Population pharmacokinetic model of recombinant single-chain factor VIII (rVIII-SingleChain) in patients with hemophilia A

Zhang Y.[1], Roberts J.[1], Bensen-Kennedy D.[1], Veldman A.[2], St Ledger K.[1], and Sidhu J.[3]

[1]CSL Behring, R&D Clinical Development, King of Prussia, USA; [2]CSL Behring GmbH, PRD, Marburg, Germany; [3]CSL, R&D Clinical Development, Parkville, Australia

Introduction

BACKGROUND

- rVIII-SingleChain, a novel recombinant Factor VIII (FVIII), is a single-chain construct in which a truncated B-domain covalently links the heavy and light chain

OBJECTIVES

- To characterize the population pharmacokinetics (PK) of rVIII-SingleChain in subjects with hemophilia A
- To identify variability in PK parameters and their potential determinants (demographic and clinical covariates)
- To simulate single-dose and steady-state FVIII activity-time profiles for various dosing scenarios of rVIII-SingleChain

Methods

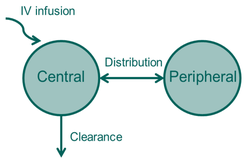
STUDY DESIGN

- CSL627_1001 was a Phase I/III safety, efficacy and PK study conducted in subjects of 12 to 65 years old
- CSL627_3002 study was a Phase III safety, efficacy and PK study conducted in subjects 0 to <12 years old
- PK was assessed using plasma FVIII activity levels measured with a validated chromogenic assay
- In those subjects who received 50 IU/kg rVIII-SingleChain, serial blood PK samples were collected over 72 hours

POPULATION PK

- rVIII-SingleChain population PK modeling was conducted using NONMEM®
- A two-compartmental model with first-order elimination rate was used in data analysis
- Investigated covariates included body weight (WT), baseline von Willebrand Factor (vWF), age, anti-drug antibody, and hematocrit
- Bootstrap and visual predictive check were performed to evaluate the model

Figure 1. Two compartmental model structure for rVIII-SingleChain



MODEL-BASED SIMULATIONS

- Individual WT and baseline vWF from subjects included in the population PK modeling were used in the simulation dataset
- Simulations were performed for doses of 20 to 50 IU/kg 2 times and 3 times per week (N = 1000)
- The 5th, median and 95th percentiles of concentration-time profiles were derived, and % of a simulated population with a steady-state trough concentration higher than 1% were calculated

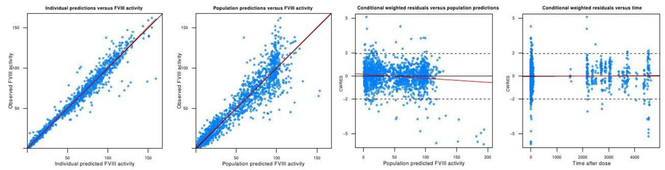
Results

- A two-compartment model with first order elimination for rVIII-SingleChain adequately described the data
- WT and vWF were significant covariates for clearance (CL), and WT was a significant covariate for volume of distribution in central compartment (V1)

Table 1. Summary of the rVIII-SingleChain population PK parameter estimates

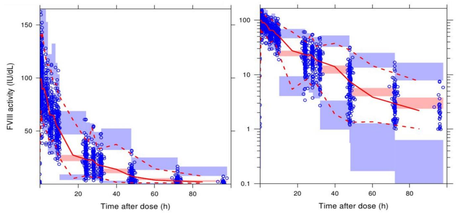
Parameter	Population estimate (RSE%)	Inter-individual variability (RSE%)
Clearance (CL) (dL/hr) ~vWF on CL ~WT on CL	2.12 (2.70%) –0.633 (8.36%) 0.756 (4.72%)	0.0583 (6.90%) – –
Volume of distribution in central compartment (V1) (dL) ~WT on V1	33.6 (2.05%) 0.903 (3.46%)	0.0388 (9.09%) –
Inter-compartmental clearance (Q) (dL/hr)	1.34 (25.6%)	–
Volume of distribution in peripheral compartment (V2) (dL)	2.65 (9.15%)	–
FVIII Baseline activity (BASE) (IU/dL)	0.765 (22.0%)	0.334 (20.8%)
Residual error Proportional error (%) Additive error (IU/dL)	0.109 (14.3%) 1.15 (16.3%)	– –

Figure 2: Goodness of fit of the rVIII-SingleChain population PK model



Red lines = regressions. Blue open circles = observations.
(a) Observed concentration versus individual predicted concentration. (b) Observed concentration versus population predicted concentration. (c) Conditional weighted residuals versus population prediction. (b) Conditional weighted residuals versus time after dose.

