caucasian study to exclude methodological bias. The aPTT assay was performed using the kaolin-trigger method on an STA compact Max 3 analyzer (MLM Medical Labs GmbH, Moenchengladbach, Germany). Prothrombin (PT) was determined also using the STA Compact Max 3 analyzer (MLM Medical Labs GmbH). FXIa activity was determined using a fluorometric analysis (Bayer AG Pharmaceutical Division, Wuppertal, Germany). FXI concentration was determined using an enzyme-linked immunosorbent assay (Bayer AG Pharmaceutical Division).

No PD analysis was performed in the Chinese study.

Data and statistical analysis

Statistical analyses were explorative and were performed using SAS version 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

Non-placebo participants with a valid PK profile and all participants with a valid PD profile on at least one of the profile days were included for PK and PD analysis, respectively. Safety data were analyzed with all participants who received at least one dose of the study treatment. Safety data from participants treated with placebo were pooled from all dose steps in the Japanese study, and from the 25 and 50 mg cohort in the Chinese study. Placebo data from the 100 mg cohort in the Chinese study were not pooled due to differences in study design.

Demographic data were summarized using descriptive statistics.

PK data

PK data were summarized descriptively. To investigate dose-proportionality, an exploratory analysis of variance (ANOVA) (including the factor treatment) was performed on the log-transformed AUC/D and C_{max}/D for the single-dose profile of asundexian (Chinese and Japanese studies) and log-transformed $AUC_{(0–24),md}/D$ and $C_{max,md}/D$ for the multiple-dose profile.

PD data

In the Japanese study, PD data were summarized descriptively. A Wilcoxon rank-sum test with a one-sided level of significance ($p = 0.05$) was used to compare each asundexian dose with placebo in a sequential order starting with the highest dose.

Interethnic analysis

The interethnic analysis compared PK and PD data from the Chinese and Japanese studies with data from the previously conducted phase I study in healthy Caucasian participants.[5] All three studies shared a similar design, including single and multiple dosing, and used doses of 25, 50, and 100 mg.

The PK characteristics AUC/D, C_{max}/D, $t_{½}$, $t_{½,md}$, $AUC_{(0–24),md}/D$, and $C_{max,md}/D$ of asundexian from all included studies were pooled and analyzed assuming log-normally distributed data.

For Chinese, Japanese, and Caucasian participants, two explorative ANOVAs were performed on the log-transformed values of AUC/D, C_{max}/D, and $t_{½}$ for the fixed factors of ethnic group and dose, and for $AUC_{(0–24)md}/D$, $C_{max,md}/D$, and $t_{½,md}$ for the fixed factor of ethnic group only for the 100 mg dose. Point estimates (least-squares [LS] means) and exploratory 90% confidence intervals (CIs) for the ratios of Chinese/Caucasian and Japanese/Caucasian were calculated by retransformation of the logarithmic results.

Analysis of covariance (ANCOVA) including ethnic group as a fixed effect and observed aPTT at baseline as covariates was performed on the logarithms for the maximal ratio to the baseline of aPTT. ANOVAs including ethnic group as a fixed effect were performed on the logarithms determined for baseline values of aPTT. Based on these analyses, point estimates (LS means) and exploratory 90% CIs for the ratio of Japanese/Caucasian were derived.

Correlation plots of ratio to baseline for aPTT and FXIa activity versus concentration of asundexian were derived by ethnic group.

RESULTS

Participant demographics and characteristics

In the Japanese study, 24 men were randomized to receive asundexian ($n = 6$ per treatment group) or placebo ($n = 2$ per treatment group), and all completed the study. In the Chinese study, 36 men were randomized to receive asundexian ($n = 9$ per treatment group) or placebo ($n = 3$ per treatment group), and 35 completed the study (one participant randomized to placebo discontinued treatment owing to a treatment-emergent AE [TEAE] after the first dose).

Japanese participants had a mean (standard deviation [SD]) age of 28.7 (5.9) years and a mean (SD) BMI of 21.69 (2.16) kg/m^2. Chinese participants had a mean (SD) age of 30.3 (5.9) years and a mean (SD) BMI of 22.91 (2.12) kg/m^2. Overall, the baseline demographics of participants were similar between the treatment groups and between the studies (Table 1). Body weight and BMI were lower in Japanese and Chinese participants than in Caucasian participants.[5]

Safety and tolerability

All TEAEs were mild, with no serious AEs or AESIs reported (Table 2). No AEs leading to discontinuation were reported after asundexian administration. In the Chinese study, one participant had a TEAE of right bulbar conjunctival hemorrhage before the start of the multiple dosing period, 4 days after the first study intervention administration. The participant was not treated for this event, which resolved spontaneously. In both studies, no clinically relevant effects of asundexian were observed in vital signs, ECG, or clinical laboratory investigations except for aPTT;

changes in aPTT were expected based on the mode of action of asundexian.

