Drugs of the Future 2021, 46(12): 955-962

CCC: 0377-8282/2021
DOI: 10.1358/dof.2021.46.12.3349024

Clarivate™

Monograph

Abelacimab

Prop INN

Anti-factor XI/XIa monoclonal antibody
Treatment of atrial fibrillation
Treatment of thrombotic disorders

J. Hardy[1], A. Sperry[1], H. Hartmann[1], R.F. Goldfaden[1], M. Ashchi[2], R. Kim[2], J. Huston[3], S. Niman[1] and R. Choksi[1]

[1]East Coast Institute for Research, Jacksonville, Florida, USA; [2]Ashchi Heart & Vascular Center, Jacksonville, Florida, USA; [3]University of Florida, College of Pharmacy, Jacksonville, Florida, USA

Contents

Summary

Thromboembolic disorders are a major cause of morbidity and mortality worldwide. Anticoagulation therapies represent the primary method for the treatment and/or prevention strategies for thromboembolic diseases. Currently available and approved anticoagulant agents, including warfarin and direct oral anticoagulants (DOACs), all interfere with the components of the common coagulation pathway, which play a key role in maintaining hemostasis. These agents' effects on the common coagulation pathway, and thus disruption on hemostasis, increase the risk of potentially fatal bleeding events. This increased risk for clinically significant bleeds highlights a large unmet need for safer antithrombic therapies. Factor XI (FXI) has surfaced as an alluring target for the development of safer anticoagulants based on human genetic, epidemiological and pharmacological evidence. The growing evidence suggests that reducing FXI levels may prevent thrombosis with potentially no-to-limited bleeding risk. This review aims to present and discuss the current clinical and scientific evidence pertaining to abelacimab, a novel FXI inhibitor.

Key words: Abelacimab – MAA-868 – Factor XI – Thrombotic disorders – Anticoagulation – Atrial fibrillation

Correspondence: Rebecca F. Goldfaden, PharmD, East Coast Institute for Research, 3550 University Blvd. South, Suite 101, Jacksonville, FL, 32216, USA. E-mail: Rebecca.Goldfaden@ecirmed.com.

MAA-868
NOV-12

Human monoclonal IgG1 λ antibody targeting human coagulation factor XI

γ1 heavy chain (1-452) [*Homo sapiens* VH (IGHV3-23*01 (93.9%) -(IGHD) -IGHJ4*01 (100%)) [8.8.15] (1-122) -Human IGHG1*03, G1m3, nG1m1 (CH1 R120 (219) (123-220), hinge (221-235), CH2 D27>A (270), P114>A (334) (236-345), CH3 E12 (361), M14 (363) (346-450), CHS (451-452)) (123-452)], (225-215')-disulfide with λ light chain (1'-216') [Human V-LAMBDA (IGLV1-44*01 (93.5%) -IGLJ2*01 (100%)) [8.3.11] (1'-110') -Human IGLC2*01 (111'-216')]; dimer (231- 231'': 234-234'')-bisdisulfide

Cortellis Drug Discovery Intelligence Entry Number: 926539

Background

Cardiovascular disease remains the leading cause of morbidity and mortality globally, of which thromboembolic disorders account for 1 in 4 deaths (1). In addition, ischemic heart disease and stroke collectively account for over 10 million deaths per year worldwide, in which the rate has increased 25-35% over the past 20 years (1, 2). Thrombosis has been identified as the common underlying pathology of myocardial infarction (MI), ischemic stroke and venous thromboembolism (VTE). In addition, certain underlying conditions, such as atrial fibrillation (AF), can increase the risk of thrombosis and predispose patients to having detrimental thrombotic events (3). Anticoagulation therapy is the mainstay approach to prevent and/or treat thromboembolic conditions with the goal of therapy to mitigate thrombosis without disturbing hemostasis (2). Current anticoagulants used for treating these conditions interfere directly or indirectly with 2 key procoagulants—thrombin and factor Xa (FXa)—both of which belong to the common pathway of the coagulation cascade (2, 4). Clinically used anticoagulants include vitamin K epoxidase antagonists (e.g., warfarin), heparins (e.g., unfractionated heparin, low

molecular weight heparins, and fondaparinux), direct inhibitors of thrombin (e.g., argatroban, bivalirudin and dabigatran), and FXa inhibitors (e.g., apixaban, rivaroxaban, edoxaban and betrixaban). These agents have demonstrated efficacy in preventing and/or treating thrombosis, but are associated with increased risk of the life-threatening adverse effect of internal bleeding, particularly intracranial, gastrointestinal and retroperitoneal hemorrhage (2).

Historically, warfarin and heparins were the anticoagulants of choice despite their patient-to-patient response variability and significant bleeding risk. In addition, warfarin use is confounded by many limitations such as various food and drug interactions and frequent INR drug monitoring which requires dosing adjustments to maintain therapeutic range. These limitations led to the development of direct anticoagulants (DOACs). DOACs addressed many of the limitations of warfarin therapy; however, even with an improved bleeding safety profile, DOACs still retain a significant bleeding risk (5, 6). Accordingly, despite the advances made in anticoagulation therapy, there is an urgent need to develop new anticoagulants that prevent and/or treat thromboembolic conditions without the risk of bleeding.

