A Potent and Selective FXIa Inhibitor as a Next-generation Antithrombotic Drug

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Technology description

The asset is a fully human anti-FXIa antibody that binds human FXIa with high affinity, potency, and selectivity. A thorough PK/PD assessment has been made in rodents, rabbits and non-human primates (NHP). Pfizer has also completed several pre-clinical studies in relevant animal models with the asset being evaluated from the standpoint of both efficacy and safety, including comparison with a leading FXa inhibitor in both thrombosis and bleeding models. Exploratory toxicology in NHP has been completed with no adverse events or microscopic signs noted. Low immunogenicity is expected. Approximately 30 grams of the asset is available. A fully human antibody reversal agent that is specific for the asset is also available.

The research describing this asset has been published in Science Translational Medicine (5). Additional confidential data packages for both the asset and the selective reversal agent are available for review. Enquires should be directed to the contact listed below.
UCSF partnered with Pfizer’ s Centers for Therapeutic Innovation (CTI) to identify an IND-ready antibody directed towards the treatment of thrombotic disease. The asset is a fully human antibody targeting the coagulation cascade serine protease FXIa for currently underserved thrombotic disease indications. A potent reversal agent has also been developed.

In an effort to produce an anticoagulant that will better separate antithrombotic effects from anti-hemostatic effects, we have generated a high affinity, high potency and selective fully human anti-FXIa mAb. FXI was initially viewed as not being critical for thrombosis because it is relatively unimportant for hemostasis, as demonstrated by a lack of bleeding seen in FXI knockout mice and the minimal hemostatic impact seen in humans with FXI deficiency. However, further assessment revealed that FXI deficiency or depletion protects against thrombosis without detectable impairment of hemostasis in animal models in multiples species, and studies in humans revealed decreased risk of venous thromboembolism and thromboembolic stoke with FXI deficiency and increased risk of the same with elevated FXI levels. Multiple therapeutic strategies against FXI/FXIa are now being pursued, including small molecules, antibodies, and antisense approaches (4). To our knowledge, the only molecule currently in clinical development is an antisense molecule to FXI that recently completed a phase 2 study involving patients undergoing knee replacement surgery. This drug achieved superiority over

standard of care (enoxaparin), but required 36 days of prior dosing to achieve adequate suppression of FXI levels and FXIa activity. Thus, a more rapid onset therapeutic with better delivery and PK properties would represent a superior and more durable approach to inhibit this now validated therapeutic target. Thrombotic disease indications where bleeding risk limits the dosing of current standards of care represent special clinical development opportunities for FXIa inhibition. Examples include prevention of venous thromboembolism (VTE) in the medically ill population where FXa inhibitors have thus far failed because small increases in efficacy were accompanied by unacceptable increases in bleeding (2), or where intrinsic pathway triggers are likely to dominate, such as in mechanical heart valve replacements where a Direct Thrombin Inhibitor failed in Phase 3 due to increases in pericardial bleeding and resulted in an early stop to the trial (2,3). VTE prophylaxis in total knee arthroplasty represents a traditional proving ground for anticoagulants and may be appealing for FXIa inhibitors given the probability of their better efficacy and safety. Stroke prophylaxis in those atrial fibrillation patients who currently receive only aspirin due to bleeding history or risk is another opportunity. The availability of a rapid reversal agent for our anti-FXIa antibody and the fact that recombinant FVIIa remains an effective prohemostatic agent in the absence of FXI function suggests that the durable action of our antibody would generally be an advantage for simplicity and compliance.

