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The safety and efficacy of novel agents targeting factor XI and XII in early phase human trials.

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Abstract

Although anticoagulation without hemorrhage is a primary aim, this vision has remained as yet out of reach. Even despite the superior safety profile of the direct oral anticoagulants, hemorrhage remains a major risk of anticoagulation. Selective inhibition of the contact pathway of coagulation, specifically coagulation factor XI (FXI) and/or factor XII (FXII), has now substantial epidemiologic and preclinical data supporting the notion that these factors contribute to pathologic thrombosis and are yet primarily dispensable for in vivo hemostasis. In this way, targeting FXI and FXII may revolutionize the future anticoagulation landscape. Several drugs are under development for this purpose, including: ISIS 416858, a FXI antisense oligonucleotide which impairs hepatic synthesis of FXI; MAA868, a monoclonal antibody that binds the procoagulant enzymatic site of both zymogen and activated FXI (FXIa); BAY 1213790, a monoclonal antibody that binds the procoagulant enzymatic site of FXIa only; and AB023, a monoclonal antibody that inhibits activated FXII-mediated activation of FXI, along with two small molecules in clinical trials. Each of these drugs have demonstrated favorable safety profiles in their phases 1 and 2 studies to date, with preclinical data also supporting efficacy of abrogating thrombosis in various animal models. Other benefits of some of these drugs include once-monthly dosing and safety in patients with renal or hepatic impairment, while others offer quickly metabolized parenteral options, thus providing more convenient and widely available anticoagulation options. Though still far from the marketplace, drugs targeting FXI and FXII have the potential to usher in a new era of anticoagulation therapy.

Keywords

thrombosis; factor XI; factor XII; contact pathway; sepsis; hemostasis

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Conflict of Interest

Dr. Shatzel reports receiving consulting fees from Aronora Inc, during the conduct of the study.

Introduction:

The core principle of anticoagulation is the delicate balance between the prevention of thrombosis and abrogating the risk of hemorrhage. No therapy has better characterized this balancing act than vitamin K antagonists (such as warfarin), which require careful monitoring of anticoagulant effect via prothrombin time (PT) and international normalized ratio to ensure adequate anticoagulant effect. With widespread adoption of direct oral anticoagulants (DOACs), safer and less tedious anticoagulation options of equal or greater efficacy are becoming the norm. Indeed, the annual risk of intracranial hemorrhage, the most feared consequence of anticoagulation, is reduced by at least one-half with DOACs compared with vitamin K antagonists.[1] Yet problems with anticoagulation remain, including a persistent and cumulative bleeding risk in patients undergoing prolonged anticoagulation, lack of defined and widely available laboratory monitoring techniques for DOACs, and frequent need to consider anticoagulation reversal in emergency situations. It would seem hemorrhage is an inevitable side effect of any anticoagulation therapy in a proportion of patients, though it is hoped the contact pathway of coagulation may provide a solution to this clinical dilemma.

The contact system consists of coagulation factor (F)XI, FXII, prekallikrein, and high-molecular-weight kininogen (HK).[2] These components are part of the intrinsic pathway of coagulation, upstream of the traditional targets for anticoagulation therapy, which target the extrinsic (tissue factor) and common coagulation pathways. FXII can be activated by a growing number of recognized substances, include negatively charged foreign surfaces (intravascular catheters, dialysis circuits, etc.), platelet-derived short-chain and bacteria-derived long-chain polyphosphates, cell-free RNA/DNA, and numerous infectious pathogens.[3] Activated FXII (FXIIa) can subsequently activate FXI; activated FXI (FXIa) contributes to coagulation by promoting thrombin-mediated fibrin generation. FXI can also be reciprocally activated by thrombin, and can reciprocally activate FXII itself.[4] In addition, FXI and FXII are intimately linked with the inflammatory and complement systems. In this way, the contact system, and FXI in particular, can be seen as a central node linking numerous pathophysiologic processes.[5] FXI deficiency is seen most often in the Ashkenazi Jewish population; importantly, a large retrospective cohort study of FXI-deficient patients in Israel revealed significantly reduced rates of venous and arterial thromboembolisms compared with those with normal FXI levels,[6] thus demonstrating the relationship between FXI and pathologic thrombosis.