Factor XI's role in the coagulation cascade

The need for safer anticoagulation therapy has shifted research toward targeting additional clotting factors, and factor XI (FXI) has generated much interest. FXI is a clotting factor upstream of the traditional targets, factor X (FX) and thrombin, and many studies have been evaluating its unique role in the coagulating cascade. The coagulation process is a crucial component in maintaining hemostasis and is a series of chemical biotransformations that encompasses the intrinsic (also referred as contact pathway), extrinsic and common pathways (Fig. 1). Both the intrinsic and extrinsic pathways lead into the common pathway that results in thrombin generation and the formation of fibrin clots. The intrinsic pathway has been shown to amplify FXa and significantly contribute to thrombosis (7, 8). Specifically, FXI contributes to fibrin formation by activating FVIII and appears to have a critical role in thrombosis with a relatively limited impact on hemostasis (8). Previous research has unveiled the intricate relationship between FXI and the extrinsic pathway, where FXI is involved in pathways required for sustained production of thrombin that impact fibrin clot formation and stability (8). To add to the propagation of thrombin, thrombin itself, as well as FXII, can further induce FXI activity via feedback mechanisms (8). In this way, FXI can be viewed as a central node linking numerous pathophysiologic conditions and therefore, it can be expected that dysregulation of FXI would contribute to thromboembolic conditions.

Because FXI displays both procoagulant and antifibrinolytic activities, it has been suggested that an underlying cardiovascular benefit may protect FXI-deficient patients. An epidemiological study that included 115 Ashkenazi Jews with severe FXI deficiency compared the incidence of ischemic stroke to that of the general Israeli population and showed

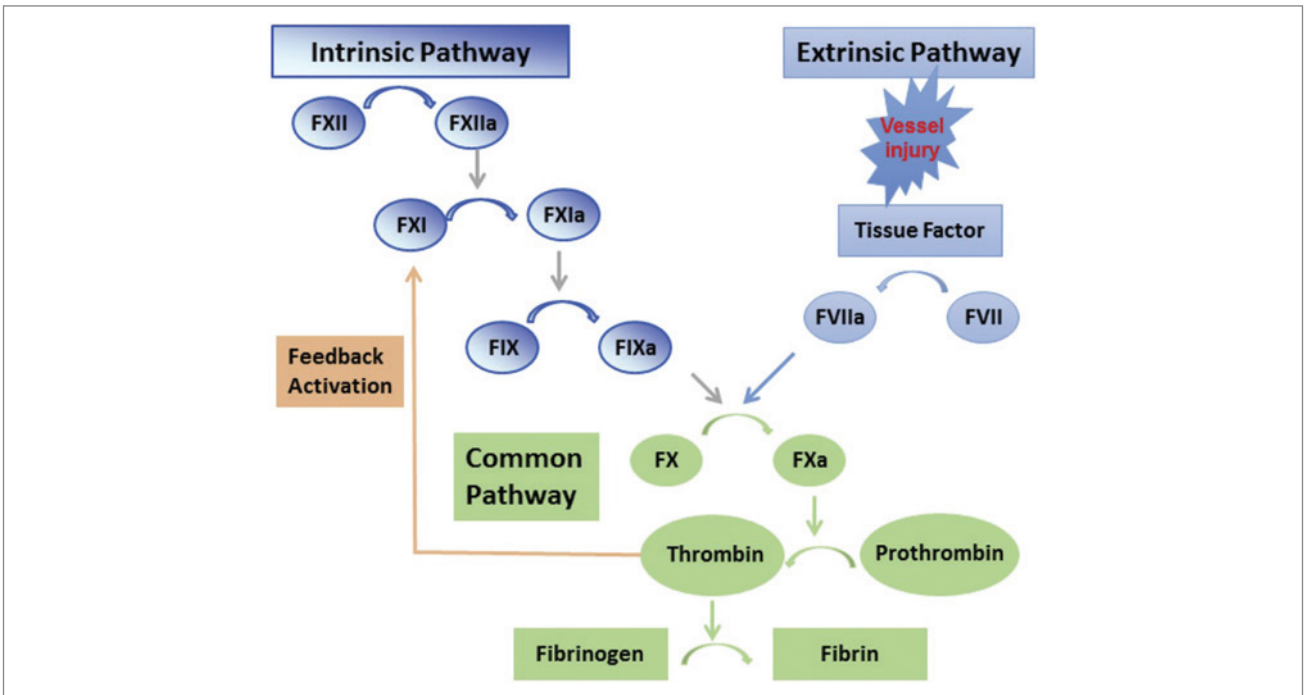

Figure 1. Schematic overview of the coagulation cascade. (Reprinted with permission from Quan, M.L. et al. *Factor XIa inhibitors as new anticoagulants*. J Med Chem 2018, 61(17): 7425-47 (12). Copyright © 2018 American Chemical Society.)

