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BAY 1213790, a fully human IgG1 antibody targeting coagulation factor XIa: First evaluation of safety, pharmacodynamics, and pharmacokinetics

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Abstract

Background: Coagulation factor XI (FXI) contributes to the development of thrombosis but appears to play only a minor role in hemostasis and is therefore an attractive anticoagulant drug target.

Objectives: To evaluate the safety, pharmacodynamic, and pharmacokinetic properties of BAY 1213790, a fully human immunoglobulin (Ig) G1 antibody targeting activated coagulation FXI (FXIa), in healthy men.

Methods: In this phase 1, single-blind, parallel-group, placebo-controlled, dose-escalation study, 83 healthy Caucasian men were randomized 4:1 to receive a single 60-minute intravenous infusion of BAY 1213790 (0.015-10 mg/kg) or placebo. Adverse events, pharmacodynamic parameters (including activated partial thromboplastin time [aPTT]) and pharmacokinetic parameters were determined. Volunteers were followed up for 150 days.

Results: BAY 1213790 demonstrated favorable safety and tolerability; there were no observed cases of bleeding or clinically relevant antidrug antibody formation. One volunteer (1.2%) experienced an infusion reaction. Following intravenous administration of BAY 1213790, dose-dependent increases in aPTT (maximal mean increase relative to baseline: 1.85 [conventional method] and 2.17 [kaolin-triggered method]) and rotational thromboelastometry whole blood clotting time were observed, as well as dose-dependent reductions in FXI activity. Bleeding times did not increase following administration of BAY 1213790 and were similar for all dose cohorts, including placebo. Measurable and dose-dependent increases in systemic exposure were detected for all doses of BAY 1213790 of 0.06 mg/kg or higher.

Conclusions: Based on these safety, pharmacodynamic, and pharmacokinetic results, further evaluation of BAY 1213790 in patients with, or at risk of, thrombosis is warranted.

KEYWORDS
anticoagulant, factor XI, hemostasis, phase 1, thrombosis

Essentials

- BAY 1213790, a fully human IgG1 monoclonal antibody, inhibits activated coagulation factor XI.
- In this phase 1 study in healthy men, BAY 1213790 exhibited favorable safety and tolerability.
- BAY 1213790 dose-dependently increased clotting time without observed effects on bleeding risk.
- Further evaluation of BAY 1213790 in patients with, or at risk of thrombosis, is warranted.

1 | INTRODUCTION

The introduction of oral direct inhibitors of factor Xa or thrombin has greatly improved medical care and safety in the prevention and treatment of thrombotic disorders. However, bleeding remains a concern, particularly in patients with risk factors such as advancing age, anemia, and renal disease.[1] As such, there remains a medical need for new agents with an improved safety profile and equivalent or superior efficacy compared with existing therapies.[2]

Factor XI (FXI) is the zymogen form of activated coagulation factor XI (FXIa). Inhibition of FXI or FXIa has potential as a novel anticoagulant therapeutic target because it is thought to block the amplification or propagation of the intrinsic coagulation pathway while leaving the extrinsic (tissue factor) pathway and the common pathway intact. Thus, the intrinsic pathway is inhibited to an extent that is sufficient to prevent thrombosis while the hemostatic response is maintained.[2-4]

Several lines of preclinical and clinical evidence support FXI inhibition as an antithrombotic strategy that may potentially be associated with a lower risk of bleeding than existing therapies. Epidemiological studies have shown that, compared with the general population, the risk of venous thromboembolism (VTE) and stroke is lower in individuals with FXI deficiency and higher in those with elevated FXI levels.[5-11] In preclinical studies, genetically altered FXI knockout mice or animals treated with pharmacological FXI/FXIa inhibitors were protected from venous and arterial thrombosis without an observed increased risk of bleeding.[3,12-21] Furthermore, in a phase 2 proof-of-concept study in patients undergoing total knee replacement, reduction in FXI levels following administration of an antisense oligonucleotide was associated with a reduced risk of VTE and a numerically lower rate of bleeding events compared with treatment with enoxaparin.[22]

BAY 1213790 is a fully human immunoglobulin (Ig)G1 monoclonal antibody (mAb) that was generated using phage display technology. Crystal structure analysis demonstrated a novel allosteric mechanism of action of BAY 1213790, which bound to a region adjacent to the FXIa active site, leading to substantial structural rearrangements (Schaefer et al., unpublished data). The objectives of this study (EudraCT number: 2014-003816-35) were to evaluate the safety, pharmacodynamics, and pharmacokinetics of intravenously administered BAY 1213790 in healthy male volunteers.

2 | METHODS

2.1 | Study population

Healthy Caucasian male volunteers aged 18-55 years with a body mass index (BMI) in the range 18-30 kg/m^2 were eligible for inclusion. Key exclusion criteria were: known coagulation disorders or conditions that increase bleeding risk; known severe allergies; hypersensitivity to study drug or excipients; use of medication that may have an impact on the study objectives; the presence of relevant disease in the 4 weeks preceding the study; and a history of smoking more than five cigarettes per day or suspicion of drug/alcohol abuse.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with the International Conference on Harmonization guidelines for Good Clinical Practice. All relevant study documents were approved by the local ethics committee, and volunteers provided written informed consent.

2.2 | Study design

In this phase 1, single-center, randomized, single-blind, parallel-group, placebo-controlled, dose-escalation study, eligible volunteers were sequentially assigned by an independent group to a unique randomization number in ascending order and randomized 4:1 to receive a single dose of BAY 1213790 or placebo (isotone sodium chloride solution, 0.9%) as a 60-minute intravenous infusion (40 mL). Bioanalysis and evaluation of adverse events were performed in nonblinded fashion.

Study drug was administered on day 1. Volunteers were admitted to the study site 1 day before drug administration and discharged on day 7. Nine doses (0.015, 0.06, 0.15, 0.3, 0.6, 1.25, 2.5, 5, or 10 mg/kg) of BAY 1213790 were studied, with a planned sample size of 10 volunteers per dose cohort (eight receiving BAY 1213790 and two receiving placebo). Dose escalation was performed on approximately a monthly basis, only after acceptable safety and tolerability had been established during days 1-7 of the previous dose step. Follow-up procedures were performed on days 14, 21, 28, and 56 (±3 days), with an optional visit at day 84, for all dose steps. Owing to a longer-than-expected elimination half-life ($t_{½}$) of BAY 1213790, the visit at day 84 subsequently became mandatory, along with an additional follow-up visit at day 150 (±7 days), for dose steps of 1.25 mg/kg or higher.

