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The Future of Monthly Abelacimab: Going Beyond Conventional Anticoagulation

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ABSTRACT:
Anticoagulants are crucial for managing thromboembolic disorders, which pose significant global health challenges by preventing clot formation while managing bleeding risks. Traditional anticoagulants, including vitamin K antagonists and direct oral anticoagulants, face limitations due to potential bleeding complications, narrow therapeutic windows, and varying efficacy among patients. Advances in understanding the coagulation cascade have identified Factor XI (FXI) as a promising target for innovative antithrombotic therapies. Suppression of FXI is essential to prevent thrombus formation without heavily impacting conventional hemostasis, positioning it as a viable method to balance treatment effectiveness and safety. Abelacimab, a human monoclonal antibody, presents a novel approach by inhibiting both FXI and its activated form, FXIa. This dual blockade disrupts the coagulation pathway, reduces thrombin generation, and simultaneously maintains tissue factor-mediated hemostasis. Pharmacokinetic studies indicate that abelacimab has a half-life of approximately 25 to 30 days, facilitating monthly subcutaneous administration. Supporting pharmacodynamic data shows sustained FXI suppression. Clinical trials have demonstrated that abelacimab significantly reduces the risk of thromboembolism, prolongs activated partial thromboplastin time, and correlates with a decreased incidence of clinically significant bleeding compared to conventional therapies. Consequently, abelacimab represents a transformative new class of anticoagulants, merging efficacy, safety, and patient convenience in treatment.In this review highlights that Abelacimab effectively treat and prevent thromboembolic illnesses with a lower risk of bleeding. Good pharmacokinetic properties linked to quick and extended Factor XI inhibition and easy once-monthly subcutaneous delivery are shown by the clinical research outcomes.

KEYWORDS: Anticoagulant, Abelacimab, Thromboembolic disorders, Venous thromboembolism and Bleeding risk

I. INTRODUCTION:

Thromboembolic conditions remain a significant global health concern, contributing to approximately one-quarter of all deaths worldwide in 2010and persistently being one of the leading causes of mortality[(1)] For more than 50 years, warfarin, among the vitamin K antagonist-class, remained the primary anticoagulant agent prescribed for prophylaxis and treatment of VTE, as well as protecting patients with increased risk of stroke . They target the vitamin K epoxide reductase complex (VKROC1), which effectively in inhibits the activation of vitamin K in the body. The variation in anticoagulant response, the limited therapeutic range requiring frequent monitoring of the international normalization ratio (INR), and the risk of severe bleeding are considered a significant limitation of warfarin. [(2)]Considering these challenges, the imperative to explore alternative drugs to address existing gaps has become evident. Consequently, recent attention has been directed towards the development of new anticoagulants that inhibit factor XI/XIa. In this focused review, we delve into an intricate exploration of abelacimab, examining its clinical pharmacology and pharmacokinetic and pharmacodynamic properties. We scrutinize its safety profile, discussing critical parameters for monitoring its effects on patients. Furthermore, we assess the evidence supporting its use and consider prospective research that may further solidify its role in anticoagulant therapy. By providing a detailed analysis of abelacimab, we aim to enhance understanding of its potential role in patients requiring anticoagulation therapy. This review aims to add to the ongoing conversation regarding developing anticoagulants with superior safety profiles. [(2)]

FACTOR XI AS A THERAPEUTIC TARGET

Factor XI (FXI) is the inactive precursor of the blood coagulation protease factor XIa (FXIa),

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which activates factor IX to aid in hemostasis maintenance. Factor XI comes before an S1 serine protease that is present in the plasma. It is necessary for the formation and stabilization of fibrin when activated to FXIa because it starts the activation of factor IX. Factor XI is a 160 kDa protein consisting of two identical chains with 607 amino acids in each. Each chain is made up of four repeating segments called apple domains (designated A1 to A4, starting at the N-terminus), each of which has 90 or 91 amino acids. By interacting with several enzymatic substrates, FXI immediately initiates the extrinsic route. At first, it was believed to be exclusive to the "contact" pathway.(3)(4)