PK analysis

Geometric mean plasma concentration-time patterns of asundexian after single dosing (first dose administration) and last dose of multiple OD dosing across treatment groups were similar in Chinese and Japanese individuals, albeit with a numerically slightly higher C_{max} observed for 100 mg in Japanese than for Chinese participants (Figure 2). In both studies, asundexian was absorbed with a median t_{max} of 3.5–4.5 h after a single administration and a median $t_{max,md}$ of 3.0–4.0 h after multiple dosing. Geometric means for C_{max}/D (range, 0.012–0.0168 h/L) and AUC/D (range, 0.319–0.380 h/L) after single administration were comparable across all asundexian groups. Geometric means for $C_{max,md}/D$ (range, 0.0197–0.0256 h/L) and $AUC_{(0-24)md}/D$ (range, 0.317–0.393 h/L) after multiple dosing were similar across all asundexian groups in both studies (Table 3). In the Japanese study, no deviation from dose proportionality for C_{max} and AUC was observed after single multiple dosing over the entire dose range of 25 to 100 mg. In the Chinese study, no deviation from dose proportionality was observed for AUC after a single administration, while C_{max}/D after asundexian 25 mg administration was slightly higher than that with 50 mg or 100 mg.

In both studies, the terminal half-life of asundexian was similar after single and multiple dosing; geometric mean values ranged from 15.2–18.6 h ($t_{½}$) and 15.6–17.9 h ($t_{½,md}$), respectively. The degree of accumulation of asundexian was relatively low for C_{max} and AUC after multiple once-daily dosing (R_AC_{max}: 1.32–1.61; R_AAUC: 1.47–1.76). Following repeated dosing for 5 days consecutively, R_{LIN} was 0.95–1.03 in both studies, indicating time-linear PK.

In the Japanese study, the geometric mean renal clearance (CL_R) was 0.299 L/h after a single dose of asundexian 100 mg. Renal elimination of unchanged drug up to 72 h after single dosing ($\%A_{E,ur}$) accounted for 11.5% of the dose. Values for $\%A_{E,ur}$ and CL_R after multiple OD dosing of 100 mg were similar to those after single dose administration (12.3% [in 24 h after last dose] and 0.304 L/h, respectively).

For the inter-ethnic comparison, the point estimators for the ratios Chinese/Caucasian and Japanese/Caucasian, together with their 90% CI limits for AUC/D and C_{max}/D (single dosing) and $AUC_{(0-24)md}/D$ and $C_{max,md}/D$ (multiple dosing; 100 mg) are presented in Figure 3. After single and multiple dosing, geometric mean C_{max}/D and $C_{max,md}/D$ were similar between Chinese and Caucasian

TABLE 1 Demographic and baseline characteristics of Japanese and Chinese participants who received study intervention.

	Japanese study					Chinese study				
	Asundexian 25 mg (n = 6)	Asundexian 50 mg (n = 6)	Asundexian 100 mg (n = 6)	Placebo (n = 6)	Total (n = 24)	Asundexian 25 mg (n = 9)	Asundexian 50 mg (n = 9)	Placebo 25 mg and 50 mg (n = 6)	Asundexian 100 mg (n = 9)	Placebo 100 mg (n = 3)	Total (n = 36)
Age, years	31.8 (5.5)	27.2 (7.2)	28.8 (6.1)	27.0 (4.8)	28.7 (5.9)	31.0 (5.1)	34.0 (6.7)	24.0 (3.0)	31.2 (4.5)	26.7 (4.0)	30.3 (5.9)
Weight, kg	66.7 (6.6)	64.0 (7.8)	61.3 (7.01)	67.4 (7.0)	64.8 (7.1)	62.9 (7.5)	68.0 (6.9)	63.0 (6.4)	69.4 (8.8)	67.1 (9.2)	66.2 (7.8)
Height, cm	173.5 (5.8)	176.1 (4.3)	170.3 (5.0)	171.8 (5.2)	172.9 (5.2)	167.2 (6.9)	170.8 (4.4)	168.9 (4.7)	172.4 (7.9)	168.8 (3.1)	169.8 (6.1)
BMI, kg/m^2	22.2 (1.6)	20.6 (1.7)	21.2 (2.9)	22.8 (2.0)	21.7 (2.2)	22.5 (2.0)	23.3 (2.2)	22.1 (2.0)	23.3 (2.4)	23.5 (2.4)	22.9 (2.1)

Note: Data are mean (SD).