that ischemic stroke was significantly less frequent in the FXI-deficient population (9). In addition, patients with severe FXI deficiency were found to be protected against deep vein thrombosis (DVT) (10). However, this protection appears to only be seen for ischemic stroke and DVT and not for MI, where a study conducted by Salomon et al. showed the incidence of MI in severe FXI-deficient patients was similar to that in the overall population (11). Animal studies appear to supplement these results, where FXI- and FXII-deficient mice exhibited equally attenuated thrombosis at the site of arterial or venous injury and unstable thrombi that undergo rapid fragmentation (4). Results in a primate model were similar: FXI knockdown with an antisense oligonucleotide (ASO) reduced thrombosis in a concentration-dependent manner once FXI levels were less than 50% of normal (4).

Epidemiological and experimental data suggest that FXI and FXII are preferred targets in the contact pathway for the development of novel anticoagulants. Several drugs targeting FXI are currently under development utilizing various mechanistic strategies including inhibition of FXI hepatic synthesis and inhibition of FXI/FXIa activation or activity (12) (Table I).

Table I. *Mode of action of factor XI (FXI)-directed anticoagulants (9, 13).*

Type of agent	Mechanism
Antisense oligonucleotides (ASO)	Reduce hepatic synthesis of factor XI
Antibodies	Bind factors XI and block its activation and its capacity to activate FXI. Bind FXIa and block its activity
Small molecules	Bind to the active site of FXIa and block its activity
Allosteric inhibitors	Bind to charged residues on FXI and modulate FXIa activity

Abelacimab Properties and Mechanism of Action

Abelacimab (MAA-868) is a humanized monoclonal immunoglobulin G1 antibody that binds with high affinity to the catalytic domain of both FXI and FXIa, preventing further activation of the coagulation pathway (13). Structurally, the fragment antigen-binding (Fab) portions of abelacimab bind to the FXI protease active site region with the heavy chain covering portions of the S3, S2, S1-β, and S1′ subsites of the protease (Fig. 2). Once bound, this interaction induces conformational changes in the protease 145- and 220-loops, leading to occlusion of the S1 and S2′ subsite as well as disorder of the surrounding 4 *N*-terminal FXI protease residues (14). The portions affected are crucial for FXI's catalytic activity. Abelacimab traps and stabilizes the active site in both FXI and FXIa, locking FXI/FXIa in an inactive zymogen-like conformation thus preventing downstream procoagulant catalytic activity (14, 15). Abelacimab does not inhibit FXIIa's ability to activate FXI to FXIa; however, the enzymatic action of both forms remains blocked by this agent (13, 14). Abelacimab's inability to block FXIIa activation of FXI allows for this agent to produce antithrombotic effects without disrupting hemostasis.

Promising data from preclinical and phase I studies demonstrated sustained prolongation of activated partial thromboplastin time (aPTT) and FXI suppression for up to 4 weeks or longer (14). The prolonged pharmacodynamic (PD) effect allows for monthly dosing, providing potential benefits of patient convenience and compliance. The safety and efficacy of abelacimab have been evaluated in phase I studies and are currently being investigated in the phase II study AZALEA-TIMI 71.

Preclinical Pharmacology

Koch et al. attempted to generate a human IgG1 with the capability to bind to FXIa and FXI at high affinity without causing inhibition at other protease-type coagulation factors, such as FVIIa, FIXa, FXa, FXII, thrombin and kallikrein (14). NOV-1090 was a phage-derived antibody clone that expressed this high FXI and FXIa inhibition when expressed as a Fab and used to test the functional testing. NOV-1090 was able to achieve an IC_{50} with a 2.8 nM concentration and did not affect any other coagulation factors. MAA-868 (abelacimab) was generated into a full human IgG1 using NOV-1090 by making the amino acid sequence to a human germline.

Binding measurements revealed that abelacimab binds with high affinity to the CD of human FXI and FXIa (K_D of 1.3 ± 0.3 pM and 4.7 ± 2.1 pM, respectively), as well as to cynomolgus monkey FXI and FXIa but not to mouse or rat FXI and FXIa, consistent with sequence differences within abelacimab-binding epitope regions (Table II). aPTT prolongation was assessed by exposing 2 female cynomolgus monkeys to multiple ascending doses of abelacimab, initially with a single 3 mg/kg s.c. dose. Both subjects had a baseline aPTT level of ~20 s which was seen to have a significant increase when plasma exposure exceeded ~20 nM, but no significant increase with plasma exposures beyond 20 nM. Abelacimab was seen to have the peak concentrations ~200 nM after the initial dose at day 2 and day 8 for subjects 1 and 2, respectively. Both subjects had aPTT increase to ~40 s, 6 h post exposure. Subject 1 sustained this effect until day 36 with a return to baseline at day 42; in contrast, subject 2 sustained this effect until day ~56 returning to baseline at day 78. Two additional doses were administered at days 85 and 114 dosed at 10 and 30 mg/kg, respectively. aPTT was seen to show a consistent prolongation to 40 s in both subjects without a drop in aPTT levels that occurred after the 3 mg/kg dose. FXI_f was at ~15 nM in both subjects before exposure of the initial dose, which dropped to ~0.5-2 nM at 6 h. FXI_f was seen to increase at the same