. Nevertheless, it was subsequently found that this extrinsic pathway-related factor can also be activated by thrombin. The contact pathway factor FIX is the primary target of FXIa. However, studies have shown that in a lab setting, FXI can cause FX. Furthermore, by activating the cofactors FVIII and FV, FXI aids in the production of thrombin. Additionally, FXIa is known to shorten clotting times without the need for FIX. Additionally, by degrading the tissue factor pathway inhibitor (TFPI), a particular type of protease that stops the TF/FVIIa/FXa complex, FXIa increases the activation of the extrinsic pathway. For FXIa to successfully assist hemostasis via the extrinsic pathway, platelets must be involved.(3)

The F11 gene, which has 15 exons and is found on the long arm of chromosome 4, encodes human FXI [4]. Hemophilia C, sometimes referred to as Rosenthal syndrome, develops when a mutation in this gene causes either a quantitative deficiency or a qualitative aberration of FXI [5]. Although few examples of dominant transmission have been reported, this autosomal coagulation condition is primarily inherited as a recessive trait [6]. Interestingly, the condition is more common in Ashkenazi Jews, with a frequency that is close to 5%. FXI deficiency is mostly associated with four different mutations in the F11 gene in this demographic [5]. Compared to patients with adequate levels of correctly organized FXI, those with congenital FXI deficiency have a lower risk of ischemic stroke and VTE. Hemophilia C is linked to the very rare frequency of spontaneous bleeding events, in contrast to hemophilia A and B [7]. According to experimental findings, in animal models, severe FXI deficiency prevents arterial and venous thrombosis without impairing hemostasis. Additionally, studies have demonstrated that patients with severe FXI impairment have a much lower incidence of DVT than the overall population [8].

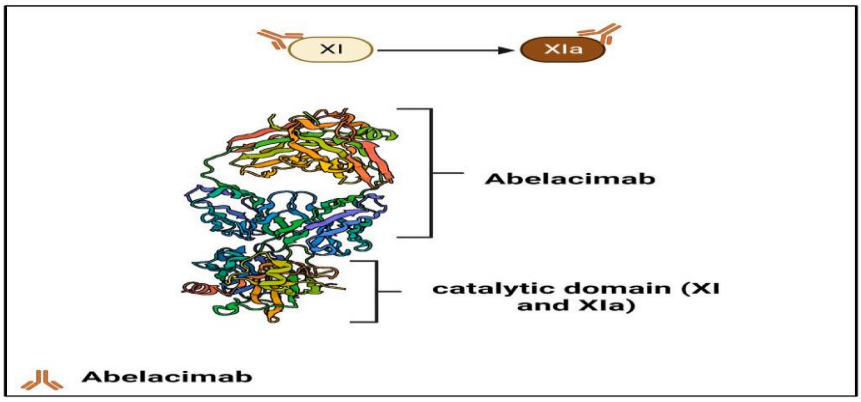

Fig. 2. Depiction of abelacimab's interaction with the catalytic domain of FXI and FXIa.

PHARMACOLOGY OF ABELACIMAB

Pharmaceutical companies began using other methods, such as monoclonal antibodies (mAbs) and antisense oligonucleotides (ASO), to modulate the coagulation cascade in the new era of pharmacology, in addition to the traditional tiny chemical compounds. FXI and FXIa inhibitors that may be authorized as novel antithrombotic medications.(8)(7)

MECHANISM OF ACTION

Both FXI and FXIa can be bound and inhibited by the monoclonal antibody abelacimab [9]. At a dose of 2.8 nM, the Fab part of abelacimab inhibited 50% of FXIa activity and had a strong binding affinity to both FXI and FXIa. Other human serine protease-type coagulation factors, such as factor VIIa, factor IXa, factor Xa, FXIIa, thrombin, and its closest analog plasma kallikrein, were found to be unaffected by this highly specific action [9]. The catalytic domain of human FXI and FXIa binds to abelacimab with a high affinity (Kd of 1.3 ± 0.3

