Population Pharmacokinetic/Pharmacodynamic Modeling of a Next Generation Recombinant Human Factor VIIa (LR769) to Derive the Dose to be Studied in Phase 3

Jules Heuberger¹, Johan Frieling², Matthijs Moerland¹, Joannes Reijers¹, Koos Burggraaf³, Cornelis Kluft³, Jean-Francois Schved⁴, Jasper Stevens¹*

¹CHDR, The Netherlands; ²LFB USA, USA; ³GBS, Netherlands; ⁴CHU Montpellier, France.

Objectives: To develop a population PK-PD model characterizing Factor VIIa concentration-effect relationship for Thrombin Generation Assay with platelets (AUC of peak, TGTp_AUC), activated partial thromboplastin time (aPTT), thromboelastography (MCF: maximum clot firmness) and Prothrombin fragments 1+2 (F1+2). This model was then used to optimize a treatment regimen that is expected to be effective in treating and preventing bleedings in hemophilia A/B patients with inhibitors.

Methods: Data after administration of 25, 75 and 225 µg/kg LR769 to 15 hemophilia A/B patients from a randomized, open label multiple dose cross-over study was used to develop a PK/PD model. FVIIa activity was assessed by modified STACLOT rTF assay. The identified population PK-PD models were used to simulate the response-curves as a function of Factor VIIa activity with different dosing regimens.

Results: A two-compartment model for bolus IV administration was selected for the pharmacokinetics of FVIIa, with lean body mass (LBM) as a covariate on Vd and inter-individual variability on the elimination rate constant. Using the PK model as a driving factor, four PD models were developed for different PD measurements. A sigmoidal maximal effect model was identified for TGTp_AUC, MCF, F1+2 (increasing with increasing FVIIa) and aPTT (decreasing with increasing FVIIa) with the latter two having a gamma fixed at 1. Also, the effect in F1+2 showed a delayed effect, which was modelled using an effect compartment. Several dose regimens were simulated and evaluated for desired effects.

Conclusions: Based on these results, LR769 showed dose responsiveness and two dosing regimens were chosen to be studied in the Phase 3 study: 75µg/kg every 3hrs and 225µg/kg, if needed followed 9hrs later by 75µg/kg were deemed to have the most optimal effect-profile. Preliminary results of the ongoing Phase 3 study indicate these doses may be effective and safe.