2.3 | Safety

Adverse events (AEs) and concomitant medication were assessed on day 1 (start and end of infusion), then at 2, 3, 4, 6, 8, 12, 15, 24, 36, 48, 72, 96, 120, and 144 hours after the end of the infusion, and at follow-up visits. Concomitant medication and the potential for AEs were assessed at screening and on the day before drug administration. AEs were classified according to intensity (mild, moderate, or severe) and importance (serious or nonserious). AEs of special interest included: fatal bleeding; hemorrhage; symptomatic bleeding in a critical area or organ; bleeding causing a fall in hemoglobin of ≥20 g/L or leading to a transfusion of two or more units of packed red blood cells; infusion reactions; hypersensitivity reactions; and the development of antidrug antibodies.

Blood samples for evaluation of antidrug antibodies were taken before BAY 1213790 administration on day 1, at 144 hours after the start of the infusion, and at each follow-up visit. Other safety assessments included clinical laboratory variables, vital signs, and electrocardiogram findings; physical examinations were also performed.

2.4 | Pharmacodynamics

The primary pharmacodynamic variables evaluated were activated partial thromboplastin time (aPTT) and FXI activity. Blood samples for pharmacodynamic analysis were taken on day −1, predose on day 1, and 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours after the start of infusion and at follow-up visits on days 14, 21, 28, 56 (±3 days) (all doses), 84 (doses of 0.3 mg/kg or higher), and 150 (±7 days) (doses of 1.25 mg/kg or higher). Citrated blood samples were collected, centrifuged for plasma preparation within 30 minutes, and frozen immediately at −20°C.

Two methods were used to evaluate aPTT: a conventional assay in which coagulation was triggered by the addition of calcium chloride, phospholipids, and silica to citrated plasma; and a kaolin-triggered assay, in which citrated plasma was recalcified in the presence of a standardized quantity of cephalin (a platelet substitute) and a factor XII activator (kaolin). The conventional aPTT assay was performed using a validated method with the Stago STA Compact coagulation analyzer and PTT test kit (Diagnostica Stago, Z.A.C. Les Châtaigniers, France; interassay precision: 0.36% coefficient of variation [CV]; intra-assay precision: 1.07%-1.58% CV). The kaolin-triggered assay was performed using a validated method with the Stago STA compact coagulation analyzer and STA-C.K. Prest test kit (Diagnostica Stago; interassay precision: 1.33%-1.82% CV, intra-assay precision: 0.78%-1.45% CV).

Apparent FXI activity was measured using a modified aPTT assay (utilizing SynthASil aPTT reagent) and an ACL TOP coagulation analyzer provided by Instrumentation Laboratory Coagulation Systems (Bedford, MA). Briefly, plasma samples were diluted and mixed with human plasma that had been immunodepleted of FXI activity. Correction of the clotting time of the FXI deficient plasma to that of the mixture was proportional to the residual activity of FXI in the plasma sample, interpolated from a calibration curve. The range of the quantitative analysis of FXI activity was 3.21%-200%. The inter- and intra-assay precisions were 2.99%-5.90% CV and 3.11%-4.31% CV, respectively.

Additional pharmacodynamic parameters included bleeding time (Surgicutt Adult device, Accriva Diagnostics Inc., San Diego, CA) and rotational thromboelastometry (ROTEM) whole blood clotting time (ROTEM delta analyzer [TEM International GmbH, Munich, Germany]), measured at screening (bleeding time only), predose on day 1, and 1, 4, 24, 48, 96, and 144 hours after the start of the infusion. To assess bleeding time, a standard incision (5 mm length, 1 mm depth) was made on the forearm, after which blood was absorbed from the incision using filter paper, every 30 seconds, until bleeding stopped. ROTEM whole blood clotting time was measured within 4 hours of blood sampling in citrated blood samples (3.2% or 3.8% citrate), using the manufacturer's reagents for in-tem (intrinsically activated test) measurements.

Blood samples for analysis of thrombosis biomarkers (D-dimer, thrombin-antithrombin complex [TAT] and prothrombin fragment 1.2 [F1.2]) were taken the day before drug administration and on days 7, 28, 84, and 150 (placebo, 0.30, 1.25, 2.5, 5, and 10 mg/kg dose steps). Blood samples were centrifuged within 15 minutes for plasma preparation and frozen immediately. Concentrations of the coagulation biomarkers D-dimer, F1.2, and TAT were measured in citrated plasma. Immunoturbidimetry was used to evaluate levels of D-dimer (STA Liatest D-DI PLUS assay kit and STA compact analyzer [Stago Deutschland GmbH, Düsseldorf, Germany], precision 2.88%-5.45% CV). Enzyme-linked immunosorbent assay (ELISA) was used to evaluate levels of F1.2 and TAT (Enzygnost F 1 + 2 MONO test kit [Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany], precision 8.44%-10.46% CV, and Enzygnost TAT micro kit [Siemens Healthcare Diagnostics, Marburg, Germany], precision 3.83%-8.75% CV).

2.5 | Pharmacokinetics

Blood samples for pharmacokinetic analysis were taken predose, at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, and 144 hours after the start of infusion, and at follow-up visits on days 14, 21, 28, 56 (±3 days) (all doses), day 84 (doses of 0.3 mg/kg or higher), and day 150 (±7 days) (doses of 1.25 mg/kg or higher). Plasma concentrations of total BAY 1213790 were measured using validated ELISA with electrochemiluminescence readout on a Sector Imager 6000 (Meso Scale Discovery, Rockville, MD) plate reader. BAY 1213790 was captured using a biotinylated anti-idiotypic antibody to the streptavidin-coated 96-well plate and detected using a SulfoTag-labeled anti-idiotypic antibody.

The calibration range of the procedure was 0.5 mg/L (lower limit of quantification [LLOQ]) to 6 mg/L. Samples more concentrated than 6 mg/L were diluted to concentrations within the calibration range. The mean interassay accuracy of back calculated concentrations (except LLOQ) in calibrators was 99%-106%, and the precision was ≤2.65%. Accuracy and precision at the LLOQ were 101% and 4.79%, respectively. Quality control samples (1.25-5 mg/L) were

determined with an accuracy of 101%-106% and a precision of 7.31%-9.95%. All samples were stored at or below −65°C and analyzed within 308 days of collection.

The evaluated pharmacokinetic parameters included: area under the plasma concentration–time curve (AUC) from time 0 to the time of the last measured plasma concentration greater than the LLOQ ($AUC_{(0-tlast)}$); AUC from time 0 to 1992 hours after dosing divided by dose ($AUC_{(0-1992)}/D$) (with dose being the absolute dose per individual, i.e, dose in mg/kg multiplied by body weight); AUC from time 0 to 1992 hours after dosing divided by dose per bodyweight ($AUC_{(0-1992),\ norm}$); maximum plasma drug concentration (C_{max}); C_{max} divided by dose (C_{max}/D); and C_{max} divided by dose per body weight ($C_{max,\ norm}$). Additional parameters were: AUC from time 0 to 1992 hours after dosing ($AUC_{(0-1992)}$); time to reach maximum plasma concentration (t_{max}); $t_{½}$; total body clearance (CL); and apparent volume of distribution at steady state (V_{ss}).