While the procoagulant aspect of the contact system deserves attention, it is the lack of contribution to normal hemostasis that makes the therapeutic inhibition of contact pathway so appealing. Preclinical animal models have shown no adverse effect of genetic FXI knockout or drug-induced FXI deficiency as far as clinical bleeding or measured bleeding times. Humans with congenital FXI deficiency (hemophilia C) may have a mild bleeding diathesis, though typically only in the face of significant surgical or traumatic hemostatic challenge, unlike FVIII and FIX deficiencies (hemophilias A and B, respectively).[7] It has thus been suggested that in vivo hemostasis is primarily reliant on the extrinsic (tissue factor) pathway of coagulation, with the intrinsic (including contact) pathway providing amplification of this process that seems nonessential for preventing clinical bleeding.[8]

In light of these points, inhibiting the contact pathway naturally represents an exciting therapeutic strategy for a variety of potential clinical scenarios, including prophylaxis against surgical and intravascular device-associated thrombosis and for prevention and treatment of coagulopathy associated with infectious diseases. Several drugs targeting FXI and FXII are currently under development. Herein, we synthesize the published data on seven of these drugs, the mechanisms of which include inhibition of hepatic FXI synthesis (ISIS 416858); inhibition of FXIIa-mediated FXI activation (CSL312, AB023); and inhibition of FXIa catalytic activity (MAA868, BAY 1213790, EP-7041, and BMS-986177 ([Table 1], [Figs. 1] and [2]).

ISIS 416858 (FXI Antisense Oligonucleotide)

The furthest upstream method of reducing contact pathway activity is to inhibit hepatic synthesis of the contact factors. Antisense oligonucleotides (ASO) are a novel therapeutic strategy being harnessed in multiple areas of medicine and function by degrading mRNA sequences that correspond to proteins of interest.[9] ISIS 416858 (ISIS) is a second-generation ASO specific to FXI. Binding of ISIS to transcribed FXI mRNA stimulates breakdown by ribonuclease H1, thus preventing translation of FXI mRNA into functional protein.

A phase 2, randomized, open-label, parallel-group study involving 300 adult subjects undergoing elective primary unilateral total knee arthroplasty has been conducted with thromboembolism prophylaxis of either 200 or 300 mg ISIS administered subcutaneously (SQ) over 5 weeks prior to surgery, or enoxaparin 40 mg SQ starting within 24 hours of surgery.[10] The primary outcome was incidence of venous thromboembolism (VTE), with a safety outcome of hemorrhage. The 200 mg ISIS regimen was equivalent in efficacy to enoxaparin, while the 300 mg regimen demonstrated superior reduction in VTE (27% VTE in ISIS 200 mg vs. 4% in ISIS 300 mg vs. 30% in enoxaparin 40 mg). Hemorrhage incidence was lower in the ISIS groups as compared with enoxaparin (3 vs. 3 vs. 8%, respectively). Mild injection site reactions were occasionally noted in the ISIS groups. Plasma FXI activity levels decreased in a dose-dependent manner in the ISIS groups. Mean levels of FXI in the 200 mg ISIS group were 0.38 units/mL during days 36 to 39, and 0.20 units/mL in the 300 mg ISIS group, as compared with 0.93 units/mL in the enoxaparin group. While activated partial thromboplastin time (aPTT) was substantially prolonged with ISIS, PT, FVIII, FIX, and FXII values were similar among all groups.

Reduction in levels of FXI is a particularly attractive option for surgical procedures, as FXI can be activated by either FXII or thrombin, both of which can be increased subsequent to tissue damage or activated platelets. Rather than focusing on FXI activation by either thrombin or FXII, simply reducing FXI levels may be the most effective option for VTE prophylaxis in surgical procedures. Drawbacks to ISIS include the potential for increased hemorrhage in select vascular beds due to that same reduction in FXI levels, as well as the extended duration of treatment necessary to significantly reduce FXI levels, making it more cumbersome for widespread clinical adoption.

Drugs Targeting Catalytic Activity of FXIa

MAA868 (Monoclonal Antibody against FXI and FXIa)—MAA868 is a fully humanized monoclonal immunoglobulin G (IgG)1 antibody that binds the catalytic domain of both FXI and FXIa with high affinity,[11] preventing further activation of the coagulation pathway. Specifically, the Fab segments of MAA868 bind to the FXI enzymatic active site region in multiple locations, inducing a conformational change in the active site structure in both the FXI zymogen and FXIa, essentially locking FXI/FXIa in a zymogen-like state and preventing further procoagulant catalytic action. MAA868 does not block the ability of FXIIa to activate zymogen FXI to FXIa, though catalytic activity of both forms remain blocked by this antibody.

