previous observations. Reduction of FVIII binding activity in von Willebrand Disease (VWD), due to either reduced VWF protein levels or lowered FVIII binding affinity, results in reduced steady-state levels of endogenous FVIII (summarized in Castaman *et al.*, Disorders of Hemostasis 88(1):94-108 (2003), and improving survival of VWF has been proposed as a viable strategy for improving FVIII stability (Denis et al., Thromb Haemost. 2008 Feb;99(2):271-8; Turecek et al., Blood, 2006, 108(11): Abstract 1002). Among severe Hemophilia A patients, a correlation between pre-infusion VWF levels and the half-life of infused FVIII has been demonstrated by Fijnvandraat and colleagues (Fijnvandraat, et al., Br J Haematol. 1995 Oct;91(2):474-6). In that study, patients with 200-300% of average VWF levels were seen to have a FVIII half-life of 15-29 hours compared to a mean of 12.5 hours in patients with normal VWF levels. In another study, patients with blood group O were demonstrated to have significantly lower VWF levels and shorter FVIII half-lives (15.3 hours) compared with those with blood group A (19.7 hours) (Vlot, et al. Thromb Haemost. 2000 Jan;83(1):65-9). Chemically modified VWF has been shown to prolong survival of rFVIII (Turecek et al., J. Thromb. Haemost. 2007 Jul 9; 5(2) abstract available at: http/www.blackwellpublishing.com/isth2007/abstract.asp?id=64898). As such, co-administration of rVWF and rFVIII is a viable strategy for the treatment of coagulation diseases such as von Willebrand Disease and Hemophilia A.

SUMMARY

[0005] Accordingly, the present disclosure provides methods and combinations for treating coagulation disease by administering recombinant von Willebrand Factor (rVWF) alone or in combination with recombinant Factor VIII (rFVIII) to a subject in need thereof, with the result that the *in-vivo* half-life of Factor VIII is increased.

[0006] In one aspect, the present disclosure provides a use of a recombinant Von Willebrand Factor (rVWF) and recombinant FVIII (rFVIII) in the manufacture of a medicament for treating Von Willebrand Disease, wherein the rVWF is a high molecular weight VWF multimer composition comprising at least 40% VWF decamers or higher order multimers, wherein the rVWF is matured in vitro by treatment with Furin, wherein the ratio of rFVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCO) to be administered to the subject is between 2:1 and 1:4, and wherein the rVWF and rFVIII are to be administered together in an initial dose and then subsequent re-dosing is conducted with rVWF alone.

In an embodiment, the present disclosure relates to a method for treating Von Willebrand Disease or Hemophilia A in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF) such that Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein the rVWF is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers, and wherein the rVWF has a higher specific activity than plasma derived Von Willebrand Factor.

[0007] In further embodiments and in accordance with the above, methods of the disclosure include co-administering to the subject recombinant Von Willebrand Factor (rVWF) and recombinant Factor VIII (rFVIII).

7. The use according to any one of claims 1 to 6, wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) to be administered is between 3:2 and 1:3, preferably wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) to be administered is between 1:1 and 1:2, more preferably wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) to be administered is about 3:4.

8. The use according to any one of claims 1 to 7, wherein the rVWF is produced through expression in a Chinese Hamster Ovary (CHO cell culture), preferably wherein the rFVIII and rVWF are produced through expression in the same cell culture.

9. The use according to any one of claims 1 to 8, wherein the rVWF and rFVIII are to be administered together in a single composition.

10. The use according to any one of claims 1 to 9, for treating Von Willebrand Disease Type 3.