Pharmacokinetic parameters were calculated using the model-independent (compartment-free) method and WinNonlin software (version 5.3; Pharsight Corp., Sunnyvale, CA) in conjunction with the Automation Extension (Version WinAE 2.90; Bayer AG, Wuppertal, Germany).

2.6 | Statistical analyses

No formal sample size calculation was performed for this exploratory study. The maximum ratio to baseline in aPTT and the minimum ratio to baseline in apparent FXI activity were compared for each active treatment group vs placebo by using an exact Wilcoxon rank-sum test, at the one-sided significance level of $\alpha = 0.05$. Tests were performed in sequential order (i.e, if all previous null hypotheses for a specific endpoint had been rejected, the next null hypothesis was tested) starting with the highest dose. For placebo, data from the different dose steps were pooled. Hodges–Lehmann estimates of the shift from placebo were determined, together with the associated two-sided 90% CIs.

The following pharmacokinetic parameters were analyzed assuming log-normally distributed data: $AUC_{(0-1992)}/D$, $AUC_{(0-1992),norm}$, C_{max}/D and $C_{max,\ norm}$. An exploratory analysis of variance (ANOVA) including the factor treatment was performed on log-transformed values of these parameters to investigate dose proportionality.

Statistical test results were not adjusted for multiplicity and were considered exploratory. There was no imputation for missing data. Analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC).

3 | RESULTS

3.1 | Volunteer disposition and demography

In total, 83 healthy Caucasian men were randomized to receive BAY 1213790 or placebo; of these, 81 received study medication (Table 1). A total of 78 volunteers completed the study (Figure 1).

3.2 | Safety

All 81 patients who received study medication were included in the safety-analysis set (Table 2). Overall, single intravenous doses of BAY 1213790 were well tolerated. In total, 54 of the 81 volunteers who received BAY 1213790 reported at least one treatment-emergent AE, with incidences in the active treatment groups ranging from 29% (two volunteers, 0.15 mg/kg group) to 100% (eight volunteers, 1.25 mg/kg group) compared with 60% (nine volunteers) in the placebo group (Table 2). The most frequently observed AEs were headache (18.5%) and nasopharyngitis (17.3%). All AEs were of mild to moderate intensity, and there was no relationship between BAY 1213790 dose and causality or intensity of AEs.

Treatment-emergent AEs with a possible relationship to study drug administration were reported in six volunteers (7.4%) (Table 2). One volunteer receiving 0.6 mg/kg BAY 1213790 experienced a generalized feeling of warmth, nausea (both mild), and vomiting (moderate) attributed to an infusion reaction; this volunteer also experienced headache (moderate), an increased urge to defecate (mild), and a feeling of cold (mild). Another volunteer in the 0.6-mg/kg dose group requested that the infusion be stopped after he experienced decreased breathing resistance and dizziness (both mild); this volunteer also experienced sensations of warmth, malaise, and headache (all mild), and a feeling of cold (moderate). The other treatment-emergent AEs were: multiple mild erythema (two lesions on the right upper arm, three on the left lower arm, and one on the left upper arm [one volunteer in the 1.25 mg/kg dose group]), mild headache (two volunteers [one in the 0.3-mg/kg dose group and one in the 5-mg/kg dose group]), and a single occurrence of nonsymptomatic mild ventricular tachycardia (one volunteer in the 2.5-mg/kg dose group).

No other signs of potential drug-related hypersensitivity reactions, spontaneous bleeding, or thrombocytopenia were observed during the study. There were no treatment-related serious AEs or deaths in any group and no findings of clinical significance with respect to laboratory tests, vital signs, electrocardiograms, or physical examinations.

Antidrug antibodies were detected in two blood samples (one on day 56 [0.015-mg/kg dose group] and one on day 14 [0.6-mg/kg dose group]), each with the lowest measurable titer of 1, and were not associated with unexpected pharmacodynamic or safety findings or altered plasma concentrations of BAY 1213790.

3.3 | Pharmacodynamics

The pharmacodynamic analysis set included data from 80 volunteers. Data from the volunteer whose infusion was terminated owing to AEs were not included.

3.3.1 | aPTT

Dose-dependent increases in aPTT were observed following BAY 1213790 administration (Figure 2A and B); the increase vs placebo was significant for all doses except the lowest dose studied (0.015 mg/kg) (Table S1). Following administration of 10 mg/kg BAY 1213790, the maximal mean increases in aPTT relative to baseline observed with the

TABLE 1 Volunteer demography (safety analysis set)

	BAY 1213790 (mg/kg)										
	Placebo (n = 15)	0.015 (n = 7)	0.06 (n = 7)	0.15 (n = 7)	0.30 (n = 6)	0.60 (n = 8)	1.25 (n = 8)	2.50 (n = 8)	5.0 (n = 8)	10.0 (n = 7)	Total (n = 81)
Sex, n (%)											
Male	15 (100)	7 (100)	7 (100)	7 (100)	6 (100)	8 (100)	8 (100)	8 (100)	8 (100)	7 (100)	81 (100)
Race, n (%)											
White	15 (100)	7 (100)	7 (100)	7 (100)	6 (100)	8 (100)	8 (100)	8 (100)	8 (100)	7 (100)	81 (100)
Age, y											
Mean (SD)	40.3 (11.1)	38.7 (11.6)	47.0 (5.7)	43.6 (0.3)	37.3 (10.9)	41.8 (6.6)	32.8 (6.3)	38.3 (9.9)	36.6 (9.4)	37.4 (14.2)	39.4 (10.1)
Range	22-54	23-52	35-52	26-53	21-51	32-50	23-39	27-54	27-53	19-55	19-55
Weight (kg)											
Mean (SD)	81.3 (5.9)	77.1 (7.0)	82 (11.4)	75 (8.0)	79.8 (8.6)	79.4 (4.7)	80.4 (10.5)	80.8 (7.8)	80 (8.8)	75.7 (11.5)	79.4 (8.2)
Range	71-92	63-85	63-94	68-88	71-92	71-84	68-95	69-93	68-94	57-88	57-95
Height, cm											
Mean (SD)	181 (5.4)	183 (10.5)	181 (7.5)	181 (2.3)	180 (6.6)	178 (6.5)	179 (4.7)	176 (6.1)	182 (7.4)	177 (8.1)	180 (6.6)
Range	171-188	163-198	170-191	177-184	167-184	170-187	169-185	165-183	175-198	168-192	163-198
BMI (kg/m^2)											
Mean (SD)	24.8 (2.2)	22.9 (0.8)	25 (2.5)	22.9 (2.3)	24.9 (3.4)	25 (2.1)	24.9 (2.4)	26 (2.0)	24.1 (2.1)	24.1 (3.8)	24.5 (2.4)
Range	21.9-29.7	21.7-23.7	21.8-28.1	21.3-26.6	21.3-29.4	22.6-29.1	22-28.1	22-28.3	22-27.8	19.3-29.1	19.3-29.7
Smoking history, n (%)											
Never	8 (53.3)	4 (57.1)	6 (85.7)	3 (42.9)	3 (50)	7 (87.5)	5 (62.5)	6 (75)	3 (37.5)	4 (57.1)	49 (60.5)
Former	5 (33.3)	1 (14.3)	0	2 (28.6)	0	1 (12.5)	1 (12.5)	0	1 (12.5)	1 (14.3)	12 (14.8)
Current	2 (13.3)	2 (28.6)	1 (14.3)	2 (28.6)	3 (50.0)	0	2 (25.0)	2 (25.0)	4 (50.0)	2 (28.6)	20 (24.7)
Alcohol use, n (%)											
Abstinent	6 (40)	1 (14.3)	1 (14.3)	3 (42.9)	4 (66.7)	1 (12.5)	0	2 (25.0)	0	0	18 (22.2)
Light	9 (60)	6 (85.7)	6 (85.7)	4 (57.1)	2 (33.3)	7 (87.5)	8 (100)	6 (75.0)	8 (100)	7 (100)	63 (77.8)