Abbreviations: BMI, body mass index; SD, standard deviation.

TABLE 2 Summary of the number of participants with TEAEs in (a) Japanese and (b) Chinese participants by primary SOC and preferred term.

(a)	Single and multiple dosing			
	Asundexian 25 mg ($n=6$)	Asundexian 50 mg ($n=6$)	Asundexian 100 mg ($n=6$)	Placebo ($n=6$)
Any TEAE	1 (16.7)	0	1 (16.7)	0
Investigations				
Lipase increased	0	0	1 (16.7)	0
Musculoskeletal and connective tissue disorders				
Myalgia	1 (16.7)	0	0	0

(b)	Single dosing			Single and multiple dosing	
	Asundexian 25 mg ($n=9$)	Asundexian 50 mg ($n=9$)	Placebo ($n=6$)	Asundexian 100 mg ($n=9$)	Placebo ($n=3$)
Any TEAE	3 (33.3)	1 (11.1)	2 (33.3)	4 (44.4)	1 (33.3)
Investigations					
Lipase increased	0	0	0	1 (11.1)	0
Blood triglycerides increased	2 (22.2)	1 (11.1)	1 (16.7)	2 (22.2)	0
Gastrointestinal disorders					
Diarrhea	0	0	1 (16.7)	0	0
Infections and infestations					
Gastroenteritis	1 (11.1)	0	0	0	0
Eye disorders					
Conjunctival hemorrhage	0	0	0	1 (11.1)	0
General disorders and administration site conditions					
Pyrexia	0	0	0	0	1 (33.3)

Note: Data are number of participants (%).

Abbreviation: NA, not applicable; TEAE, treatment-emergent adverse event.

individuals, and slightly higher in Japanese individuals; AUC/D and $AUC_{(0-24)md}/D$ were similar between Chinese and Japanese individuals but slightly higher than in Caucasian individuals. After single dosing and multiple dosing, $t_{½}$ and $t_{½,md}$, respectively, were similar across all ethnicities over the dose levels investigated (15–19 h). Geometric mean point estimates for the ratios of all key PK parameters were close to 1 (range, 0.89–1.33); the 90% CI did not include unity for some parameters.

Key PK parameters for the pharmacologically inactive metabolite M10 in Chinese and Japanese participants are presented in Table S1. The metabolic AUC ratios in different ethnicities after a single dose are summarized in Table S2.

PD analysis

Dose-dependent prolongation of aPTT after single and multiple dosing of asundexian was observed over time in the Japanese study, while no effects were observed for placebo ($p=0.001$ for all comparisons; Figure 4a). The geometric means of maximal ratios to baseline of aPTT were 1.605, 1.948, and 2.249 after administration of 25, 50, and 100 mg asundexian OD, respectively. Maximum prolongation of aPTT was observed at the median of 2.3–4.5 h after a single administration of asundexian, and at 2.6–3.4 h after multiple dosing; aPTT remained elevated 24 h after the last dosing. Median (min, max) time to maximal aPTT for Japanese and Caucasian participants following administration of 25, 50, and 100 mg asundexian is shown in Table S3.

In the exploratory analysis using ANCOVA to assess the influence of ethnicity (Japanese/Caucasian) on the maximal ratio to baseline for aPTT, the geometric LS-mean (90% CI) for the 25, 50 and 100 mg OD regimens was 0.973 (0.904, 1.047), 0.948 (0.878, 1.024), and 0.967 (0.868, 1.077), respectively, implying overall similar changes in aPTT for both Japanese and Caucasian participants. Additionally, in the interethnic analysis of baseline aPTT, the geometric LS-mean (90% CI) for the ratio Japanese/Caucasian was 1.115 (1.086, 1.145).