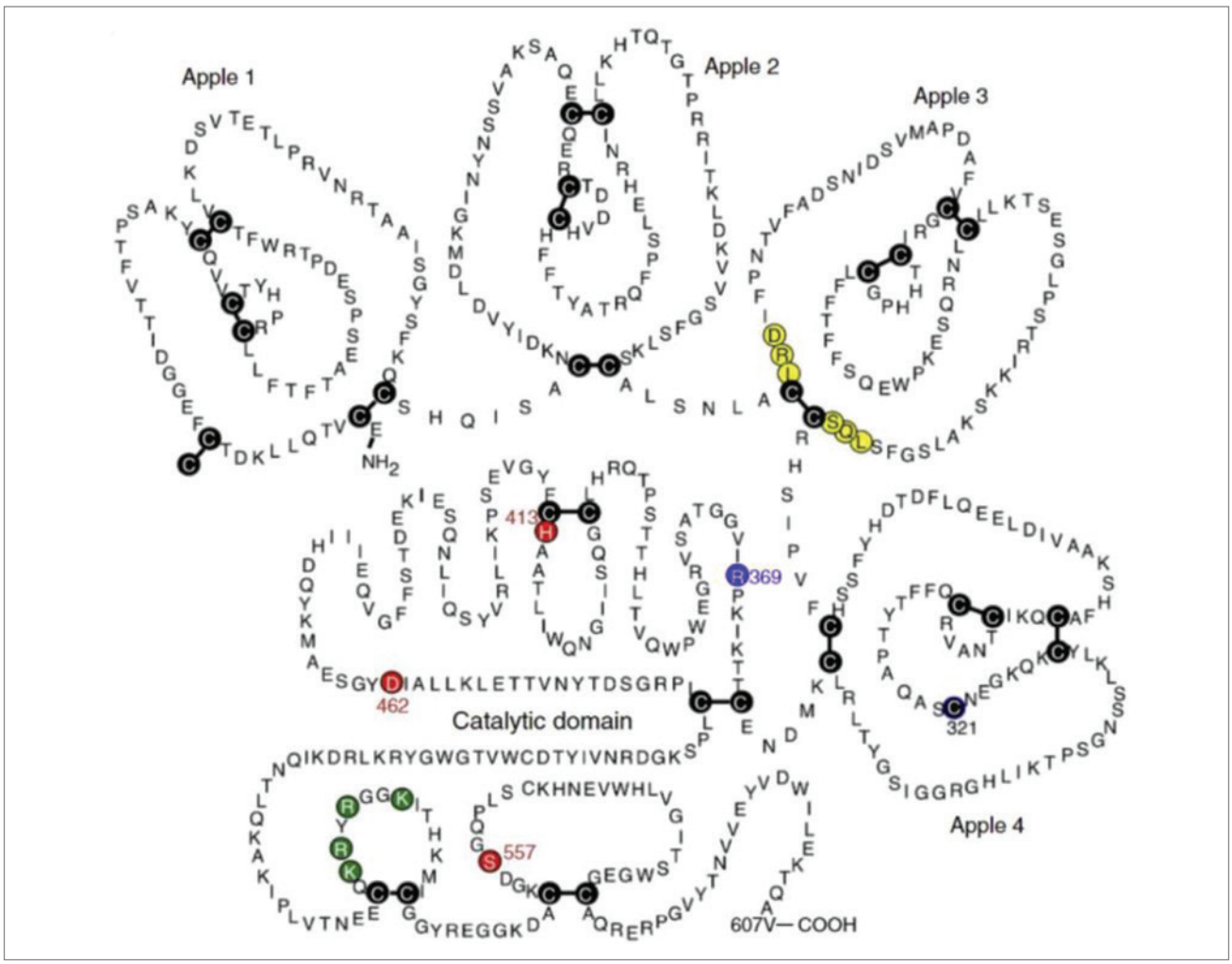

Figure 2. Schematic diagram of factor XI (FXI). Displayed are the primary amino acid sequence, disulfide bonds (cysteine residues shown in black circles) and domain structure of human plasma FXI. The histidine (413), aspartic acid (462) and serine (557) residues of the protease active site catalytic triad are shown in red. Conversion of FXI to FXIa involves a proteolytic cleavage after Arg369 (marked in blue) that can be done by FXIIa or thrombin. Residues that are required for FIX binding to the A3 domain are marked in yellow, and residues that make up the polyanion (heparin) binding site on the catalytic domain are in green. Mature FXI is a dimer of the protein shown in this figure. The unpaired cysteine residue at position 321(Cys321) in a FXI subunit forms a disulfide bond with Cys321 from the other subunit of the dimer. (Reprinted with permission from McMullen, B.A. et al. *Location of the disulfide bonds in human coagulation factor XI: the presence of tandem apple domains*. Biochemistry 1991, 30(8): 2056-60 (21). Copyright © 1991 American Chemical Society.)