BMI, body mass index; SD, standard deviation.

conventional and kaolin-triggered methods were 1.85 (corresponding to an absolute value of 61.9 seconds) and 2.17 (corresponding to an absolute value of 65.4 seconds), respectively.

For doses of 0.6 mg/kg or higher, aPTT (conventional and kaolin-triggered methods) remained elevated above baseline for at least 20 days. Mean aPTT values above the upper limit of normal (40 seconds for the conventional method and 33 seconds for the kaolin-triggered method) were still observed 55 days after drug administration for doses of 1.25 mg/kg or higher. Measurements made using both methods demonstrated low interindividual variability, with standard deviations below 7.5 seconds for all dose steps.

3.3.2 | FXI activity

There was a dose-dependent reduction in apparent FXI activity from baseline following BAY 1213790 administration (Figure 3). For doses of 0.15 mg/kg or higher, the reduction in FXI activity was significant vs placebo (Table S2). The minimum mean ratio to baseline was 0.176, which was observed 1 hour after administration of 10 mg/kg BAY 1213790. For all doses, FXI activity was maximally inhibited almost immediately after drug administration and gradually returned to values close to baseline after approximately 55 days. The interindividual variability in the effect of BAY 1213790 on FXI activity was moderate with standard deviations of 10%-20% for all dose steps (Figure 3).

3.3.3 | Bleeding time

Bleeding times did not increase following BAY 1213790 administration and were similar across all study dose cohorts, including placebo, during the first 6 days following drug administration (Figure 4).

3.3.4 | ROTEM whole blood clotting time

Following administration of BAY 1213790, there was a dose-dependent increase in clotting time (Figure S1). Clotting time remained elevated in a dose-dependent manner for at least 144 hours after administration of all doses of BAY 1213790.

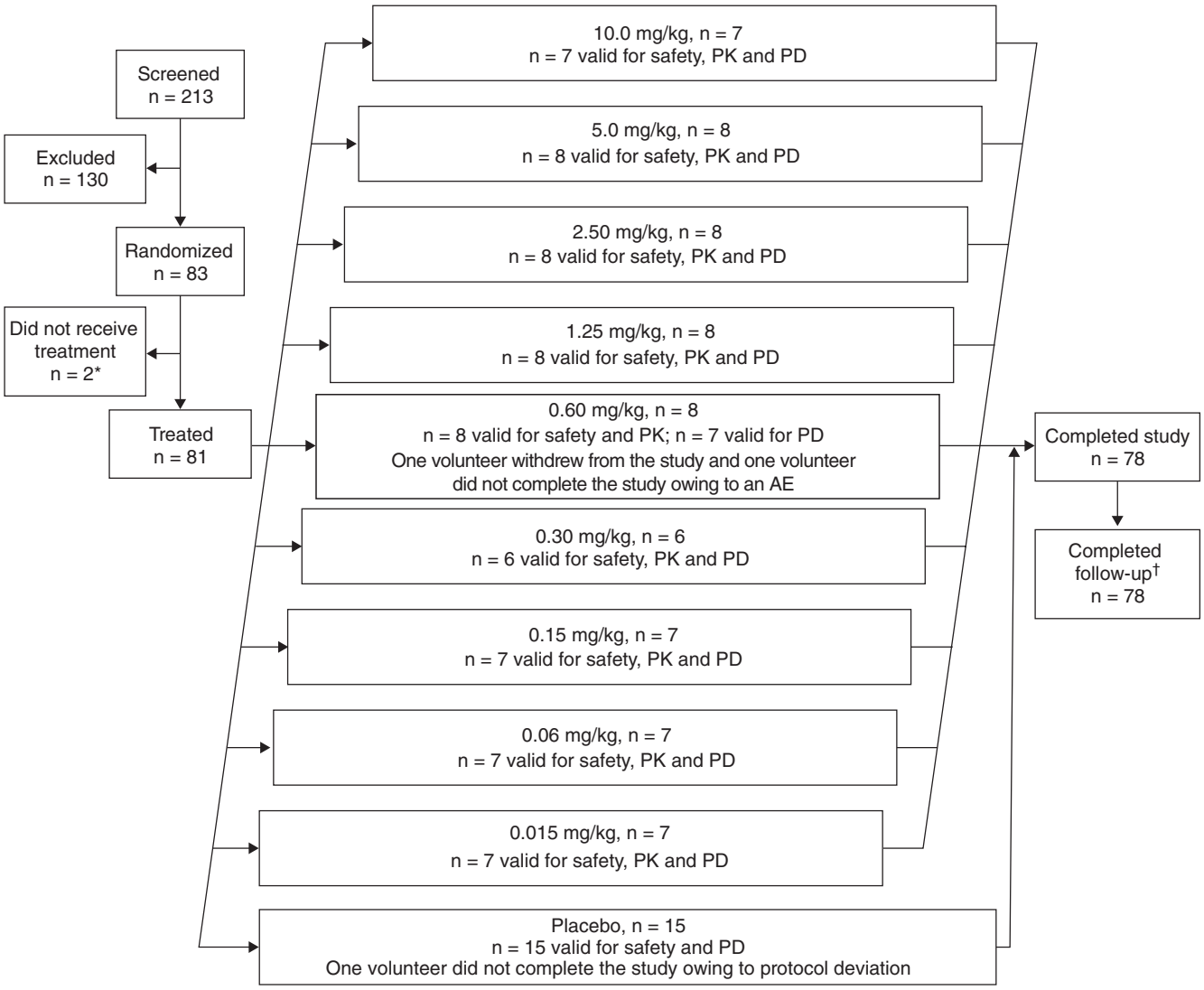

FIGURE 1 Volunteer disposition. *One volunteer in the placebo group and one in the BAY 1213790 0.06 mg/kg group were randomized but did not receive treatment. †One volunteer in the BAY 1213790 0.6 mg/kg group who did not complete the study owing to an AE completed follow-up; one volunteer who completed the study was lost to follow-up. AE, adverse event; PD, pharmacodynamics; PK, pharmacokinetics