Figure 3: Visual predictive check for the rVIII-SingleChain population PK model



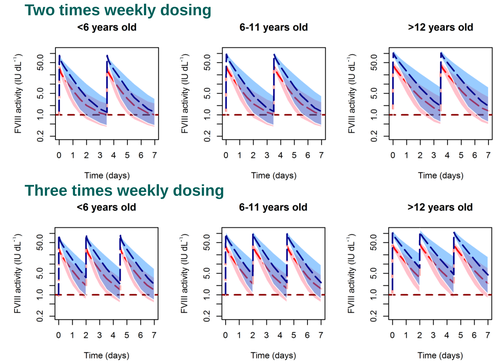
Blue open circles represent observations. Red lines represent the median of each shadow. Shadows represent the 90% prediction interval of 5% (blue), median (red) and 95% (blue) percentiles for each simulation data (N = 1000).
Model evaluation deemed adequate.

SIMULATION RESULTS

- The model estimates that for 2-times-weekly dosing (every 3.5 days) at the lowest dose of 20 IU/kg, more than 63%, and at the highest dose level of 50 IU/kg, more than 75% of subjects were predicted to maintain FTOT activity level above 1% at all times
- The model estimates that for 3-times-weekly dosing (day 0, 2 and 4.5) at the lowest dose of 20IU/kg, more than 85%, and at the highest dose level of 50 IU/kg, more than 93% of subjects were predicted to maintain FTOT activity level above 1% at all times

Results (cont.)

Figure 4: Predicted steady-state FVIII activity profiles for rVIII-SingleChain at two different dosing schedules: 20 IU kg^{-1} (red) and 50 IU kg^{-1} (blue) for varying age groups



Dashed lines represent median predicted values and shaded regions represent 90% prediction intervals. The red horizontal dashed lines represent the equivalent of 1% (1 IU/dL) of normal FVIII activity

Table 2. Summary of the simulated steady-state trough FVIII activity following multiple doses of 20 and 50 IU/kg

Simulation	Age group	Median trough (90% PI) (IU/dL)	25th percentile trough (IU/dL)	% Subjects maintaining rVIII-SingleChain FVIII activity level above 1%
20 IU/kg 2 times weekly, Day 3.5 and 7	<6	1.0 (0.39-2.4)	0.67	49.4
	6 to <12	1.0 (0.40-2.6)	0.70	52.0
	≥12	1.3 (0.48-3.9)	0.88	67.9
50 IU/kg 2 times weekly, Day 3.5 and 7	<6	1.2 (0.45-3.4)	0.80	62.4
	6 to <12	1.3 (0.45-4.1)	0.83	65.0
	≥12	1.9 (0.58-8.0)	1.1	80.3
20 IU/kg 3 times weekly, Day 2	<6	2.0 (0.71-4.8)	1.3	87.1
	6 to <12	2.3 (0.78-6.0)	1.5	89.6
	≥12	3.5 (1.1-9.5)	2.2	96.6
20 IU/kg 3 times weekly, Day 4.5	<6	1.4 (0.54-3.7)	0.97	72.8
	6 to <12	1.6 (0.57-4.6)	1.0	76.6
	≥12	2.4 (0.76-7.8)	1.5	89.3
20 IU/kg 3 times weekly, Day 7	<6	1.4 (0.54-3.6)	0.96	72.8
	6 to <12	1.6 (0.57-4.4)	1.0	76.6
	≥12	2.4 (0.76-7.5)	1.5	89.1
50 IU/kg 3 times weekly, Day 2	<6	3.6 (0.92-10.2)	2.2	94.3
	6 to <12	4.2 (1.1-13.3)	2.5	96.5
	≥12	7.5 (1.8-22.1)	4.3	99.1
50 IU/kg 3 times weekly, Day 4.5	<6	2.2 (0.67-7.3)	1.4	86.5
	6 to <12	2.5 (0.73-9.6)	1.5	88.9
	≥12	4.5 (1.1-17.9)	2.4	95.9
50 IU/kg 3 times weekly, Day 7	<6	2.2 (0.67-7.1)	1.3	86.5
	6 to <12	2.5 (0.73-9.3)	1.5	88.3
	≥12	4.4 (1.1-17.3)	2.4	95.7

The LOQ for the chromogenic assay is 1 IU/dL. Simulated activity may go below LLOQ

Conclusions

- FVIII activity was well described by a two-compartment population PK model with WT and vWF being the significant covariates
- The population PK simulation supported the dose regimens of 20 to 50 IU/kg rVIII-SingleChain 2 times and 3 times weekly, so that the majority of subjects maintain total FVIII activity level above 1%

Biotherapies for Life™ CSL Behring