Since DFXIs inhibit both free and prothrombinase bound coagulation FXa (European Medicines Agency, 2008. CHMP assessment report for Xarelto, Procedure No. EMEA/H/C/000944. Doc.Ref.: EMEA/543519/2008), effective restoration of normal hemostasis would therefore require either full replacement of circulating coagulation FXa or effective removal of inhibitory compounds from blood.

Currently, there are no specific reversal strategies to prevent and stop potential life-threatening bleeding complications associated with DFXI therapy available. Next to life-supporting and surgical therapies, non-specific reversal therapy using 3- and 4-factor PCC may be considered based on limited evidence (Siegal et al., 2014. Blood 123: 1152-1158; Levi et al., 2014. J Thrombosis Haemostatis, Published online 8 May 2014; doi: 10.1111/jth.12599). A reversal strategy specific for DFXI-associated bleeding is in development, which is based on a catalytically inactive form of recombinant FXa (andexanet alpha) that serves as a decoy for DFXIs by binding and thereby trapping circulating DFXIs, thereby enabling endogenous coagulation FXa to normally participate in coagulation (Lu et al., 2013. Nature Medicine 19: 446). A downside to this approach is that high doses of andexanet alpha need to be administered since stoichiometric concentrations are required to attain inhibition (400mg IV bolus in phase III trial; Portola News Release March 19, 2014). Furthermore, since the half life of DFXI partially depends on renal clearance, the amount of decoy FXa required to trap all circulating inhibitory molecules may even be higher in case of renal failure. This reversal strategy does not provide a fast and direct procoagulant response, as the response is dependent on the generation of free, endogenous coagulation FXa.

At this moment, a direct, adequate reversal strategy to prevent and stop potential life-threatening bleeding complications associated with DFXI anticoagulant therapy is not available.

In one aspect, there is provided a recombinant protein comprising a coagulation factor Xa polypeptide, said polypeptide having an alteration in a region of amino

acid residues corresponding to the region of amino acid residues between Gly-289 and Asp-320, preferably between His-311 and Asp-320 of SEQ ID NO: 1; wherein the alteration is an insertion of at least one amino acid residue.

In another aspect, there is provided a nucleic acid molecule comprising a DNA sequence that encodes the protein as described herein.

In yet another aspect, there is provided an expression vector comprising the nucleic acid molecule as described herein.

In yet another aspect, there is provided a host cell comprising the nucleic acid molecule as described herein or the expression vector as described herein.

In yet another aspect, there is provided a pharmaceutical composition comprising the protein as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another aspect, there is provided a method of completely or partially reversing an anti-coagulant effect of a coagulation inhibitor in a subject, said method comprising administering to said subject a therapeutically effective amount of the protein as described herein or the pharmaceutical composition as described herein.

In yet another aspect, there is provided use of the protein as described herein, for the manufacture of a medicament for completely or partially reversing an anti-coagulant effect of a coagulation inhibitor in a subject.

Detailed Description

The present invention solves this problem by providing, as an adequate reversal strategy to prevent and stop potential life-threatening bleeding complications