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pM and 4.7 ± 2.1 pM, respectively) [9].The protease is trapped and stabilized in an inactive conformation by the antibody, according to an investigation of the X-ray structure of the Fab part of abelacimab in association with the FXIa catalytic domain. According to this activity, abelacimab decreased the amount of thrombin in human plasma in a concentration-dependent manner and extended the clotting timing, as measured by the aPTT assay [9]. These in vitro investigations showed that abelacimab did not affect the initial thrombin burst caused by the extrinsic pathway, but it did suppress FXIa, which was activated by both thrombin and FXIIa in the intrinsic pathway [9]. Therefore, abelacimab blocks any FXIa that has already developed and stops circulating (zymogen) FXI from being activated.

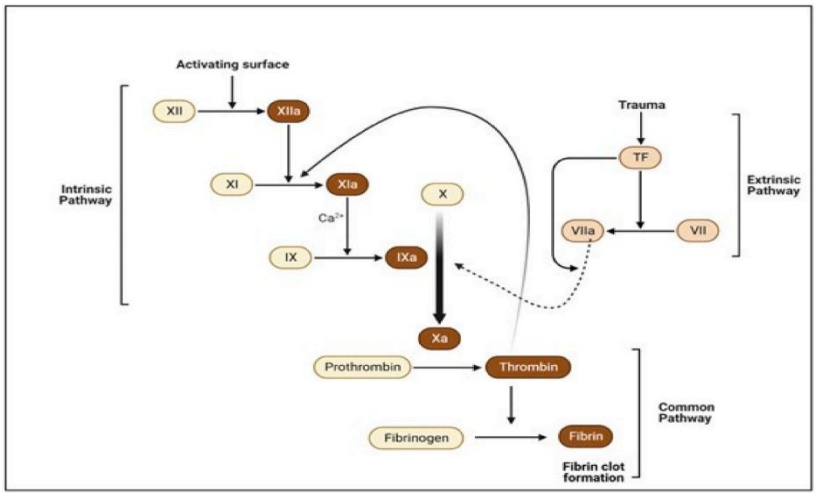

Fig. 1. Blood coagulation enzyme processes. This illustrates the cascade model for thrombin formation initiated by FXII activation.

PHARMACOKINETICS

A single s.c. administration of increasing doses (5 mg to 240 mg), the pharmacokinetic (PK) characteristics of abelacimab were evaluated in humans [9]. Within the examined dose range, abelacimab exposure is dose proportionate with moderate inter-subject variability [9]. Dose-independent, the median time to peak abelacimab plasma concentrations varied from 7 to 21 days. However, by 24 hours, levels sufficient to increase aPTT by more than two times were reached. The range of the terminal elimination half-life (T1/2) was 20.1 to 28.6 days.Moderately lower abelacimab Cmax and AUC were linked to severe obesity. Two additional studies were carried out with a single intravenous (IV) dosage of abelacimab in healthy volunteers and with several once-monthly injections to investigate the PK and PD characteristics of the drug following various modes of administration.c. administration in AF patients [10].The Tmax of abelacimab was found to be independent of the dose and ranged from 1.75 to 2.0 hours (from the commencement of the 1-hour infusion) following a single intravenous delivery [10]. In the dose range of 30–150 mg, the systemic exposure (C0) increased proportionately, while for AUC inf, it increased more than proportionately. The half-life time of elimination (T1/2) varied between 595 and 709 hours (25–30 days) [10].Following intravenous and subcutaneous administration, the volume of distribution (Vd) ranges from 5 L to 13.3 L, respectively. A substantial reduction (30–45%) in abelacimab exposure (C0 and AUC) and Vd (8.29%) was linked to severe obesity (median BMI 44.3 kg/m2).