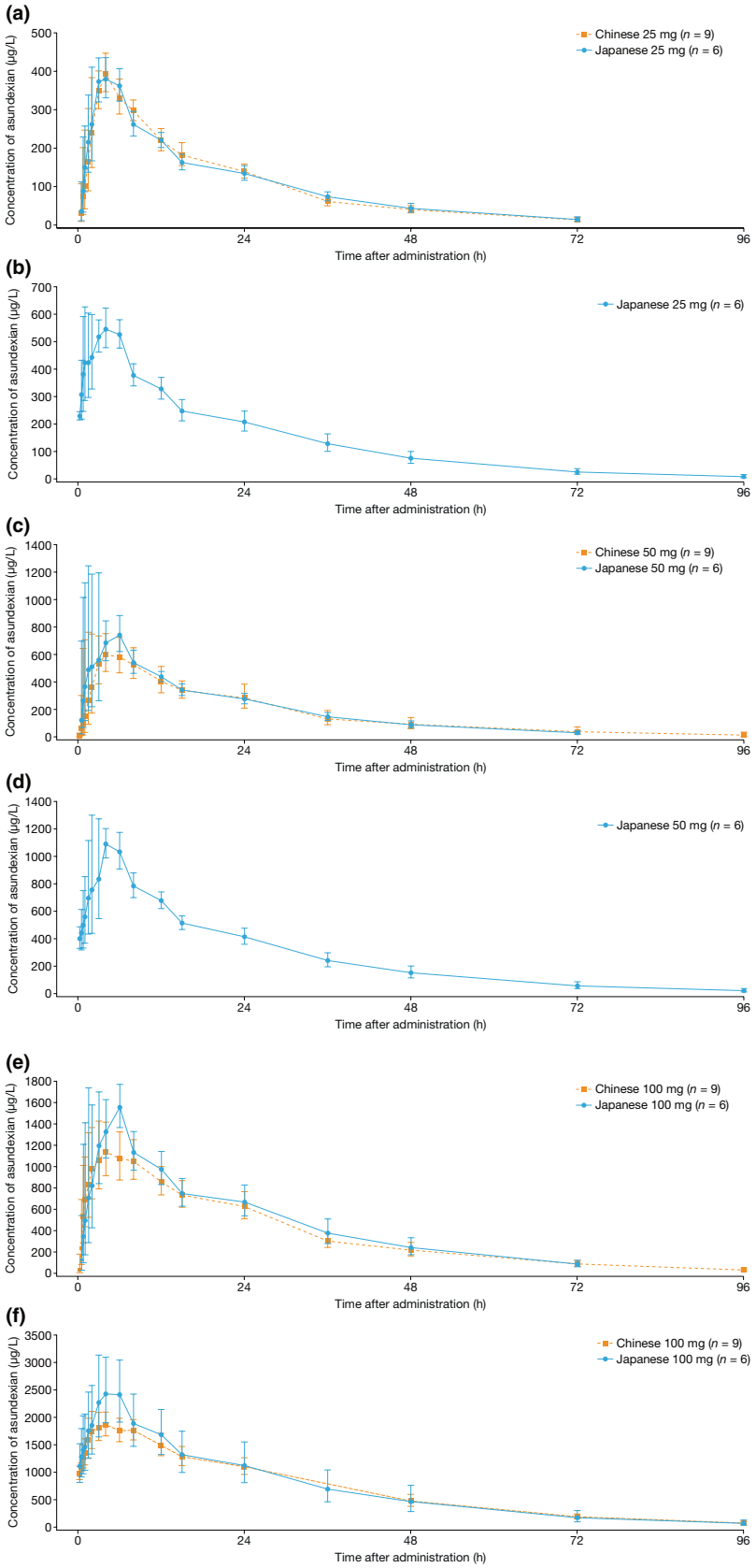

FIGURE 2 Plasma concentration–time data for asundexian after single dosing (a: 25 mg; c: 50 mg; e: 100 mg) and after last dose of multiple once-daily dosing in Japanese (b: 25 mg; d: 50 mg; f: 100 mg) and Chinese participants (f: 100 mg). *Note*: Data are geometric mean (SD). The Japanese study involved single and multiple dosing of asundexian 25, 50, and 100 mg. The Chinese study involved single-dose administration of asundexian 25 and 50 mg, and single and multiple dosing of asundexian 100 mg. SD, standard deviation.

A rapid, dose-dependent decrease in FXIa activity was observed after single and multiple administration with asundexian at all doses, while no effects were observed for placebo (Figure 4c). Complete inhibition of FXIa activity below the lower limit of quantification (LLOQ) of 1.9% was dose-dependent. FXIa activity below LLOQ was observed

TABLE 3 Plasma PK parameters of asundexian following single and multiple once-daily doses in Japanese and Chinese participants.