In a model of FXI knockout (FXI^{-/-}) mice reconstituted with exogenous FXI, administration of MAA868 reduced the formation of occlusive carotid artery thrombi when exposed to topical FeCl₃. Interestingly, the same model performed using DEF, a FXIa active site-specific antibody with higher affinity for FXI than MAA868, showed less effective protection against thrombosis. In a dose-escalation pharmacodynamic study in cynomolgus monkeys, both intravenous and subcutaneous administration of MAA868 showed saturable kinetics above 20 nM of drug plasma exposure, leading to significant increases in aPTT and decreases in free FXI levels without any bleeding or other adverse effects. At a plasma level of > 30 nM, the aPTT was maximally prolonged at 70s. FXI levels were maximally reduced to 3% of normal in the 150 and 240 mg groups. Finally, MAA868 was tested in a phase 1, randomized, blinded, placebo-controlled, single ascending dose study examining the tolerability of SQ MAA868 in 61 healthy adult subjects. MAA868 prolonged the aPTT in a dose- and time-dependent manner, with significant prolongation beginning at the 50 mg dose and lasting ~ 29 days. At the highest administered dose of 240 mg, the aPTT remained elevated up to day 57. MAA868 also suppressed free FXI antigen and FXI activity in plasma for at least 4 weeks. The maximal inhibition was observed on day 2 with a mean FXI of 3% of baseline (95% confidence interval: 2–4%). No complete suppression (< 1% FXI) was observed at any time point. The drug had no effect on the PT or thrombin time. Time to peak MAA868 plasma concentration ranged from 7 to 21 days and was dose independent. Severe obesity decreased maximum antibody concentration and inhibition effect. Half-life ranged from 20.1 to 28.6 days.

There were seven mild adverse events in the treatment group and two in the placebo group thought to be drug related, with headache being the most common. Fatal cardiac arrest occurred in one subject who had received MAA868, but was thought to be unrelated to the drug as free FXI levels had returned to pretreatment baseline (> 90%) at the time of the event.

Despite the low likelihood of bleeding events, the investigators acknowledged that identifying a method of correcting the coagulopathy associated with MAA868 might be clinically useful. To that end, they performed in vitro thromboelastometry with human blood treated with MAA868 and recombinant activated FVII (rFVIIa), showing that rFVIIa was able to correct the clotting time back to within the reference range.

MAA868 is novel in that it seems to effectively inhibit FXI procoagulant activity in both the zymogen and active form, theoretically offering more complete FXI procoagulant inhibition (as suggested by comparison studies using the FXIa-specific antibody DEF). While certainly plausible, it remains to be seen whether this distinction of MAA868 translates to improved clinical efficacy compared with other FXI inhibitory drugs. Similarly, the correction in clotting time with rFVIIa seen on in vitro thermoelectrometry is not proof of its clinical efficacy in the event of serious bleeding, though the authors are to be commended for exploring a potential reversal solution at this early stage in clinical design. Decreased MAA868 exposure in obese individuals may also limit its use, though this may represent a problem with any such monoclonal antibody. Benefits of MAA868 include its infrequent and convenient subcutaneous administration.

BAY 1213790 (Monoclonal Antibody against FXIa)—BAY 1213790 (BAY), similar to MAA868, is a fully humanized IgG1 monoclonal antibody targeting FXIa. BAY binds to a region adjacent to the FIXa active site, thus inducing allosteric structural changes which render the enzymatic site of FXIa inactive. Additional details of the specific mechanism of action are currently unavailable. In a rabbit liver-incision model, preadministration with BAY 1213790 did not increase bleeding times compared with vehicle-treated animals, while bivalirudin-treated rabbits showed substantially higher bleeding times. BAY 1213790 was also able to reduce thrombosis in a mouse carotid artery FeCl₃-induced thrombosis model. [12] A phase 1, single-blind, parallel-group, placebo-controlled, single ascending dose study in 83 healthy Caucasian adult males, was conducted to evaluate for safety.[13] Cohorts received one of nine intravenous doses between 0.015 and 10 mg/kg BAY 1213790. The aPTT and whole blood clotting time (assessed via rotational thromboelastometry) increased and FXI activity decreased in a dose-dependent fashion. The maximum aPTT fold-change relative to baseline using the highest tested dose (10 mg/kg) of BAY 1213790 was 2.17 using a kaolin assay. The aPTT remained elevated above baseline for at least 20 days in all doses of 0.3 mg/kg or higher. In the highest dose cohort, the aPTT was prolonged for up to 150 days. FXI activity was significantly reduced compared with placebo at doses higher than 0.15 mg/kg, with a minimum mean ratio to baseline of 0.176, and occurred almost immediately after drug administration. Time to maximum concentration of BAY 1213790 ranged from 1.05 to 4 hours depending on dose and half-life ranged from 30 to 44 days.