Table II. *Pharmacokinetic properties of abelacimab in mice (14).*[a]

Parameter	hFXI	hFXI + control IgG (1:3)	hFXI + abelacimab (3:1)	hFXI + abelacimab (1:1)	hFXI + abelacimab (1:3)	hFXI + DEF (1:1)	hFXI + DEF (1:3)
Antithrombotic activity (%)	12	13	20	45	86	10	20
Max aPTT prolongation (%)	30	35	32	65	80	35	40
hFXI free plasma concentration (nM)	28	28	19	3	1	32	30
MAb plasma concentration (nM)	0	175	10	30	180	45	150

aPTT, activated partial thromboplastin time; hFXI, human factor XI; IgG, immunoglobulin G; DEF, active factor XIa-specific antibody; MAb monoclonal antibody.
[a]Estimated levels.

rate and time as aPTT decreased when the plasma exposure of abelacimab dropped below 20 nM. Subcutaneous and intravenous doses of abelacimab were administered in the same manner at days 1, 85 and 114 at doses of 3, 10 and 30 mg/kg, respectively, to assess the pharmacokinetic (PK) parameters between both formulations. The i.v. doses showed a larger t_{max}, C_{max} and $AUC_{0\text{-}14d}$ than the s.c. doses by ~4×, ~2.5-3× and ~1.5×, respectively (Table III) (14).

Clinical Evaluation

Phase I clinical studies

A phase I first-in-human study reported by Koch et al. evaluated the safety, tolerability, PK and PD of single ascending doses of abelacimab in healthy participants between the age of 18 and 60 years with a body mass index (BMI) 18-35 kg/m^2 (Table IV) (14). Dosing cohorts included 5,

Table III. *Pharmacokinetic properties of abelacimab at various doses in female cynomolgus monkeys (14).*[a]

Parameter	3 mg/kg i.v.	10 mg/kg i.v.	30 mg/kg i.v.	3 mg/kg s.c.	10 mg/kg s.c.	30 mg/kg s.c.
t_{max} (h)	0.25	0.25	1.08	168	132	132
C_{max} (µg/mL)	96	325	1170	36	101	344
$AUC_{0\text{-}14days}$	544	1810	6770	360	1160	4140

[a]Estimated levels.

Table IV. *Details of completed and ongoing studies evaluating abelacimab.*

Study/ phase	Design	Time frame	N	Age (years)	Investigational drug, dose and route	Control	Population	Main efficacy endpoints	Main outcomes of efficacy parameter
Koch et al. (14) Phase I	R, DB, PC, SAD	~38 days	61	18-60	Abelacimab single dose (5, 15, 50, 150, 240 mg)	Placebo	Normal body weight or severely obese (35 mg/m^2)	Incidence of AEs, SAEs, and PK and PD parameters	No drug-related SAEs occurred. No DC due to AEs. All AEs were similar in the active and control groups
Verhamme et al. (16) Phase II	R, OL	110 days	412	18-80	Abelacimab single dose (30, 75, 150 mg)	Enoxaparin	Elective TKA	Incidence of VTE and bleeding events	VTE occurred in 13%, 5% and 4% (abelacimab 30, 75 and 150 mg, respectively) vs. 22% enoxaparin; $P < 0.001$ for 75- and 150-mg cohorts. Bleeding was similar in the active and control groups
Phase II trial dose-range study (17) Phase II	R, PC, DR	170 days	18	18-85	Abelacimab (low, high and undetermined dose)[c]	Placebo	PAF or AFL	FXI activity levels at day 91	N/A
AZALEA-TIMI 71[a] (18) Phase II	MC, R, AC	~17 months	1,200[b]	≥ 55	Abelacimab (mid or high dose)[c]	Rivaroxaban	AF or AFL	Rate of bleeding events (major or CRNM)	N/A

AC, active-controlled; AE, adverse events; AF, atrial fibrillation; AFL, atrial flutter; CRNM, clinically relevant nonmajor; DB, double-blinded; DC, discontinuation; DR, dose range; TKA, total knee arthroplasty; MC, multicentered; N/A, not available; OL, open-labeled; PAF, paroxysmal atrial fibrillation; PC, placebo-controlled; PD, pharmacodynamic; PK, pharmacokinetic; R, randomized; SAD, single ascending dose; SAEs, severe adverse events; VTE, venous thromboembolism.
[a]Study is currently ongoing.
[b]Estimated enrollment.
[c]Dose strength unknown, listed as described.

