KY1049 – A Factor VIII Mimetic Bispecific Antibody

KY1049 is a fully-human common light chain bispecific antibody (BiAb) discovered using the IntelliSelect® Bispecific platform, part of Kymab’s IntelliSelect® suite of technologies. KY1049 simultaneously binds coagulation factor IXa (F IXa) and factor X (F X) on the surface of platelets, bringing both coagulation factors into close proximity. This coincident binding stimulates the F IXa catalysed activation of F X resulting in restoration of the coagulation cascade in the absence of factor VIII (F VIII) (Fig 1 A / B). Here we outline the derivation and optimisation of KY1049 using high-throughput screening. We demonstrate KY1049’s ability to restore haemostatic function in F VIII-depleted and hemophilia A patient plasma with and without inhibitory allo-antibodies.

KY1049 has recently achieved Development Candidate (DC) nomination and is expected to enter clinical trials in 2021/22.

KY1049 Purification

KY1049 can be purified using a routine purification process in line with Chemistry, Manufacturing and Controls (CMC) standards. After Protein A capture, ion-exchange chromatography (iEX) was applied to separate the desired F IXa:F X heterodimer from the two homodimers (F IXa:F IXa and F X:F X) using a salt gradient elution (Fig 3 A / B). The purity of the F IXa:F X heterodimer was determined by analytical HPLC and shown to be greater than 95 % (Fig 3 C).

Further developability processing has achieved > 3.5 g L⁻¹, with significant room for further optimization. Cell lines for KY1049 have been generated, demonstrating enrichment for F IXa:F X heterodimer during cell line development (CLD) selection.

KY1049 Thrombin Generation

Coagulation is driven by the formation of thrombin, the key clotting factor responsible for converting fibrinogen to fibrin. Thrombin Generation Assay (TGA) characterises the formation of thrombin in real-time. TGA analysis reveals that KY1049 demonstrates greater potency at lower concentrations compared to a sequence identical analogue (SIA) of emicizumab using F VIII-depleted plasma (Fig 4 A). Moreover, KY1049 is able to rescue prolonged clotting in severe hemophilia A patients with and without inhibitors (Fig 4 B), demonstrating again greater potency at lower concentrations compared to emicizumab.

KY1049 Rescues Clotting Ex Vivo

KY1049 is a factor VIII mimetic bispecific antibody originating from Kymab’s IntelliSelect® Bispecific antibody platform. A fully-human common light chain bispecific IgG antibody, KY1049 exhibits strong potency in ex vivo studies. KY1049 shows favourable efficacy at reduced dosing levels compared to a sequence identical analogue (SIA) of emicizumab. Manufacturing process development for KY1049 demonstrates good expression, purification and analytical profiles. Clinical trial commencement is planned for 2021/22.

Conclusion

KY1049 – A Factor VIII Mimetic Bispecific Antibody Functionally Rescues Factor VIII Deficiency Ex Vivo


Kymab Ltd, The Bennet Building, Sabrannah Research Campus, Cambridge, CB2 2JY, United Kingdom.