Notably, no clinical bleeding was observed in any patient, nor were bleeding times increased. Adverse events were common but mild in both treatment and placebo groups, with headache and nasopharyngitis being the most common. No discernable association between dose and frequency of adverse events was noted. Events with possible relationship to BAY 1213790 included five possible infusion reactions.

While precise details on structure and mechanism of action of BAY 1213790 are currently unavailable, the drug seems to be distinguished from MAA868 by its lack of inhibitory effect on the zymogen FXI. Rather, it only inhibits the active site of FXIa. In settings of profound contact activation, competition of BAY 1213790 with natural FXIa substrates including FIX could potentially overwhelm its inhibitory effect. This will become clearer with future, larger clinical trials. As with MAA868, animal and phase 1 human data for BAY 1213790 are compelling in their lack of any notable bleeding signal despite prolongations in

several laboratory coagulation tests. In addition, as a monoclonal antibody, BAY 1213790 benefits from metabolism independent of renal or hepatic function, thus making it a potentially useful drug for patients with impairment of either or both organs. Its long half-life also raises the possibility of convenient once-monthly dosing.

EP-7041 (Small Molecule FXIa Active Site Inhibitor)—At least two small selective small molecule FXI inhibitors have been trialed in humans, although minimal data have been published to date on their safety and efficacy. EP-7041 is a selective, small molecule, FXIa inhibitor which has completed initial phase 1 testing. In the phase 1a/1b clinical trial, published in abstract form only, healthy volunteers received intravenous (IV) bolus administration of single ascending doses of EP-7041 or continuous IV infusions for 5 days with matching placebo cohorts.[14] There were no serious adverse events. The drug appeared to have predictable dose-related increases of aPTT (2.2-fold increase at 1.0 mg/kg and 1.7-fold increase at 0.6 mg/kg/h $\times$ 5 days) with rapid onset and offset without altering PT. These findings would make the drug appealing as an infusional therapy which can be rapidly reversed with simply holding the therapy, similar to IV heparins and other commonly used parenteral anticoagulants. No other phase 1 or phase 2 trials of EP-7041 are known to currently be active.

BMS-986177 (Small Molecule FXIa Active Site Inhibitor)—A second selective, small molecule, FXI inhibitor BMS-986177, has completed multiple phase 1 clinical trials, although no data have been published to date. Oral administration of BMS-986177 has been trialed in healthy subjects (,), subjects with renal impairment (,), renal impairment on hemodialysis (,), with potentially interacting medications (,), and in conjunction with aspirin (,). Data specific to these studies have not yet been published.

Drugs Inhibiting FXIIa-Mediated Activation of FXI

AB023 (Monoclonal Antibody against FXI)—AB023 (Xisomab, 3G3) is a humanized, IgG2b monoclonal antibody with a mechanism of action distinct from MAA868 and BAY 1213790. AB023 binds to the apple 2 domain of the zymogen FXI, specifically inhibiting the action of FXIIa to generate FXIa as well as interactions between FXIa and HK.[15] The ability of thrombin to reciprocally activate FXI, as well as the enzymatic active site of formed FXIa itself, is left uninhibited. With this different mechanism, AB023 has also proven effective at preventing thrombosis in several animal models. The murine precursor to AB023, 14E11, was tested in a mouse carotid artery FeCl₃-induced thrombosis model, as well as in a model of thromboplastin-induced pulmonary embolism (PE). Preadministration with 14E11 significantly prolonged carotid artery patency in the arterial model, and prolonged the time to cessation of breathing in the PE model. No increase in bleeding was noted in any of these animal models despite prolongations in the aPTT.[16]

In a baboon model of an externalized, collagen-coated vascular graft, a single dose of the humanized antibody AB023 nearly completely abolished platelet and fibrin accumulation within and downstream of the graft compared with controls, which showed progressive accumulation of both platelets and fibrin. The aPTT remained elevated beyond 24 hours of administration, though no differences in clinical bleeding were observed.