3.3.5 | Biomarkers of thrombosis

Levels of D-dimer, TAT, and F1.2 did not significantly increase from baseline following administration and, throughout the study, were similar to levels measured in volunteers who received placebo (Figure S2). Overall there were no signs of procoagulant activity following BAY 1213790 administration.

3.4 | Pharmacokinetics

The pharmacokinetic analysis included data from 66 volunteers who received BAY 1213790. There was a dose-dependent increase in exposure to BAY 1213790 with measurable systemic exposure for all doses of 0.06 mg/kg or higher (Figure 5). Summary statistics were not calculated for the 0.015 mg/kg dose group and are not shown in Figure 5 because measurable plasma concentrations were only detected in one volunteer. For the eight dose steps evaluated, $AUC_{(0-tlast)}$ and C_{max} increased with increasing dose. Variability in these parameters was low to moderate with geometric CVs of 12.7%-34.5% and 11%-20.3%, respectively (Tables 3 and S3).

The median t_{max} of BAY 1213790 was between 1.05 and 4 hours after the start of the infusion, and the mean elimination half-life of total BAY 1213790 was approximately 30-44 days (715-1050 hours). The mean CL and mean V_{ss} were in the range 0.13-0.29 L/day and 4-11 L, respectively. An exploratory ANOVA of selected exposure parameters normalized by dose or by dose and body weight did not suggest clear dose proportionality (Table S4).

4 | DISCUSSION

This first-in-human, phase 1, dose-escalation study demonstrated that single intravenous doses of the fully human IgG1 mAb,

TABLE 2 Safety profile of BAY 1213790 in healthy volunteers

		BAY 1213790 (mg/kg)								
	Placebo (n = 15)	0.015 (n = 7)	0.06 (n = 7)	0.15 (n = 7)	0.3 (n = 6)	0.6 (n = 8)	1.25 (n = 8)	2.5 (n = 8)	5 (n = 8)	10 (n = 7)
AEs, n (%)	9 (60)	3 (43)	5 (71)	2 (29)	5 (83)	4 (50)	8 (100)	5 (63)	7 (88)	6 (86)
Mild	6 (40)	2 (29)	2 (29)	1 (14)	2 (33)	2 (25)	4 (50)	4 (50)	6 (75)	5 (71)
Moderate	3 (20)	1 (14)	3 (43)	1 (14)	3 (50)	2 (25)	4 (50)	1 (13)	1 (13)	1 (14)
Treatment-related AEs, n (%)	0	0	0	0	1 (17)[a]	2 (25)[b,c]	1 (13)[d]	1 (13)[e]	1 (13)[a]	0
Serious AEs, n (%)	0	0	1 (14)[f]	0	0	0	0	0	0	0
Serious treatment-related AEs, n (%)	0	0	0	0	0	0	0	0	0	0
AEs leading to discontinuation, n (%)	0	0	0	0	0	1 (13)[b]	0	0	0	0

AE, adverse event.
[a]Headache (mild).
[b]Dizziness, decreased breathing resistance, feeling of warmth in the face, malaise and headache (all mild), and feeling cold (moderate)—infusion was stopped prematurely in this volunteer.
[c]One volunteer experienced a generalized feeling of warmth, nausea, feeling cold, increased urge to defecate (all mild), headache, and vomiting (moderate).
[d]Multiple erythema (mild); two lesions on the right upper arm, three on the left lower arm, and one on the left upper arm.
[e]Nonsymptomatic ventricular tachycardia (mild), which was not associated with any signs of hypersensitivity reaction, was observed 19 h and 46 s after the start of the infusion and lasted four beats with a rate of 160 beats per min. A cardiologic examination the same day did not demonstrate any signs of relevant ischemic or structural heart disease in this volunteer, and no recurrence of this AE was reported during the remainder of the study.
[f]Contusion of left shoulder after a bicycle accident.

BAY 1213790 (0.015-10.0 mg/kg), had a favorable safety profile and were well tolerated. BAY 12313790 administration was associated with increases in aPTT and ROTEM whole blood clotting time and decreases in apparent FXI activity that were dose-dependent. Bleeding times in volunteers who had received BAY 1213790 (all doses) were similar to bleeding times in volunteers who had received placebo.

There were no signs of spontaneous, prolonged, or hidden bleeding following BAY 1213790 administration. BAY 1213790 is a fully human mAb, and accordingly the incidence of infusion reaction in the present study was low (1.2%). In addition, no clinically relevant antidrug antibody formation was observed. Infusion-related reactions, ranging in severity from mild to severe, have been observed following administration of mAbs and can occur at the first or following repeated exposure.[23] The risk of these reactions is lower with fully human mAbs than with humanized or chimeric mAbs; for example, the incidence of infusion reactions has been reported as 4% for the fully human mAb panitumumab compared with 77% for rituximab, a human/mouse chimeric mAb.[24,25] Moreover, nontherapeutic, neutralizing antidrug antibodies can develop after mAb administration and bind epitopes needed for biological activity, which can potentially alter the pharmacokinetics, safety, and/or efficacy of the mAb.[23] Fully human antibodies, such as BAY 1213790, are associated with a lower risk of such immune responses in humans than mouse or chimeric antibodies.[26]

Generally, the effects of BAY 1213790 on aPTT, FXI activity, and ROTEM whole blood clotting time are consistent with its mechanism of action. Importantly, evaluation of biomarkers of coagulation (D-dimer, F1.2, and TAT) did not demonstrate any evidence of procoagulant activity over the course of BAY 1213790 exposure and up to 150 days after drug administration. Preclinical data have demonstrated that BAY 1213790 inhibited FXIa activity (biochemical FXIa assay) with a half-maximal inhibitory concentration of 2 nmol/L and prolonged aPTT in human plasma by 1.5-fold at a concentration of 20 nmol/L, with no significant effect on prothrombin time,[27] highlighting the specific inhibitory effects of BAY 1213790 on the intrinsic coagulation pathway. In the present study, aPTT was evaluated using a conventional silica-based assay and a kaolin-triggered assay. Results with both assays were similar, but the different reagents used afforded different sensitivities; the maximal mean increases of aPTT to baseline observed in the 10 mg/kg dose group were 1.85 and 2.17 for the conventional assay and the kaolin-triggered assay, respectively. These data highlight the importance of consistency when selecting reagents for aPTT assays to evaluate the effects of BAY 1213790. Approaching the aPTT plateau indicates that the maximum achievable FXIa activity inhibition with BAY 1213790 has been reached.