				Asundexian dose		
Parameter	**Unit**	**Ethnicity**	***n***	**25 mg**	**50 mg**	**100 mg**
Single dosing						
AUC	μg·h/L	Chinese	9	8070 (13.0)	15,900 (30.1)	34,400 (15.4)
		Japanese	6	8140 (12.4)	16,600 (12.3)	38,000 (18.5)
AUC/*D*	h/L	Chinese	9	0.323 (13.0)	0.319 (30.0)	0.344 (15.4)
		Japanese	6	0.325 (12.4)	0.333 (12.3)	0.380 (18.5)
C_{max}	μg/L	Chinese	9	401 (12.3)	634 (24.0)	1220 (23.4)
		Japanese	6	398 (14.1)	839 (12.9)	1630 (8.09)
C_{max}/D	/L	Chinese	9	0.0160 (12.3)	0.0130 (12.8)	0.0122 (23.4)
		Japanese	6	0.0159 (14.1)	0.0168 (12.9)	0.0163 (8.09)
t_{max}[a]	h	Chinese	9	4.00 (0.75–4.00)	4.00 (3.00–6.00)	4.00 (1.50–6.00)
		Japanese	6	3.50 (1.50–6.00)	4.50 (0.75–6.00)	4.50 (1.50–6.00)
$t_{½}$	h	Chinese	9	16.7 (15.3)	18.6 (21.2)	17.6 (7.1)
		Japanese	6	15.2 (15.2)	15.2 (12.8)	16.7 (3.5)
CL_R[b]	L/h	Japanese	6	—	—	0.299 (59.5)
$\%A_{E,ur(0–72)}$[b,c]		Japanese	6	—	—	11.5 (4.54)
Multiple dosing						
$AUC_{(0–24)md}$	μg·h/L	Chinese	9	—	—	35,000 (8.65)
		Japanese	6	8080 (9.49)	15,800 (10.6)	39,300 (25.7)
$AUC_{(0–24)md}/D$	h/L	Chinese	9	—	—	0.350 (8.65)
		Japanese	6	0.323 (9.49)	0.317 (10.6)	0.393 (25.7)
$C_{max,md}$	μg/L	Chinese	9	—	—	1970 (11.4)
		Japanese	6	605 (6.95)	1110 (8.76)	2560 (23.2)
$C_{max,md}/D$	/L	Chinese	9	—	—	0.0197 (11.4)
		Japanese	6	0.0242 (6.95)	0.0222 (8.76)	0.0256 (23.2)
$t_{max,md}$[a]	h	Chinese	9	—	—	3.00 (2.00–8.00)
		Japanese	6	3.00 (0.750–4.00)	4.00 (1.00–4.00)	3.50 (3.00–6.00)
$t_{½,md}$	h	Chinese	9	—	—	17.9 (12.7)
		Japanese	6	15.6 (11.7)	17.4 (17.8)	17.6 (11.6)
$CL_{R,md}$[b]	L/h	Japanese	6	—	—	0.304 (52.1)
$\%A_{E,ur,md(0–24)}$[b,c]		Japanese	6	—	—	12.3 (3.36)
Accumulation ratio						
R_AAUC		Chinese	9	—	—	1.74 (13.3)
		Japanese	6	1.54 (5.26)	1.47 (14.1)	1.76 (18.4)
R_AC_{max}		Chinese	9	—	—	1.61 (21.0)
		Japanese	6	1.52 (10.8)	1.32 (18.6)	1.57 (17.3)
R_{LIN}		Chinese	9	—	—	1.02 (12.4)
		Japanese	6	0.993 (5.50)	0.953 (10.8)	1.03 (12.6)

Note: Data are geometric mean (%CV) unless otherwise stated.

Abbreviations: $\%A_{E,ur(0–72)}$, percentage of drug excreted in the urine in the 72 h after a single dose; $\%A_{E,ur,md(0–24)}$, percentage of drug excreted in the urine in the 24 h after the last dose following multiple dosing; /*D*, divided by dose; $AUC_{(0–24)md}$, area under the plasma concentration–time curve within the dosing interval following multiple dosing; AUC, area under the plasma concentration–time curve from zero to infinity after single dosing; CL_R, renal clearance; $CL_{R,md}$, renal clearance after multiple dosing; C_{max}, maximum observed plasma concentration; $C_{max,md}$, C_{max} after multiple-dose administration; CV, coefficient of variation; PK, pharmacokinetic; R_AAUC, accumulation ratio calculated from $AUC_{(0–24)md}$ after multiple dosing and $AUC_{(0–24)}$ after single dosing; R_AC_{max}, accumulation ratio calculated from $C_{max,md}$ after multiple dosing and C_{max} after single dosing; R_{LIN}, linearity factor calculated as ratio of $AUC_{(0–24)md}$ after multiple dosing and AUC after single dosing based on identical doses; $t_{½}$, half-life associated with the terminal slope; $t_{½,md}$, half-life associated with the terminal slope after multiple-dose administration; SD, standard deviation; t_{max}, time to reach C_{max}; $t_{max,md}$, time to reach $C_{max,md}$ (multiple dosing).