PARAMETER	FINDINGS
Route of administration	Single subcutaneous (s.c.) doses (5–240 mg) and single intravenous (iv) doses (30–150 mg)
Exposure	Dose-proportionate with moderate inter-subject variability
Time to peak concentration (tmax)	S.C.: 7–21 days (dose-independent) iv: 1.75–2.0 hours (after 1-hour

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PARAMETER	FINDINGS
	infusion)
Onset Of Effect	Within 24 Hours, Plasma Levels Sufficient To Double Aptt
Half-Life (T1/2)	S.C.: 20.1–28.6 Days Iv: 595–709 Hours (≈25–30 Days)
Systemic Exposure (C0, Auc)	Proportionate Increase With Dose (30–150 Mg Iv); Auc Increased More Than Proportionately
Volume Of Distribution (Vd)	S.C.: 13.3 L Iv: 5 L
Effect Of Obesity	Severe Obesity (Median Bmi 44.3 Kg/M²) Reduced Exposure (C0 And Auc ↓30–45%) And Vd ↓8.29%
Pharmacodynamic Correlation	Sustained Fxi Suppression And Prolonged Aptt In Relation To Serum Concentration

PHARMACODYNAMICS

Factor XI concentrations have been rapidly reduced by 99% with abelacimab intravenous infusion (IV) at doses of 30 mg, 50 mg, and 150 mg. Factor XI level recovery was dosage-dependent; the 30 mg dose produced the earliest FXI activity around day 10 [(11)]. For all doses, the activated partial thromboplastin time (aPTT) ratio increased after the first hour after IV infusion and returned to baseline in a dose-dependent fashion [(12)]. Similar to this, factor XI was continuously reduced by abelacimab subcutaneous injection (SubQ) for around 11 days prior to reaching its nadir, and FXI levels restored to baseline prior to the next monthly dose when SubQ injections were administered.SubQ injections caused the aPTT ratio to double, and the increase in aPTT was maintained in relation to the serum concentration of abelacimab.

PARAMETER	FINDINGS
Route of Administration	Intravenous (Iv) And Subcutaneous (Subq)
Iv Dose Range	30 Mg, 50 Mg, And 150 Mg
Reduction In Factor Xi	Rapid 99% Reduction After Iv Infusion Across All Doses
Recovery Of Fxi Activity	Dose-Dependent; Earliest Recovery At Day 10 For 30 Mg Dose
Aptt Changes (Iv)	Increased Within 1 Hour Post-Infusion; Returned To Baseline In A Dose-Dependent Manner
Subq Effect On Fxi	Continuous Reduction For ~11 Days, Reaching Nadir Before Recovery To Baseline Prior To Next Monthly Dose
Aptt Changes (Subq)	Ratio Doubled And Remained Elevated In Proportion To Serum Abelacimab Concentration
Duration Of Effect	Sustained Fxi Inhibition For Approximately One Month
Overall Pharmacodynamic Profile	Rapid Onset, Prolonged Suppression Of Fxi Activity, And Predictable Recovery Pattern

FACTOR XI: A POTENTIAL TARGET IN THE BALANCE BETWEEN THROMBOSIS AND HAEMOSTASIS

Although FXI is essential for thrombosis, hemostasis does not require it [13]. In fact, it plays a significant role in the intrinsic pathway of coagulation. Factor XII is first activated by molecules including collagen, kallikrein, and high molecular weight kininogen. After Factor XII is activated, Factor XI is activated, then Factor IX is activated. In the end, this cascade produces thrombin in the common pathway, which causes a stable intraluminal clot to develop and thrombosis, or the halt of blood flow within the afflicted channel.On the other hand, FXI plays a modest role in the extrinsic pathway, which is initiated by chemicals released during endothelial cell damage and ends through the same pathway as hemostasis, which is the process of sealing off a vascular wall lesion with a solidified clot. As a result, research on congenital FXI impairment shows a low risk of bleeding, even when FXI levels are much lower, and

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a decreased incidence of thrombosis [14]. According to this dual discovery, blocking FXI may offer effective thromboprophylaxis with a reduced risk of bleeding, which is an alluring prospect for individuals whose bleeding is a major worry. The potential to "uncouple" thrombosis prophylaxis from the danger of bleeding consequences is provided by this special feature of FXI in the coagulation cascade [12]. FXI inhibitors may specifically hinder the generation of pathological clots while maintaining hemostasis, whereas existing anticoagulants target shared pathways influencing both hemostasis and thrombosis physiological hemostasis[13].