Data from the explorative evaluations of bleeding time with the Surgicutt test demonstrated no relevant or dose-dependent changes in the first 6 days following BAY 1213790 administration and are in agreement with preclinical observations in rabbits.[27] Preclinical and clinical studies of other pharmacological inhibitors of FXI or FXIa also provide supportive evidence that selective inhibition of FXI or FXIa is not associated with an increased risk of bleeding.[3,12-22]

The pharmacokinetic profile of BAY 1213790 was consistent with that of other intravenously administered human IgG1 mAbs.[28] After reaching a peak, BAY 1213790 plasma concentrations declined slowly

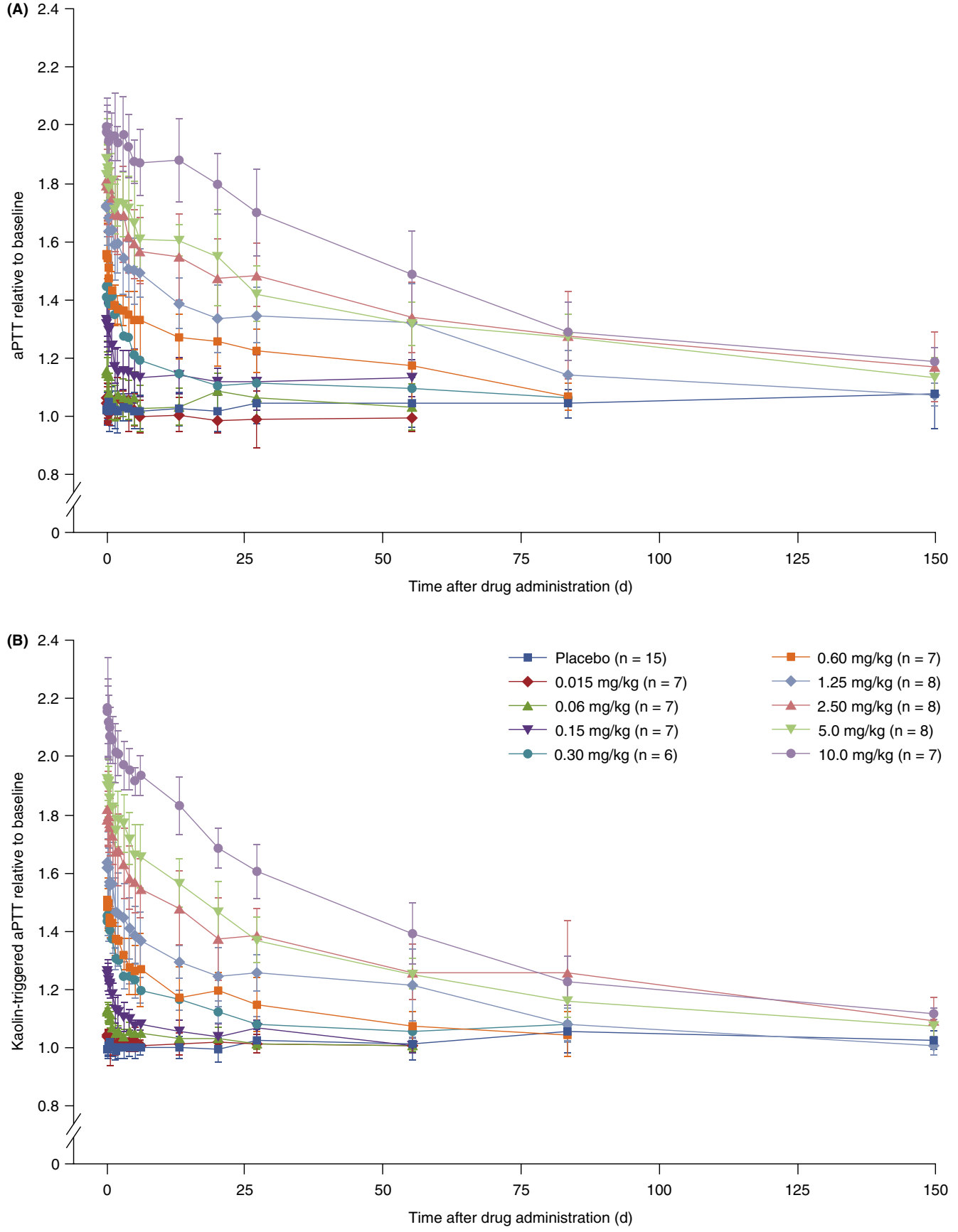

FIGURE 2 Effects of increasing doses of BAY 1213790 on aPTT in healthy volunteers measured using (A) a conventional method and (B) a kaolin-triggered method. Data are presented as mean and standard deviation. aPTT, activated partial thromboplastin time