[a]Median (minimum, maximum).

[b]Data are not available for Chinese study.

[c]Arithmetic mean (SD).

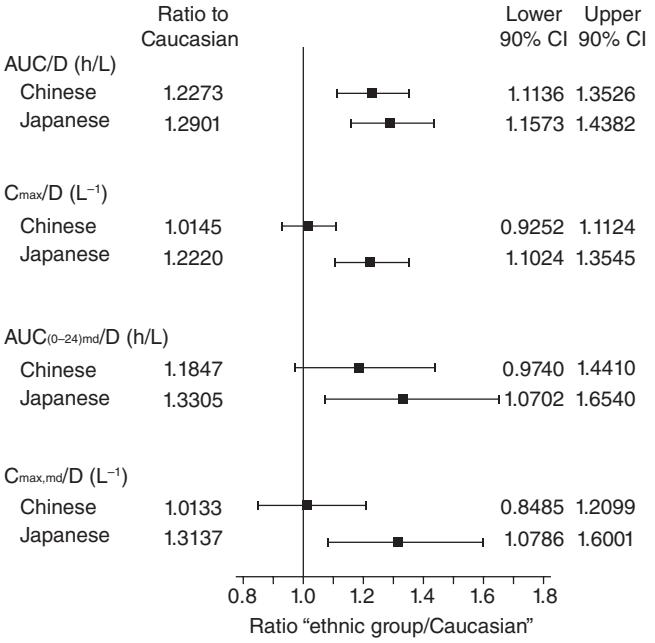

FIGURE 3 Overview of point estimators and lower and upper limits of 90% confidence intervals of the ratios (Chinese/Caucasian and Japanese/Caucasian) of AUC/D and C_{max}/D for single dosing and $AUC_{(0–24)md}/D$ and $C_{max,md}/D$ for multiple dosing (100-mg dose). *Note*: Black squares represent point estimators and whiskers indicate upper and lower 90% confidence intervals. AUC/D, area under the plasma concentration–time curve from zero to infinity after single (first) dose divided by dose; $AUC_{(0–24)md}/D$, area under the plasma concentration–time curve within the dosing interval divided by dose; C_{max}/D, maximum observed drug concentration in measured matrix after single-dose administration divided by dose; $C_{max,md}/D$, C_{max} after multiple-dose administration divided by dose.

in more than one-third of participants, at 4 h after a 25-mg dose, from 2 to 12 h after a 50-mg dose, and continuously from the previous dose until 24 h after a 100-mg dose.

No effect of asundexian on PT, INR, or FXI concentration was observed (Figure S2).

Increasing plasma concentrations of asundexian correlated with aPTT prolongation and FXIa activity reduction. Similar PK/PD relationships were observed between Caucasian and Japanese individuals (Figure 4b,d). No correlations were observed between plasma concentrations and FXI concentrations or PT (data not shown).

DISCUSSION

These two phase I studies investigated the PK, PD, and safety of asundexian after single and multiple OD dosing in healthy Japanese and Chinese participants and provided data for an interethnic comparison with data from a previous multiple-dose escalation study in Caucasian participants.[5]

Single and multiple doses of asundexian for up to 5 days consecutively were well tolerated in Japanese and Chinese participants; all TEAEs were mild in severity. No clinically relevant AEs related to bleeding, or changes in vital signs, ECG, or clinical laboratory evaluations were observed. No AESI was reported. The incidence and severity of TEAEs were generally similar to those reported from the multiple-dose study in healthy Caucasian participants.[5]

Systemic exposure to asundexian increased dose proportionally after single and multiple OD dosing in the Japanese study in the investigated dose range of 25–100 mg. In Chinese participants, AUC also increased dose proportionally after single dose administration in the dose range 25–100 mg. Similar half-lives of asundexian after single and multiple dosing were observed, suggesting time-independent PK, which was further confirmed by the R_{LIN} value being close to 1. A low accumulation of asundexian was observed following multiple OD dosing, which is consistent with the observed $t_{½}$, values. The accumulation ratios were also similar to those observed in Caucasian individuals.[5,8] Renal elimination of unchanged asundexian was a minor route of elimination in Japanese participants, which is in line with published data.[5,8]