CLINICAL TRIAL EVIDENCE

Although clinical research has demonstrated the potential, promising efficacy, and safety of abelacimab (MAA868), it is still not FDA-approved. A subcutaneous dose between 5 and 240 mg/kg was found to be safe and effective in both healthy and obese adults in the first phase I clinical trial, which used a progressive single dosage (9). Notably, the activated partial thromboplastin time (aPTT) was prolonged for at least four weeks at a dose of 150 mg/kg. Prothrombin time (PT) and thrombin time were found to be unaffected by this. Furthermore, recombinant activated factor VII reversed the effects of MAA868. Additionally, it was noted that patients with atrial fibrillation could safely receive several subcutaneous doses or intravenous administration.

The ANT-005 TKA trial is one significant study that has led these debates (12). Patients receiving total knee arthroplasty were the subject of the phase 2, open-label ANT-005 TKA experiment. Following surgery, 412 Pa were randomly randomized to receive either a daily dose of enoxaparin or different doses of abelacimab (30 mg, 75 mg, or 150 mg). Venous thromboembolism (VTE) was the main objective, while major or clinically significant non-major bleeding up to one month after surgery was the secondary emphasis. The incidence of VTE was lowered to 13%, 5%, and 4% for the 30-mg, 75-mg, and 150-mg abelacimab groups, respectively, compared to 22% of patients on enoxaparin.(12)Notably, abelacimab's two higher dosages had better efficacy than enoxaparin. The safety results were also promising, with very few bleeding episodes overall. Two percent of patients in the 30-mg and 75-mg abelacimab groups and none in the 150-mg group suffered bleeding. In a similar vein, none of the enoxaparin group's subjects reported bleeding(.9) Another phase 2 research, the AZALEA-TIMI 71 trial, had to be stopped early because abelacimab patients showed significantly better bleeding reduction than rivaroxaban patients (Ruff, 2013). 1287 atrial fibrillation patients with a moderate-to-high risk of stroke participated in this study. Abelacimab 150 mg once monthly, abelacimab 90 mg once monthly, or rivaroxaban 20 mg daily were administered to patients in a 1:1:1 randomization. The results of this encouraging study have not yet been released. Abelacimab is set to transform anticoagulant therapy due to its remarkable outcomes in lowering both bleeding and thrombosis.(15)

PHASE I CLINICAL STUDIES

A phase I first-in-human study reported by Koch et al examined the safety, tolerability, PK, and PD of single ascending doses of abelacimab in healthy individuals with a body mass index (BMI) of 18–35 kg/m2 who were between the ages of 18 and 60 (16). Subcutaneous doses of 5, 15, 50, 150, and 240 mg (cohorts 1-5A) were delivered; only the 240-mg (5B) cohort comprised healthy individuals who were significantly obese (BMI > 35 kg/m2). All safety endpoints up to and including day 106 post-dose were included in the primary outcomes. Abelacimab plasma concentrations, PK parameters, and aPTT variations from baseline were assessed as secondary outcomes. Free and total FXI coagulation activity were among the exploratory results. The baseline characteristics of the 61 participants who were randomly assigned to receive either abelacimab or a placebo were generally well-balanced.

All groups' baseline BMIs ranged from 25.7 to 40.6 kg/m2, with a mean age of 40. Every participant finished the trial and was taken into account for the safety and comprehensive analyses. Overall, there were no discernible variations between the treatment groups and the placebo group in the percentages of patients reporting adverse events. Nine moderate adverse events (AEs) were identified as potentially drug-related (abelacimab n = 7, placebo n = 2). The most frequent and only AE reported in more than one participant was headache (11.5% [n = 4]). Furthermore, there were no reports of hypersensitivity or injection-site reactions among abelacimab recipients. Three adverse events (SAEs) were observed, including one fatal cardiac arrest in a highly obese participant who took abelacimab. This incident was deemed unrelated to treatment because at the time of the event, FXI levels had returned to pretreatment levels (> 90%). One participant in the 50-mg group who had bone restoration and popliteal

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artery bypass surgery experienced the other two SAEs, which were likewise unrelated to treatment. This participant later developed an unrelated wound infection. There were no reports of significant bleeding in this subject despite a longer aPTT (2.5-fold).