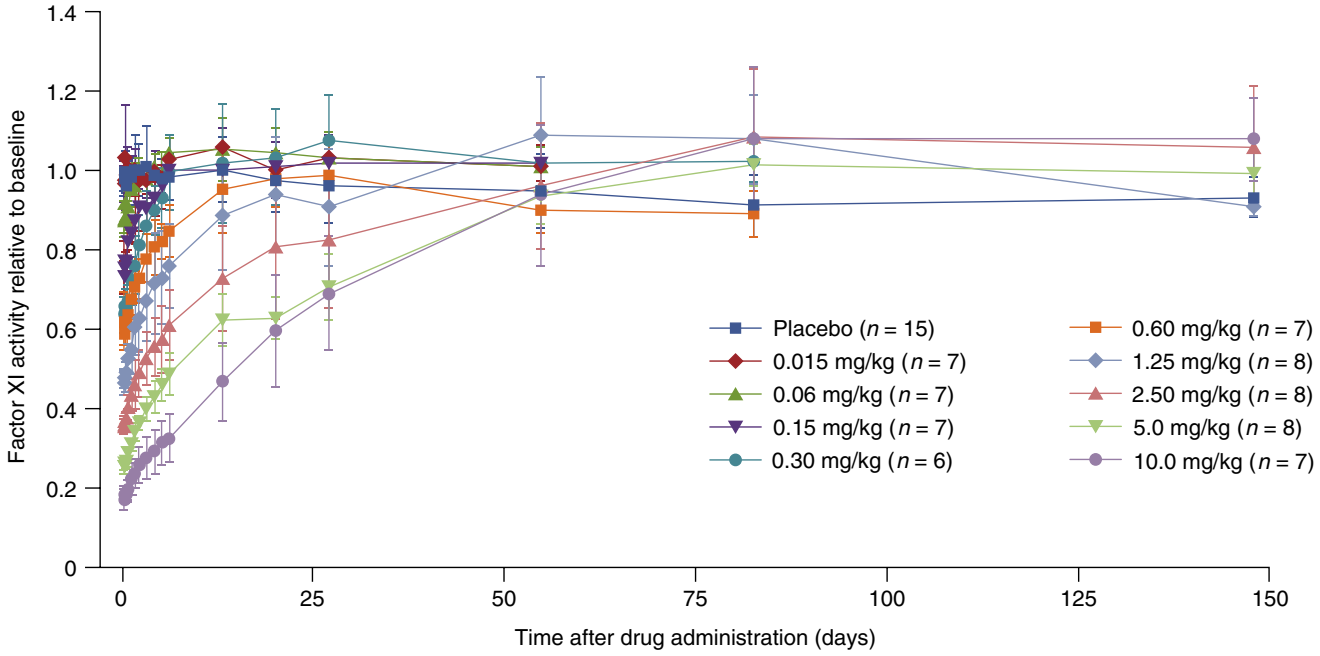

FIGURE 3 Effects of increasing doses of BAY 1213790 on apparent factor XI activity in healthy volunteers. Data are presented as mean and standard deviation

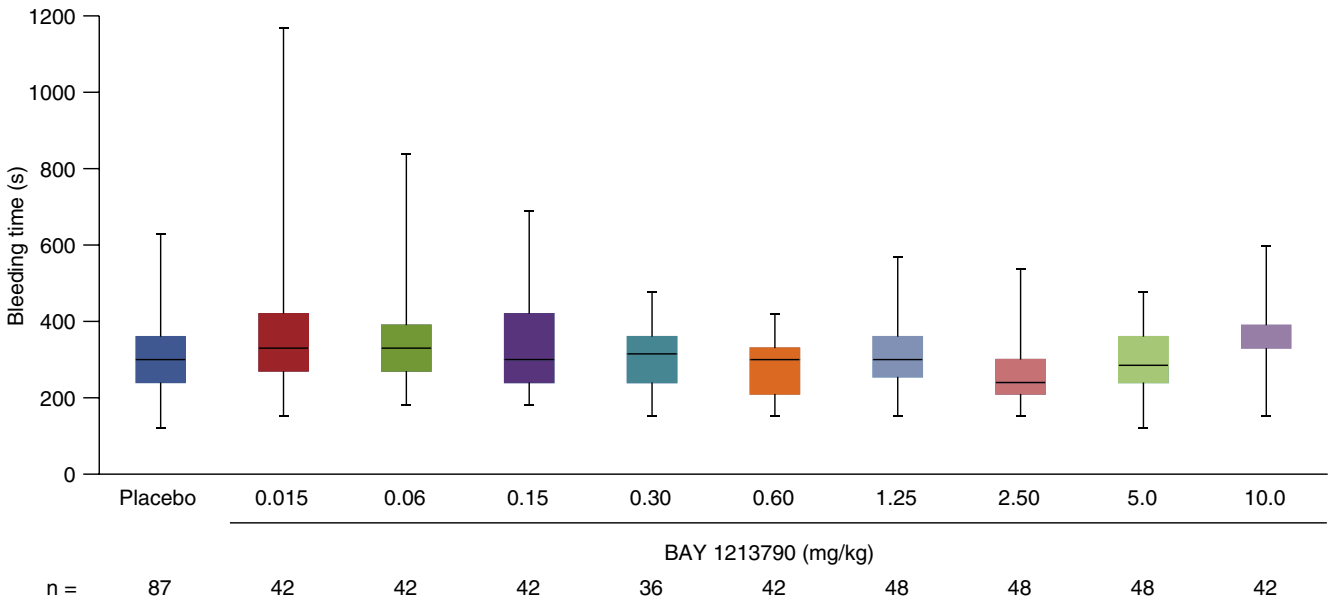

FIGURE 4 Effect of increasing doses of BAY 1213790 on bleeding time in healthy volunteers measured using the Surgicutt system. Data are presented as box-and-whisker plots and represent pooled values for d 1-7; upper and lower lines of the box denote the upper and lower quartiles, respectively, midlines denote the medians, and upper and lower lines denote the maximum and minimum values, respectively

in a multiphasic pattern. Concentrations of BAY 1213790 declined only marginally from the end of the infusion to 3 hours thereafter. Variability in the median t_{max} of BAY 1213790 (1.05-4 hours after the start of the infusion) might be explained by bioanalytical assay variability. The low clearance (CL: 0.13-0.29 L/day) and volume of distribution (V_{ss}: 4-11 L) of BAY 1213790 are consistent with published data for other mAbs.[28,29] The half-life (30-44 days) of BAY 1213790 tended to increase dose-dependently; however, this observation is considered to be biased by the detection limit of the assay and differences in plasma concentration–time data owing to longer follow-up periods with high vs low doses. An exploratory ANOVA of selected exposure parameters normalized by dose or by dose and body weight did not suggest clear dose proportionality, which might be driven by lower-than-expected exposures for the high-dose steps.