Data from these two Asian studies showed that the overall exposure of asundexian in Japanese and Chinese individuals was similar to that previously described in Caucasian participants.[5] In the present exploratory interethnic analysis, numerically slightly higher C_{max}/D and $C_{max,md}/D$ in Japanese individuals than in Chinese or Caucasian individuals, and numerically slightly higher AUC/D and $AUC_{(0–24)md}/D$ in Chinese or Japanese individuals than in Caucasian individuals were observed. One hypothesis for the numerically higher exposure could be the lower mean body weight in Asian individuals. The investigation of the impact of body weight and other covariates on the PK of asundexian will be part of the population PK analysis using the data from phase II and/or III studies with more diverse demographic features. However, these minor differences were not considered clinically relevant given the overlapping overall range, flat PK-PD relationship, and similar PD effect. The final assessment of clinical relevance will be performed based on the exposure-response analysis of the currently ongoing phase III study.

Asundexian is mainly metabolized via carboxylesterase 1 (CES1) with oxidative biotransformation via CYP3A4 as a minor pathway. The plasma exposure of the major metabolite of asundexian (M10) which was formed by amide hydrolysis via CES1 and subsequent *N*-acetylation was also investigated in both Chinese and Japanese studies. A similar metabolic AUC ratio (M10/asundexian