The median time to maximum plasma concentration (tmax) after abelacimab single-dose injections was dose-independent and varied from 7 to 21 days [(1)]. However, within 24 hours, concentration levels were reached that extend aPTT by more than two times. Over the examined dose range, maximum plasma concentration (Cmax) was dose-dependent, and extreme obesity was linked to lower maximal antibody concentration and inhibitory effect. The half-life (t½) varied between 20.1 and 28.6 days. Dose and time-dependent aPTT prolongations were noted and statistically significant; aPTT prolongations were more than twice as long beginning with the 50-mg dose and continued for about 29 and 57 days, respectively, with the 150 and 240 mg (cohort 5A) treatment groups. Prothrombin time remained constant while prolongation time was selective for aPTT. Furthermore, from day 2 to day 29, abelacimab doses of 150 or 240 mg (cohorts 5A and 5B) showed significant and long-lasting decreases in FXI (free and concentration) of 80% or higher. The first-in-human phase I study's results offer more clinical proof that abelacimab can block FXI/FXIa activity [(16)].

PHASE II CLINICAL STUDIES

Phase II studies of abelacimab include the AZALEA-TIMI 71 study [(17)], which is anticipated to be finished in May 2023, a thromboembolic prophylaxis study in patients who had total knee arthroplasty (TKA) [(12)], and a dose-range-finding study in patients with AF or atrial flutter (AFL) [(18)]. One more phase II trial for the prevention of thromboembolism in AF patients was planned for abelacimab, however it has since been canceled. Verhamme et al. conducted an open-label trial to examine the safety and effectiveness of enoxaparin and abelacimab in patients receiving total knee arthroplasty [(19)]. 412 individuals were randomly assigned (1:1:1:1) to receive either a daily dose of 40 mg of enoxaparin or one of three intravenous single doses of abelacimab (30, 75, or 150 mg) following surgery40 mg via subcutaneous injection.The main result was a composite of VTE, which comprised symptomatic VTE (symptomatic DVT or nonfatal pulmonary embolism [PE]), asymptomatic DVT (detected and confirmed with unilateral ascending venography between day 8 and 12 postoperative), fatal PE, or unexplained death inconclusive of PE. Clinically relevant bleeding, which is defined as a composite of major or clinically relevant nonmajor (CRNM) hemorrhage through day 30, was the main safety outcome. In contrast to 22% of participants who got enoxaparin, 13%, 5%, and 4% of participants who received abelacimab (30, 75, and 150 mg, respectively) experienced VTE. With the exception of 1%, which was symptomatic VTE and happened in the enoxaparin group, the majority of VTE incidents observed were asymptomatic DVT. Every abelacimab regimen satisfied the requirement for noninferiority to enoxaparin;But only the regimens including 75 and 150 mg of abelacimab were found to be superior ($P < 0.001$). Clinically significant bleeding on day 30 was comparable in all trial groups, with the abelacimab 75-mg group experiencing one significant bleed. Furthermore, all groups had similar preoperative and postoperative HgB levels and blood transfusion rates. SAEs happened in 1%, 3%, and 1% of patients who received abelacimab 30, 75, and 150 mg, respectively, and none with enoxaparin [(12)]. Abelacimab seems to have a reasonably benign AE profile.No abelacimab infusion was stopped early due to hypersensitivity responses, and no antidrug antibodies were found. In contrast to enoxaparin, which did not rise, aPTT increased in a dose-dependent way for all abelacimab dosages aPTT.

