Background

In hemophilia A, a deficiency in coagulation factor VIII leads to an increased risk of bleeding. Hemophilia A mice exhibit a phenotype similar to human hemophilia A patients, making them a suitable model for evaluating therapeutic interventions. The objective of this study was to evaluate the tolerability of ALN-AT3 in a hemophilia disease condition, and hemophilia A (HA) mice were used to model the intended therapeutic setting. Wild-type (WT) mice, with intact coagulation systems, were used as controls in this study.

Methods

Hemophilia A mice (B6;129S-F8) were used to model the intended therapeutic setting. Wild-type (WT) mice, with intact coagulation systems, were used as controls in this study. ALN-AT3, a subcutaneously administered RNAi therapeutic targeting antithrombin (AT), is currently being developed for the treatment of hemophilia.

Results

Repeat administration of ALN-AT3 was well tolerated in HA mice at all doses tested, with no adverse findings up to 100 mg/kg. In addition, therapeutic down-modulation was achieved for all doses tested, with the percentage of plasma AT protein inhibition at 80% for doses ≥10 mg/kg at Day 44. No significant changes were observed in coagulation parameters (APTT, FIB, PLT, NEU) between WT and ALN-AT3-treated HA mice, with the exception of an expected increase in FIB and decrease in PLT due to the consumption of erythrocytes.

Conclusion

The no observed adverse effect level (NOAEL) was 100 mg/kg in hemophilia A mice, demonstrating an expanded therapeutic index in the disease condition. ALN-AT3, the first RNAi therapeutic targeting AT in any animal model, is a potential therapeutic option for reducing the risk of bleeding events in hemophilia A patients.