AB023 was subsequently evaluated in a phase 1, randomized, double-blind, placebo-controlled, single ascending dose trial, involving 21 healthy adult volunteers (16 on treatment and 5 on placebo). Cohorts of subjects received intravenous doses of AB023 ranging from 0.1 to 5.0 mg/kg. The aPTT reached a maximum prolongation at doses of 0.5 mg/kg or higher, reflecting maximum saturation of FXI with AB023. aPTT reached its maximal prolongation at all concentrations between 0.25 and 24 hours and decreased thereafter at predictable rates, with lower doses experiencing a quicker decrease. At the maximum dose of 5.0 mg/kg, the aPTT remained prolonged for ~60 days. Plasma concentration of AB023 increased in a dose-dependent manner, with maximal concentration occurring between 0.08 and 0.65 hours after dosing depending on the cohort, while half-life ranged from 1.3 to 121.5 hours. Clearance decreased with increasing doses, ranging from 37.46 to 0.01 L/h. Data on FXI activity were not provided in the report.[15]

AB023 administration resulted in no serious adverse events, including no bleeding events or prolongation in bleeding time compared with controls. Total treatment emergent adverse events were similar between treatment and placebo groups (44 and 60%, respectively). The most commonly encountered AE was productive cough, though this was considered unrelated or unlikely to be treatment related.

By selectively inhibiting FXI activation by FXIIa, but leaving the FXI active site and thrombin-activatable mechanisms intact, AB023 halts the coagulation process otherwise initiated by contact activation, essentially rendering AB023 less a FXI inhibitor and more of a functional FXIIa inhibitor. In this way, clinical bleeding risk may be even lower with this antibody compared with other FXI-inhibiting strategies. Indeed, patients with congenital FXII deficiency, while rarely encountered, have not been shown to have any abnormal bleeding phenotype.[17] The complete neutralization of FXI function may be more likely to result in a risk of hemorrhage similar to that of individuals with congenital FXI deficiency (i.e., sometimes also known as hemophilia C); that is, minimal but clinically significant under certain circumstances. As with the other anti-FXI antibodies discussed, additional clinical data are necessary to support or refute this hypothesis. Another potential benefit AB023 mechanism of action, similar to MAA838, is the avoidance of competition between the inhibitory antibody and natural FXIa substrates. As the normal functions of the contact factors continue to be defined, AB023 is also attractive due to potentially fewer off-target effects by allowing FXIa to continue its normal function.

CSL312 (Monoclonal Antibody against FXIIa)—CSL312 is a humanized, IgG4 monoclonal antibody that binds and inhibits the FXIIa enzymatic active site.[18] CSL312, and its precursor compound 3F7, has been evaluated in a variety of animal models of not only thrombosis but also hereditary angioedema (HA). 3F7 showed similar efficacy as FXI-inhibiting antibodies at reducing carotid artery thrombotic occlusion in a FeCl₃ mouse model and reduced thrombosis in a rabbit arteriovenous shunt model. 3F7 was also effective in a rabbit extracorporeal membrane oxygenation (ECMO) model at reducing ECMO-circuit thrombosis compared with controls, and showed bleeding times equivalent to controls but lower than with unfractionated heparin.[19] Recently, CSL312 was developed as a more potent anti-FXII antibody with 44-fold increased affinity for FXIIa compared with 3F7. Both of these antibodies were tested in animal models of HA. When administered prior to antigen

exposure, 3F7 showed a more profound and longer lasting reduction in edema in mouse ears compared with traditional angioedema drugs, including icatibant (a bradykinin receptor 2 antagonist) and ecallantide (a kallikrein inhibitor). CSL312 was also found to display greater inhibition of bradykinin generation in human plasma in vitro than icatibant or ecallantide. CSL312 also appears to have a favorable safety profile, as demonstrated in the discussed animal models. CSL312 increased aPTT in a dose-dependent fashion in cynomolgus monkeys, but did not affect PT. The injection was well tolerated. Phase 1 data for CSL312 have not yet been published.