Additional Information

Other Information

The evidence that FXIa inhibition can reduce thrombosis without having a proportional effect on hemostasis is increasingly supported by numerous genetic and inhibitor studies in both animal and human studies (4). In preclinical studies, we achieved a prominent antithrombotic effect at 1-2 mg/kg in both the FXI humanized-mouse model of arterial thrombosis and the rabbit VTE thread model of thrombosis. In both cases, evaluation of plasma from dosed animals showed that protection coincided with inhibition of FXIa. In the rabbit VTE thread model this was confirmed by assessing clotting times in both the APTT and PT coagulation assays run on plasma from dosed animals. The antithrombotic effects of treatment correlated with increased clotting times as seen in the APTT assay. The level of protection seen with treatment was comparable to that seen with rivaroxaban treatment, but without any of the effects on PT or hemostasis that were seen with this small molecule FXa inhibitor.
These results are consistent with the view that FXIa inhibition does not impair hemostasis because it spares extrinsic triggers of coagulation (Tissue Factor) and has no effect on common pathway proteases like FXa and Thrombin, which are essential to clot formation following a disruption of a blood vessel (hemostasis). Further, the antithrombotic, protective effects were observed in these two different animal models at similar dose levels. These data, in conjunction with an initial PK/PD assessments in NHP, lead us to believe that similar protective effects are likely achievable in humans at comparable doses. The high potency and selectivity of the asset, combined with its long half-life (seen in both rabbits and cyno) would likely allow for infrequent dosing in any future therapeutic settings. Selective inhibition of the intrinsic pathway without affecting the extrinsic or common pathway should separate antithrombotic effects from anti-hemostatic effects to a greater extent. Yet rapid on/off

pharmacological control of the FXIa therapeutic target may nevertheless be clinically desirable given the target patient populations. Therefore, we have additionally generated a fully human specific mAb that rapidly blocks the activity of the asset in human plasma and in rabbits in vivo. The combination of these two high affinity and highly effective mAbs enables us rapid pharmacological on/off control of FXIa therapeutic targeting in vivo.

Publications

1. Chaudhari K, Hamad B, Syed BA . Antithrombotic drugs market. Nat Rev Drug Discov. 2014, 13(8): 571-2.
2. Tahir F, Riaz H, Riaz T, Badshah MB, Riaz IB, Hamza A, Mohiuddin H. The new oral anticoagulants and the phase 3 clinical trials- a systematic review of the literature. Thrombosis Journal 2013, 11:18.
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4. Gailani D, Bane CE, Gruber A. Factor XI and contact activation as targets for antithrombotic therapy. Journal of Thrombosis and Haemostasis 2015, 13: 1-13.
5. Tovo D, Kim YC, Ely L, Rodon I, Gao H, O' Brien P, Bolt, MW, Coyle AJ, Garcia JL, Flounders EA, Mikita T, Coughlin SR. Factor XIa–specific IgG and a reversal agent to probe factor XI function in thrombosis and hemostasis. Science Translational Medicine 2016, 8(353): 353ra112.

Application area

Possible chronic indications:

Patients with mechanical heart valves (estimated 50,000 patients/$530M per year)

Atrial fibrillation patients with reduced kidney function or elevated bleeding risk (estimated 100,000 patients/$215M per year)

Possible acute indications:

VTE prophylaxis in medically ill patients (estimated 3.5 million patients/$300M per year)

Acute coronary syndrome (estimated 800,000 patients/$1B per year)

VTE prophylaxis in knee and hip arthroplasty and hip fracture surgery (estimated 1.3 million patients/ $350-500M per year)

Possible niche indications:

LVAD, ECMO, Cardiopulmonary bypass, indwelling catheters, vascular grafts, wires and other devices.

Advantages

Thrombotic disease afflicts millions of people with a wide range of conditions ranging from atrial fibrillation to venous thromboembolism. The overall market for antithrombotic drug sales is currently $24 billion and growing (1). A major class of antithrombotic drugs is the anticoagulants that target enzymes (or cofactors) in the coagulation cascade. The widely used anticoagulant Coumadin targets

the extrinsic and common pathways in this enzymatic cascade by inhibiting normal biogenesis of several key coagulation factors. More recent oral medications target specific common pathway proteases, FXa (apixaban, rivaroxaban) and Thrombin (dabigatran), and have achieved greater efficacy in several clinical trials largely on the basis of more predictive dosing and metabolic clearance that improve safety margins. Yet these newer medication still carry sufficient bleeding risk, as evidenced by some recent clinical trial failures: RE-ALIGN, Magellan, Adopt (2, 3), that precludes their use in certain patient populations. Such risk highlights the opportunity for improved therapeutics in the antithrombotic field.

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