15, 50, 150 and 240 mg (cohorts 1-5A) administered subcutaneously; healthy severely obese participants (BMI > 35 kg/m^2) were only enrolled in the 240-mg (5B) cohort. The primary outcomes included all safety endpoints (e.g., adverse events [AEs], severe AEs [SAEs], safety laboratory parameters) up until and including day 106 post dose. Secondary outcomes evaluated were plasma concentrations and PK parameters of abelacimab, and aPTT changes from baseline. Exploratory outcomes included free and total FXI coagulation activity. A total of 61 participants were randomized (8:2 ratio for each cohort) to either abelacimab or placebo and baseline characteristics were generally well-balanced between groups. The mean age was 40 years old and baseline BMI across all groups ranged from 25.7 to 40.6 kg/m^2. All participants completed the study and were included in the safety and full analyses. Overall, no systematic differences in the proportions of participants reporting AEs were observed between the treatment groups and the placebo group. There was a total of 9 mild AEs considered to be potentially drug related (abelacimab n = 7, placebo n = 2) with headache (11.5% [n = 4]) being the most common and only AE reported in more than 1 participant. In addition, there were no reports of injection-site reactions or hypersensitivity reactions in participants who received abelacimab. Three SAEs were reported including 1 fatal cardiac arrest that occurred in a severely obese participant who received abelacimab but was considered unrelated to treatment as FXI levels had returned to pretreatment levels (> 90%) at the time of the event. The other 2 SAEs, also unrelated to treatment, occurred in 1 participant who was in the 50-mg group that underwent popliteal artery bypass surgery and bone reconstruction who later developed a wound infection unrelated to treatment. Despite a prolonged aPTT (2.5-fold), there were no reports of excessive bleeding in this participant.

Following single-dose injections of abelacimab, median time to maximum plasma concentration (t_{max}) ranged from 7 to 21 days and was dose-independent (14). However, concentration levels to prolong aPTT by more than 2-fold were achieved by 24 h. Maximum plasma concentration (C_{max}) was dose-dependent over the analyzed dose range and severe obesity was associated with decreased maximal antibody concentration and inhibition effect. Half-life ($t_{½}$) ranged from 20.1 to 28.6 days. Dose and time-dependent prolongations in aPTT were observed and statistically significant; aPTT prolongations were more than 2-fold starting with the 50-mg dose and were maintained with 150 and 240 mg (cohort 5A) treatment groups up to approximately 29 and 57 days, respectively. Prolongation time was selective for aPTT and prothrombin time was unchanged. In addition, abelacimab dosed at 150 or 240 mg (cohorts 5A and 5B) displayed robust and sustained reductions in FXI (free and concentration) of 80% or greater from day 2 up to day 29. Findings from the first-in-human phase I study provide further clinical evidence that supports abelacimab's ability to inhibit activity of FXI/FXIa (14).

Phase II clinical studies

Phase II studies of abelacimab include a thromboembolic prophylaxis study in patients that underwent total knee arthroplasty (TKA) (16), a dose-range-finding study in patients with AF or atrial flutter (AFL) (17), as well as the AZALEA-TIMI 71 study (18) which is estimated to complete in May 2023 (Table IV). Abelacimab had one additional phase II study planned for thromboembolic prophylaxis in patients with AF, but it has since been withdrawn.

An open-label study by Verhamme et al. evaluated the safety and efficacy of abelacimab compared to enoxaparin in participants undergoing TKA (16). A total of 412 participants were randomized (1:1:1:1) to receive 1 of 3 single doses of abelacimab (30, 75 or 150 mg), all administered intravenously post surgery, or a daily dose of enoxaparin 40 mg via subcutaneous injection. The principal outcome was a composite of VTE, which included asymptomatic DVT (detected and confirmed via unilateral ascending venography between day 8 and 12 postoperative), symptomatic VTE (symptomatic DVT or nonfatal pulmonary embolism [PE]), fatal PE, or unexplained death inconclusive of PE. The primary safety outcome was clinically relevant bleeding defined as a composite of major or clinically relevant nonmajor (CRNM) bleeding through day 30. VTE occurred in 13%, 5% and 4% of participants who received abelacimab (30, 75 and 150 mg, respectively) compared to 22% of participants who received enoxaparin. Asymptomatic DVT comprised most of the VTE incidences reported except 1%, which was symptomatic VTE and occurred in the enoxaparin group. All regimens of abelacimab met the criterion for noninferiority to enoxaparin; however, only the 75- and 150-mg abelacimab regimens were found to be superior ($P < 0.001$). On day 30, clinically relevant bleeding was similar across the trial groups, with 1 major bleed occurring in the abelacimab 75-mg group. In addition, preoperative and postoperative HgB levels and the frequency of blood transfusions were comparable among all groups. Abelacimab appeared to have a relatively benign AE profile, and SAEs occurred in 1%, 3% and 1% in participants that received abelacimab 30, 75 and 150 mg, respectively, and none with enoxaparin (16).

There was no early stoppage of any abelacimab infusion due to hypersensitivity reactions and no antidrug antibodies were detected. For all doses of abelacimab, aPTT was increased in a dose-dependent manner as opposed to enoxaparin which did not increase aPTT. Free FXI levels and FXI activity decreased inversely with plasma concentrations of abelacimab. All regimens of abelacimab displayed robust lowering of levels on day 3 (post dose) and remained low on day 10 with 75- and 150-mg regimens.