CSL312 functions most similarly to AB023 in that both essentially neutralize the enzymatic function of FXIIa on FXI. Both drugs leave FXI enzymatic activity unaffected, yet both drugs demonstrate excellent ability to reduce pathologic thrombosis in animal models. The additional inhibition of CSL312 on the kinin/kallikrein pathway, however, provides additional therapeutic potential for disease such as HA, but also potential off-target effects that have yet to be defined. For instance, given bradykinin influence on vascular permeability and leukocyte recruitment, patients with infectious diseases may respond differently to FXIIa versus FXI inhibition, a concept for which preclinical data are accumulating. A potential drawback to FXIIa-targeted drugs in terms of inhibiting FXI activation is competition with other substrates for the FXIIa catalytic domain, though how this may translate to efficacy is only speculative.

Future Directions

Several of the drugs discussed in this review are currently undergoing further evaluation in larger phase 2 clinical trials. ISIS 416858 is being studied in a phase 2 trial examining safety, pharmacokinetics, and pharmacodynamics in patients with end-stage renal disease (ESRD) on chronic hemodialysis (HD) (). AB023 is currently recruiting subjects for a phase 2 trial in patients with ESRD on chronic hemodialysis, with the goal of evaluating safety and efficacy for reducing dialysis circuit thrombosis (). A phase 1 trial will soon begin recruiting to study the safety and tolerability of BAY 1213790 in patients with ESRD on HD (). The phase 2 FOXTROT trial, evaluating BAY 1213790 for prevention of VTE in patients undergoing total knee arthroplasty, has completed subject recruitment (). A phase 2, placebo-controlled study is currently recruiting subjects to examine CSL312 for HA (). MAA868 had two separate phase 2 trials planned for thromboembolic prophylaxis in subjects with atrial fibrillation and total knee arthroplasty, but both studies have since been withdrawn. Finally, a phase 2 trial of BMS-986177 in conjunction with aspirin or clopidogrel for secondary prevention of ischemic stroke is currently enrolling ().

Conclusion

Achieving anticoagulation without increased risk of hemorrhage is the holy grail of hemostasis and only time will tell if targeting FXI and/or FXII may provide the solution. Substantial preclinical and early clinical data make a strong argument that inhibiting the contact pathway, while allowing the extrinsic and common pathways to function, would lower the likelihood of hemorrhage and provide protection against thrombosis. In addition, many of the antibodies under development offer the potential for convenient, infrequent

dosing, and independence from renal or hepatic metabolism or clearance. Much research is still needed for all drugs discussed, but the future of anticoagulation is looking bright.

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Fig. 1. Sites of action of factors XI and XII inhibitory drugs under development. AS, activation site for conversion of zymogen to active form of coagulation factor; CD, catalytic domain of coagulation factors.

Fig. 2.
Activity of factors XI and XII inhibitory drugs under development.

Table 1

An overview of current agents targeting FXI and FXII in clinical trials

	Mode of action	Mode of administration	Site of action	Mode recent published trial	Sample size	Total adverse events
ISIS 416858	Antisense	Subcutaneous	FXI mRNA	Phase 2 in postoperative VTE prevention	221 (FXI-ASO)/72 (enoxaparin)	80% (FXI-ASO)/65% (enoxaparin)
MAA868	Antibody	Subcutaneous	FXI and FXIa action site	Phase 1	49 (MAA)/12 (placebo)	8.2% (MAA)/8.3% (placebo)
BAY 12123790	Antibody	IV 60 min infusion	Adjacent to FXIa action site	Phase 1	66 (BAY)/15 (placebo)	68% (BAY)/60% (placebo)
AB023	Antibody	IV bolus	Apple 2 domain of FXI and FXIa	Phase 1	16 (AB023)/5 (placebo)	44% (AB023)/60% (placebo)
CSL312	Antibody	IV bolus and subcutaneous	Binds FXIIa	Preclinical (Phase 1 reported as complete)	N/A	N/A
EP-7041	Small molecule	IV bolus and IV drip	Selective small molecule FXIa inhibitor	Phase 1 (abstract only)	N/A	N/A
BMS-986177	Small molecule	Oral	Selective small molecule FXIa inhibitor	Preclinical (Phase 1 reported as complete)	N/A	N/A