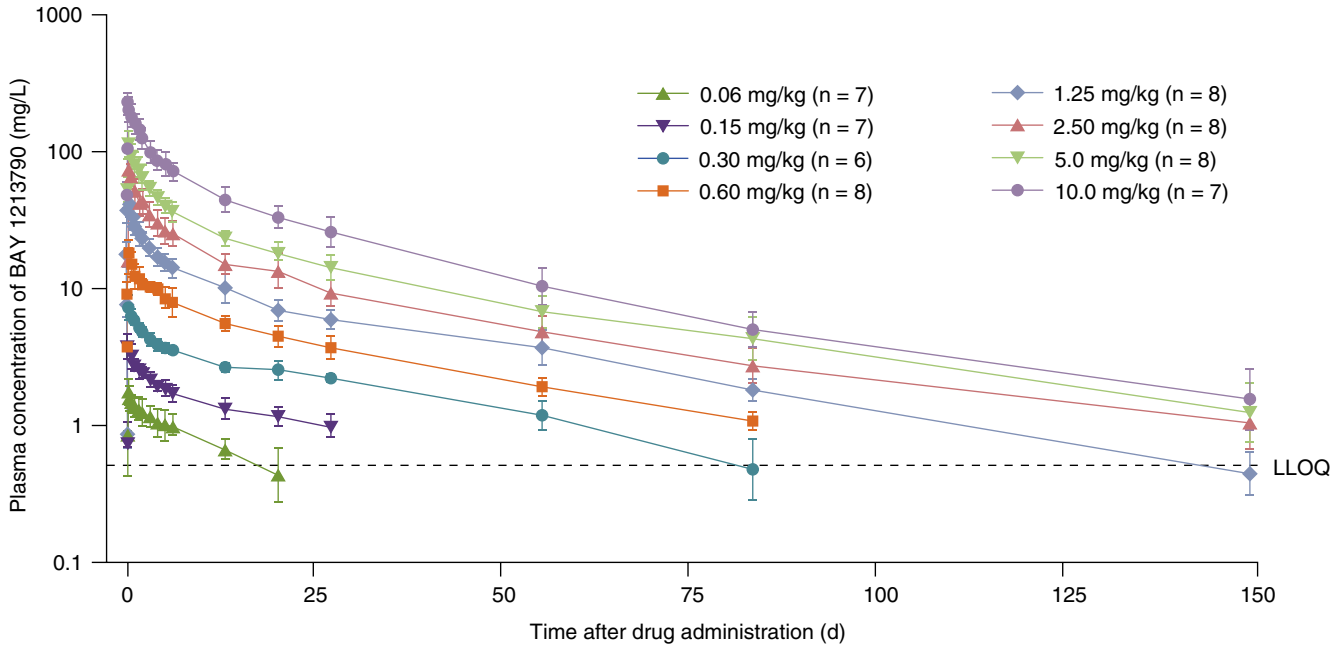

FIGURE 5 Plasma concentration–time profile of total BAY 1213790 (0.06-10 mg/kg)* in healthy volunteers following a 60-minute intravenous infusion. *Data for the 0.015 mg/kg dose group are not shown because measurable plasma concentrations were only detected in one volunteer. LLOQ, lower limit of quantification

TABLE 3 Pharmacokinetic parameters of BAY 1213790 in healthy volunteers

	BAY 1213790 (mg/kg)[a]							
	0.06 (n = 7)	0.15 (n = 7)	0.3 (n = 6)	0.6 (n = 8)	1.25 (n = 8)	2.5 (n = 8)	5 (n = 8)	10 (n = 7)
C_{max} (mg/L)	1.98 (11)	3.85 (16.8)	8.01 (11.6)	22.3 (14.2)	42.6 (12.5)	78.5 (13)	116 (13.1)	240 (20.3)
$AUC_{(0-tlast)}$ (mg h/L)	415 (28)	1270 (34.5)	3610 (17.9)	7200 (12.7)	14 200 (15.8)	23 700 (16)	35 000 (18.5)	60 400 (19.3)
t_{max}[b] (h)	1.98 (1.03-7.98)	1.07 (1-4)	1.52 (1.02-2.03)	2.02 (1.07-12.1)	4 (1.02-8)	3 (1-8)	2 (1-4)	1.05 (1.02-4)
$t_{½}$ (h)	422 (49.9)	715 (25.2)	748 (14.3)	729 (12.7)	809 (11.8)	1050 (16.5)	936 (18.3)	848 (15.9)
CL (10^{-3} L/h)	6.36 (45.1)	5.44 (26.8)	5.35 (9.2)	5.65 (12.8)	6.63 (19.3)	7.87 (18.1)	10.8 (24.5)	11.9 (24.8)
V_{ss} (L)	3.82 (21.6)	5.41 (5.93)	5.6 (9.25)	5.43 (12.1)	6.58 (17.2)	8.69 (14.7)	10.9 (18.1)	9.62 (25.6)

Data are presented as geometric mean (% coefficient of variation) unless stated otherwise.
AUC, area under the plasma concentration–time curve; $AUC_{(0-tlast)}$, AUC from time 0 to the time of the last measured plasma concentration greater than the lower limit of quantification; CL, total body clearance; C_{max}, maximum plasma drug concentration; $t_{½}$, elimination half-life; t_{max}, time to reach maximum plasma concentration; V_{ss}, apparent volume of distribution at steady state.
[a]Only one volunteer in the lowest dose group (0.015 mg/kg) had measurable plasma concentrations of BAY 1213790, so summary statistics were not calculated.
[b]Data are presented as median (range).

The liver and kidneys do not generally play significant roles in the elimination of mAbs.[30] BAY 1213790 therefore offers the potential for use in patients with renal or hepatic impairment and a low risk of pharmacokinetic drug–drug interactions. The long half-life of BAY 1213790 will facilitate convenient, infrequent dosing (e.g, once per month) to achieve stable, steady-state plasma levels, which will be desirable for long-term thromboprophylaxis.

The limitations of this study are inherent to phase 1 studies. In order to minimize risk to volunteers at this early stage of clinical development, women were excluded because data from reproductive studies were not available at the time of study conception. Data from a small number of healthy Caucasian men might not necessarily apply to other populations, including women, patients requiring thromboprophylaxis or those with acute thrombosis. In addition, the association between the results of aPTT or FXI activity assays and clinical outcomes in patients receiving BAY 1213790 are unknown. Further studies of the safety, pharmacodynamics, and pharmacokinetics of BAY 1213790 in heterogenous patient populations are needed. The first clinical

investigation of the efficacy and safety of BAY 1213790 in patients undergoing total knee-replacement surgery is under way (ClinicalTrials.gov identifier: NCT03276143). The long half-life of BAY 1213790 may raise concerns regarding bleeding. A specific reversal agent is under evaluation, but the true clinical need for such an agent is unknown.

Based on the results obtained in this study, BAY 1213790 offers promise as a potential long-acting novel anticoagulant. Further evaluation in patients with, or at risk of, thrombosis is warranted.

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RELATIONSHIP DISCLOSURES

D. Thomas, K. Thelen, S. Kraff, S. Schwers, S. Schiffer, S. Unger, and A. Yassen are employees of Bayer AG, which provided funding for this study. S. Boxnick is an employee of CRS Clinical Research Services, which received funding from Bayer AG for conducting this study.

AUTHOR CONTRIBUTIONS

D. Thomas, S. Schwers, S. Schiffer, and A. Yassen were involved in the design, analysis, and interpretation of the pharmacodynamic experiments. K. Thelen and S. Kraff were involved in the design, analysis, and interpretation of the pharmacokinetic experiments. S. Unger was involved in statistical analyses. S. Boxnick was the principal investigator and was responsible for the design and conduct of the study, and the reporting of data. All authors were involved in critically revising the manuscript for important intellectual content and approved the final version of the manuscript.

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SUPPORTING INFORMATION

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

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