The findings from this study demonstrated that postoperative initiation of abelacimab was an effective method of reducing the risk of VTE in patients that underwent TKA and was associated with a low risk of bleeding (16).

Results from the recently completed dose-range-finding study are currently pending. This study evaluated the safety and efficacy of abelacimab in participants with paroxysmal AF or AFL between the ages of 18 to 85 years old (17). In addition, participants were required to have a low CHA_2DS_2-VASc score (males 0-1, females 1-2), not be currently receiving anticoagulation treatment and have no previous history of ischemic stroke, transient ischemic attack or systemic embolism. A total of 18 participants were actively enrolled and randomized to receive 3 doses (on day 1, day 30 and day 90) of either abelacimab (low, high or unknown dose) or placebo for a duration up to 170 days. This study's primary outcome measure was the inhibition of FXI at day 91. Secondary objectives include the incidence of major bleeding events, CRNM bleeding events and total bleeding.

The results generated from this study will provide essential evidence to determine whether marked FXI level reductions attained with multiple injections of abelacimab will translate into a safer bleeding profile and provide validation of the dose-PD response model observed in the phase I study. In addition, these anticipated results may provide insightful information to support abelacimab's use as an efficacious antithrombotic agent. However, given the relatively small number of participants and the short duration of the study, no definitive conclusions can be drawn regarding the long-term side effect profile of abelacimab.

To address these limitations, the bleeding outcomes study, AZALEA-TIMI 71, will be assessing the long-term safety and tolerability of abelacimab compared to rivaroxaban (18). To be eligible, participants are required to be 55 years of age or older and have AF or AFL (with planned indefinite anticoagulation) with an elevated CHA_2DS_2-VASc score (score ≥ 4 or ≥ 3 with at least 1 of the following: concomitant antiplatelet use or a CrCl ≤ 50 mL/min). This study is currently ongoing and will include up to 1,200 participants for an anticipated duration of 2.5 years. The standard rivaroxaban dose of 20 mg daily (dose adjusted for renal function) for stroke prevention in AF will be utilized and will be compared to a mid-level and high-level dose of abelacimab given once monthly. This active-comparator study will provide information on whether abelacimab exhibits a similar safety profile as rivaroxaban and can help draw conclusions if its anticoagulant effects are comparative to the novel oral anticoagulant class. Although assumptions can be made about the potential benefits of abelacimab, its efficacy in preventing thrombotic disease remains ill-defined. The data from both phase II studies will provide crucial clinical evidence to evaluate abelacimab's ability to prevent and/or treat thromboembolic events in future studies.

Discussion

FXI has emerged as a promising therapeutic target for novel anticoagulant therapy. By blocking upstream from the common pathway and preventing further activation of the coagulation process, developing agents that target FXI provides the potential of a hemostasis-sparing (e.g., minimal-to-none bleeding) anticoagulant. In the phase I study, abelacimab dosed at 150 or 240 mg prolonged aPTT by 2-fold for a sustained duration in addition to reducing FXI levels over 80% without any indication that this reduction attenuated over a month-long time period (14). Thus, the observed durability enables an infrequent dosing regimen (e.g., monthly) and may contribute to higher patient adherence.

Patients undergoing TKA are at high risk for postoperative VTE, driven mainly by the exposed tissue factor at the surgical site that initiates coagulation through the extrinsic pathway and triggers thrombin generation. It is uncertain the importance of the intrinsic pathway in the pathogenesis of postoperative VTE, but thrombin's ability to activate FXI via feedback pathways can further amplify thrombin generation and promote thrombus formation. A study conducted by Buller et al. compared the effects of an FXI ASO-targeting agent to standard of care enoxaparin in patients undergoing elective unilateral TKA (19). The FXI ASO therapy, administered preoperatively, was shown to exhibit equivalent efficacy in preventing postoperative VTE and a lower incidence of hemorrhage when compared to enoxaparin (3% vs. 8%, respectively) (19). Comparable results were observed in the FOXTROT trial which evaluated osocimab, an FXI-targeting fully human monoclonal immunoglobulin G antibody, administered pre- and post-TKA operation (20). Osocimab demonstrated superiority to enoxaparin when administered preoperatively for VTE prevention; however, it met noninferiority to enoxaparin when administered postoperatively (20).

The recently published phase II results of abelacimab were the first to show that postoperative FXI inhibition was effective in reducing the risk of VTE in TKA patients as well as confirmed FXI's involvement in the pathogenesis of VTE (16). Additionally, with a similar mechanistic approach of inhibiting FXI activity, abelacimab showed similar effects in the reduction of bleeding risk. Given the assumed safety profile associated with FXI inhibition, abelacimab may serve as the first long-term anticoagulant agent with monthly dosing, including in patients with high bleeding risk. Therefore, abelacimab has the potential to propose a new model approach in anticoagulation therapy, shifting away from once-daily agents toward safe, long-acting, efficacious FXI inhibitors. The data from the phase II studies should provide the necessary information to conclude

the clinical utility of abelacimab in patients with AF or AFL and support its further investigation in phase III studies to determine safety and efficacy compared with current anticoagulant agents.