FXI activity and free FXI levels declined inversely with abelacimab plasma concentrations. On day 3 (post dose), all abelacimab regimens showed a significant reduction in levels, and on day 10, the 75- and 150-mg regimens continued to be low.The results of this study showed that starting abelacimab after surgery was a low risk of bleeding and an efficient way to lower the risk of VTE in patients who had TKA [(12)].The dose-range-finding study was just finished, and the results are still pending. In individuals with paroxysmal AF or AFL between the ages of 18 and 85, this study assessed the safety and effectiveness of abelacimab [(17)].A low CHA2DS2-VASc score (males 0-1, females 1-2), no current anticoagulant therapy, and no prior history of ischemic stroke, transient ischemic attack, or systemic embolism were other prerequisites for participation. For a period of up to 170 days, a total of 18 volunteers were actively recruited and randomly assigned to receive either a placebo or three doses of abelacimab (low, high, or unknown dose) on days 1, 30, and 90. The inhibition of FXI at day 91 served as the main outcome measure for this investigation. The frequency of major bleeding

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events, CRNM bleeding events, and overall bleeding are secondary goals.

The findings of this study will validate the dose-PD response model seen in the phase I study and offer crucial evidence to ascertain whether significant FXI level reductions achieved with multiple injections of abelacimab will translate into a safer bleeding profile. Furthermore, these anticipated outcomes can offer useful information to support the use of abelacimab as a successful antithrombotic medication. However, no firm conclusions on the long-term side effect profile of abelacimab can be made due to the study's brief length and comparatively small number of participants. The bleeding outcomes study, AZALEA-TIMI 71, will evaluate the long-term safety and tolerability of abelacimab in comparison to rivaroxaban in order to overcome these shortcomings [17]. In order to qualify, participants must to be at least 55 years old, have AF or AFL (with planned indefinite anticoagulation), and have an increased CHA2DS2-VASc score (score > 4 or ≥ 3 with at least 1 of the following: concurrent antiplatelet treatment or a CrCl ≤ 50 mL/min). Up to 1,200 people will participate in this continuing study, which is expected to last for 2.5 years. A mid-level and high-level dose of abelacimab administered once monthly will be compared to the conventional rivaroxaban dose of 20 mg daily (dose adjusted for renal function) for stroke prevention in AF.This active-comparator trial can assist determine whether abelacimab's anticoagulant effects are comparable to those of the novel oral anticoagulant class and whether it shows a similar safety profile to rivaroxaban. The effectiveness of abelacimab in avoiding thrombotic illness is still unknown, despite hypotheses on its possible advantages. In subsequent research, the data from both phase II trials will offer vital clinical evidence to assess abelacimab's capacity to prevent and/or treat thromboembolic events.

PHASE III CLINICAL TRIALS

Abelacimab is presently undergoing a Phase III clinical trial to examine the safety and effectiveness of this novel Factor XI/XIa inhibitor in anticoagulation. Atrial fibrillation and cancer-related venous thromboembolism (VTE) are the subjects of significant phase III investigations. [19]

LILAC-TIMI 76 (NCT05712200) is a Phase III, randomized, double-blind, placebo-controlled study of subcutaneous abelacimab administered once a month to patients with atrial fibrillation who are intolerant to oral anticoagulation. Preventing ischemic stroke or systemic embolism is the main goal, and significant bleeding is a crucial safety result.

ASTER (NCT05171049): A Phase III, randomized trial of abelacimab versus apixaban for the treatment of cancer-associated venous thromboembolism (VTE). The trial measures recurrent VTE and significant bleeding to see if Factor XI inhibition can offer effective anticoagulation with less bleeding risk.

MAGNOLIA (NCT05171075): A Phase III trial comparing abelacimab to dalteparin in patients with gastrointestinal or genitourinary cancer-associated VTE, populations at high risk of bleeding. The experiment looks at recurrent VTE, severe hemorrhage and safety overall.