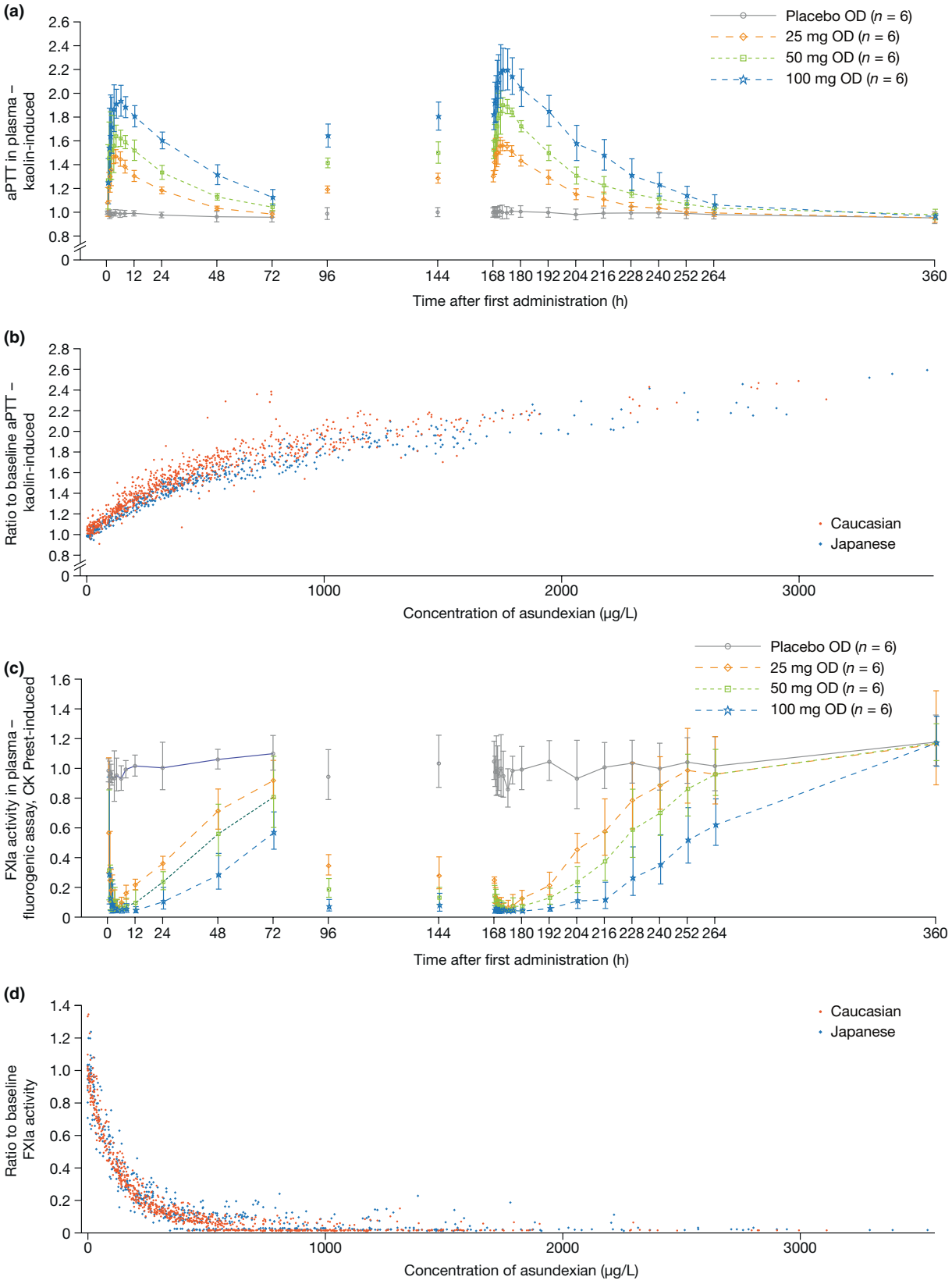

FIGURE 4 Geometric means with standard deviation for ratio to baseline of aPTT (a) and FXIa activity (c) in plasma over time in Japanese participants and correlation of aPTT ratios (b) and FXIa activity ratios (d) to baseline and plasma concentrations of asundexian. *Note*: Data are geometric mean (SD) for single and multiple dosing of asundexian 25, 50, and 100 mg. aPTT, activated partial thromboplastin time; FXIa, activated factor XI; OD, once daily; SD, standard devaitaion.

corrected for molecular weight) was observed in Chinese and Caucasian individuals, while a slightly higher metabolic AUC ratio was observed in Japanese individuals, with an overlapping overall range (Table S1). As M10 is not pharmacologically active, the slightly higher exposure to M10 in Japanese participants is not considered relevant.

A dose-dependent prolongation of aPTT and inhibition of FXIa activity were observed, similar to the data previously reported in Caucasian participants.[5] This adds further confidence to asundexian's consistent and predictable effects across different ethnic groups. A marginally higher (approximately 3 s) but significant baseline aPTT was noted in Japanese than in Caucasian individuals. The minor difference is within the normal variation range for aPTT and is not considered clinically relevant. Asundexian did not affect PT, reinforcing a specificity for inhibition of the intrinsic coagulation pathway, without affecting the extrinsic or common pathway. Despite the effect on FXIa activity, no effects of asundexian on FXI concentration were observed, implying that asundexian did not influence the production of FXI protein.

There were some differences in the study design for the Japanese and Chinese studies (e.g. length of wash-out period, urine PK collection, sample size in each cohort), because the two studies were designed and conducted separately at different times when the knowledge about the properties of asundexian was evolving and taking into account the local country-specific registration requirement, biosample administration regulation, and clinical practice. Despite minor differences, the study design in both studies was considered appropriate to evaluate potential inter-ethnic differences and to support future clinical development (e.g., initiation of multi-region clinical trials) in China and Japan.

One limitation of both studies is that they included only young healthy male participants, who may not fully represent the target patient population. Therefore, investigation of population PK/PD in large Asian patient populations is recommended for further clinical development.

Despite this limitation, the available phase I data were supportive of further clinical development of asundexian in patient populations of different ethnicities with the same dose. Three international phase II dose-finding studies of asundexian have been completed, each including Japanese and/or Chinese participants in their study populations. PACIFIC-AF (NCT04218266) compared asundexian with the oral anticoagulant apixaban, in patients with atrial fibrillation.[9] PACIFIC-AMI (NCT04304534) investigated the use of asundexian together with a dual antiplatelet therapy to prevent adverse cardiovascular outcomes in patients following a recent myocardial infarction.[10] Both studies included Japanese patients. PACIFIC-STROKE (NCT04304508) investigated asundexian in combination with antiplatelet therapy in patients following a recent noncardioembolic ischemic stroke and included Chinese and Japanese patients.[11] Building on the early-phase data, a phase III pivotal study is currently ongoing at multiple study sites including sites in Japan and China that is evaluating asundexian versus placebo for the prevention of ischemic stroke (OCEANIC-STROKE) after noncardioembolic acute ischemic stroke or high-risk transient ischemic attack.

In conclusion, the reported studies in healthy Japanese and Chinese participants showed that asundexian, an oral FXIa inhibitor, was well tolerated, with no clinically relevant bleeding, and predictable PK and PD profiles. Compared with a study reported previously for Caucasian individuals,[5] there were no clinically relevant differences in PK parameters across the healthy male Japanese and Chinese study populations and no clinically relevant difference in PD parameters in Japanese individuals. The results of these investigations support that there is no dose adjustment needed for Chinese or Japanese participants in the currently ongoing phase III study.

AUTHOR CONTRIBUTIONS

H.C., K.H., F.K., C.B., S.S., and T.L. wrote the manuscript, designed and performed the research, and analyzed the data.

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CONFLICT OF INTEREST STATEMENT

HC, KH, FK, CB, SS, and TL are employees of Bayer AG.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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