Conclusions

Abelacimab has demonstrated promising safety and efficacy when compared to placebo as a novel anticoagulant agent. Abelacimab provides an innovative mechanism uncoupled from the required, physiological hemostatic pathway, that may reduce pathological thromboembolism. In summary, abelacimab has the potential to be the first hemostasis-sparing anticoagulant for the treatment and/or prevention of thromboembolic diseases.

Disclosures

The authors state no conflicts of interest.

Submitted: July 13, 2021. Revised: August 17, 2021. Accepted: September 6, 2021.

References

1. Wendelboe, A.M., Raskob, G.E. *Global burden of thrombosis: epidemiologic aspects.* Circ Res 2016, 118(9): 1340-7.
2. Al-Horani, R.A., Afosah, D.K. *Recent advances in the discovery and development of factor XI/XIa inhibitors.* Med Res Rev 2018, 38(6): 1974-2023.
3. Lahewala, S., Arora, S., Patel, P. et al. *Atrial fibrillation: utility of CHADS2 and CHA2DS2-VASc scores as predictors of readmission, mortality and resource utilization.* Int J Cardiol 2017, 245: 162-7.
4. Weitz, J.I., Fredenburgh, J.C. *Factors XI and XII as targets for new anticoagulants.* Front Med (Lausanne) 2017, 4: 19.
5. Chan, N., Sobieraj-Teague, M., Eikelboom, J.W. *Direct oral anticoagulants: evidence and unresolved issues.* Lancet 2020, 396(10264): 1767-76.
6. Chai-Adisaksopha, C., Crowther, M., Isayama, T., Lim, W. *The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis.* Blood 2014, 124(15): 2450-8.
7. Bane, C.E., Jr., Gailani, D. *Factor XI as a target for antithrombotic therapy.* Drug Discov Today 2014, 19(9): 1454-8.
8. Puy, C., Rigg, R.A., McCarty, O.J. *The hemostatic role of factor XI.* Thromb Res 2016, 141(Suppl 2): S8-S11.
9. Cave, B.E., Shah, S.P. *Turning up to eleven: factor XI inhibitors as novel agents to maximize safety and maintain efficacy in thromboembolic disease.* Curr Probl Cardiol 2021, 46(3): 100696.
10. Salomon, O., Steinberg, D.M., Zucker, M., Varon, D., Zivelin, A., Seligsohn, U. *Patients with severe factor XI deficiency have a reduced incidence of deep-vein thrombosis.* Thromb Haemost 2011, 105(2): 269-73.
11. Salomon, O., Steinberg, D.M., Dardik, R. et al. *Inherited factor XI deficiency confers no protection against acute myocardial infarction.* J Thromb Haemost 2003, 1(4): 658-61.
12. Quan, M.L., Pinto, D.J.P., Smallheer, J.M. et al. *Factor XIa inhibitors as new anticoagulants.* J Med Chem 2018, 61(17): 7425-47.
13. DeLoughery, E.P., Olson, S.R., Puy, C., McCarty, O.J.T., Shatzel, J.J. *The safety and efficacy of novel agents targeting factors XI and XII in early phase human trials.* Semin Thromb Hemost 2019, 45(5): 502-8.
14. Koch, A.W., Schiering, N., Melkko, S. et al. *MAA868, a novel FXI antibody with a unique binding mode, shows durable effects on markers of anticoagulation in humans.* Blood 2019, 133(13): 1507-16.
15. Weitz, J.I., Chan, N.C. *MAA868 locks factor XIa in a zymogen-like state.* Blood 2019, 133(13): 1393-4.
16. Verhamme, P., Yi, B.A., Segers, A. et al. *Abelacimab for prevention of venous thromboembolism.* N Engl J Med 2021, 385(7): 609-17.
17. *A dose-range finding study of MAA868 in patients with atrial fibrillation (NCT04213807)*. ClinicalTrials.gov Website. Dec 30, 2019. Accessed July 6, 2021.
18. *Safety and tolerability of abelacimab (MAA868) vs. rivaroxaban in patients with atrial fibrillation (AZALEA-TIMI 71) (NCT04755283)*. ClinicalTrials.gov Website. Feb 16, 2021. Accessed July 6, 2021.
19. Buller, H.R., Bethune, C., Bhanot, S. et al. *Factor XI antisense oligonucleotide for prevention of venous thrombosis.* N Engl J Med 2015, 372(3): 232-40.
20. Weitz, J.I., Bauersachs, R., Becker, B. et al. *Effect of osocimab in preventing venous thromboembolism among patients undergoing knee arthroplasty: the FOXTROT randomized clinical trial.* JAMA 2020, 323(2): 130-9.
21. McMullen, B.A., Fujikawa, K., Davie, E.W. *Location of the disulfide bonds in human coagulation factor XI: the presence of tandem apple domains.* Biochemistry 1991, 30(8): 2056-60.