The Phase III development program is intended to demonstrate if abelacimab can offer effective thromboembolic protection with less bleeding than conventional anticoagulants, and perhaps provide a safer alternative for high-risk patients.[19]

SAFETY AND THERAPEUTIC ADVANTAGES

SAFETY

Reduced risk of bleeding: Abelacimab specifically inhibits Factor XI/XIa, the primary cause of pathological thrombosis, while preserving normal hemostasis for the most part. In this manner, compared to normal anticoagulant medications, the risk of severe and clinically significant non-major bleeding is reduced. [20]

Excellent tolerance According to clinical studies, abelacimab is quite safe; the majority of side effects are minimal, and there is no clinically significant bleeding. [21]

Decreased incidence of gastrointestinal bleeding: Compared to rivaroxaban, abelacimab dramatically reduced the number of gastrointestinal bleeding patients in the AZALEA-TIMI 71 trial. [20] No noteworthy medication interactions Because abelacimab is a completely human monoclonal antibody, there is less chance of serious drug-drug interactions because it is not processed by the cytochrome P450 system.[21]

THERAPEUTICS:[19,20,21]

Abelacimab's novel mode of action allows for strong anticoagulation with no impact on physiological hemostasis by blocking both Factor XI and activated Factor XI (FXIa).

Effective thrombosis prevention: Clinical research has demonstrated its effectiveness in preventing venous thromboembolism and its continued

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development in relation to atrial fibrillation and cancer-related thrombosis.

Long half-life: Because the drug's terminal half-life is approximately 25–30 days, it can be used as a subcutaneous medicine once a month, improving patient adherence.

Fast and long-lasting FXI inhibition: Abelacimab efficiently suppresses FXI both immediately after delivery and for approximately a month.

Effective therapeutic option for patients with greater bleeding risk: Abelacimab may be safer than direct oral anticoagulants (DOACs) for patients with an increased risk of bleeding since it decouples the antithrombosis effect from normal hemostasis.

II. FUTURE CLINICAL APPLICATIONS

For individuals with atrial fibrillation (AF) who have a high risk of bleeding or who are unable to undergo conventional oral anticoagulation medication, abelacimab may be a good alternative to direct oral anticoagulants (DOACs) in terms of preventing stroke. [21]

Cancer-Associated Venous Thromboembolism (CAT): Phase III ASTER and MAGNOLIA study results may indicate that abelacimab is a safer anticoagulant for cancer patients, particularly those with gastrointestinal or genitourinary malignancies. [22]

Prevention of Venous Thromboembolism (VTE): In individuals who need anticoagulation for an extended length of time, abelacimab may help prevent and treat DVT and pulmonary embolism.

Extended Secondary Prevention of VTE: Due to its once-monthly dosing and favorable safety profile, abelacimab may be appropriate for prolonged anticoagulant therapy.[23]

Perioperative Thromboprophylaxis: Abelacimab may be evaluated for thromboprophylactic reasons following other complicated orthopedic or hazardous surgical procedures due to the favorable results when utilized following total knee arthroplasty. [24]

High Bleeding Risk Groups: Since conventional anticoagulants increase bleeding risk, abelacimab may be a particularly effective treatment for elderly patients, those who have had significant bleeding in the past, or those with a number of comorbid disorders.[25]

III. CONCLUSION:

This study concluded that abelacimab, a monoclonal antibody that selectively inhibits Factor XI and activated Factor XI (FXIa), represents a promising advancement in anticoagulant therapy. Its targeted mechanism may provide effective prevention and treatment of thromboembolic disorders while reducing the bleeding risk associated with conventional anticoagulants. Clinical studies have demonstrated favorable pharmacokinetic properties, including rapid and sustained Factor XI inhibition, together with the convenience of once-monthly subcutaneous administration. Encouraging results from Phase II studies and Phase III trials, including LILAC-TIMI 76, ASTER, and MAGNOLIA, suggest that abelacimab may offer a safer alternative, particularly for patients with atrial fibrillation, cancer-associated venous thromboembolism, and a high risk of bleeding. However, further long-term studies are needed to confirm its efficacy, safety and real-world clinical benefits.

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