A Phase 1 Study to Evaluate the PK, Safety and Tolerability of a PEGylated-Recombinant Human Coagulation Factor VIII-Fc Fusion Protein (FRSW117) with Extended Half-Life in Patients With Severe Hemophilia A

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INTRODUCTION

- The current mainstay treatment of hemophilia A in China is FVIII replacement treatment, which can be further categorized into on-demand treatment and prophylaxis treatment. Prophylaxis treatment plays an essential role in hemophilia A management to maintain normal joint and muscle function. The objective of prophylaxis treatment is to maintain FVIII activity above 1% at all times.[1] In some patients, a trough level of 1 IU/dL (1%) was deemed unadequate. Most clinicians would prefer to target higher trough levels (>3%-5%, or higher)[2].
- With standard half-life (SHL) FVIII, it is difficult to achieve trough FVIII activity higher than 1%.[2] To do so would require very frequent infusions (possibly daily) that many patients are likely unwilling or unable to do.
- FRSW117 is a a PEGylated recombinant human coagulation factor VIII Fc fusion protein (PEGylated rhFVIII-Fc), which is developed as a novel extended half-life rhFVIII. It demonstrated superior long-acting efficacy compared with Xythan in preclinical studies.
- The pharmacokinetic (PK), safety and tolerability profiles of a single dose of FRSW117 in previous treated patients with severe hemophilia A were evaluated in SS-117-I01 study.

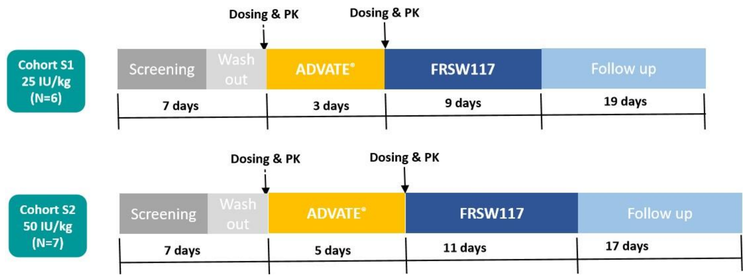
OBJECTIVES

To assess the PK, safety and tolerability of a single IV dose of FRSW117 in subjects with severe HA.

METHODS

- SS-117-I01 is a first-in-human phase 1 study of FRSW117 in previously treated adult and adolescent patients with severe hemophilia A conducted in China **(Figue 1)**.

Figure 1. Study Schema



- Patients were dosed with a single IV dose of Advate® followed by a PK sampling period, then administered a single IV dose of FRSW117 followed by another PK sampling period. Subjects underwent safety observation for 28 days following FRSW117 administration, which includes inhibitor assessments 14 and 28 days after FRSW117 dosing.
- Two doses have be evaluated in study: 25 IU/kg single dose (S1) and 65 IU/kg single dose (S2).

RESULTS

- 13 male subjects were enrolled at 4 sites in China, 6 in Cohort S1 and 7 in Cohort S2. All subjects completed the study as planned.

RESULTS

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline

Characteristic	S1 (N=6)	S2 (N=7)	Total (N=13)
Age(yr) , Median (range)	30.5 (27, 33)	33.0 (20, 54)	32.0 (20, 54)
Weight (kg) , Median (range)	75.5 (43.9, 87.0)	57.0 (44.2, 81.8)	72.3 (43.9, 87.0)
Time since hemophilia diagnosis (year) , Median (range)	17.0 (13.0, 33.3)	24.0 (13.0, 34.0)	21.9 (13.0, 34.0)
History of FVIII inhibitor, n (%)	0	0	0
Factor VIII regimen, n (%)			
Prophylaxis	4 (66.7)	2 (28.6)	6 (46.2)
On-demand	2 (33.3)	5 (71.4)	7 (53.8)
FVIII activity, % Mean (SD)	0.6 (0.3)	0.4 (0.2)	0.5 (0.2)

Pharmacokinetics

- C_{max} and $AUC_{0-\infty}$ of FVIII activity appeared to increase in a dose-dependent manner (**Figure 2**).
- Time to 3% and 1% of FVIII activity is 121.6h and 169.6h in S1, 165.1h and 206.5h in S2, respectively, more than 2.5 times those of ADVATE® (**Table 2**).
- PK parameters were derived by noncompartmental analysis method corrected by baseline FVIII activity according to the one-stage assay and are summarized in **Table 3.**
  - The elimination half-life of FRSW117 was more than 2 times that of ADVATE® (30.9 h vs. 13.7 h in S1; 30.8h vs. 14.0h in S2).
  - The incremental recovery (IR) was 3.0 [IU/dL] /[IU/kg] in S1 and 2.6 [IU/dL] /[IU/kg] in S2.

Figure 2. Factor VIII Activity in the Two Dose Groups

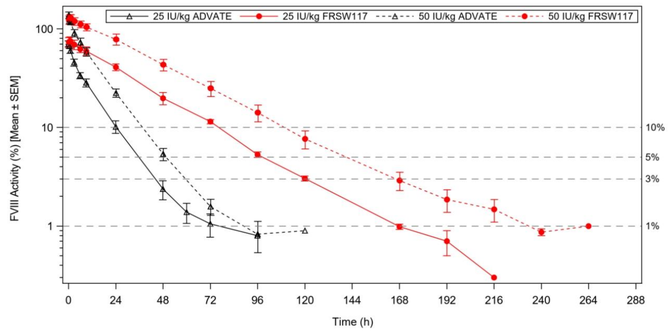


Table 2. Time to 10%, 5%, 3% and 1% of FVIII Activity (Geometric Mean)

Characteristic	S1 (N=6)			S2 (N=7)		
	ADVATE®	FRSW117	Ratio	ADVATE®	FRSW117	Ratio
Time to 10% FVIII activity (h)	25.1	74.2	3.0	40.5	106.7	2.6
Time to 5% FVIII activity (h)	38.2	100.2	2.6	51.2	138.1	2.7
Time to 3% FVIII activity (h)	45.9	121.6	2.6	60.2	165.1	2.7
Time to 1% FVIII activity (h)	65.4	169.6	2.6	83.1	206.5	2.5

RESULTS

Table 3. PK Parameters (Geometric Mean)

Characteristic	S1 (N=6)			S2 (N=7)		
	ADVATE®	FRSW117	Ratio	ADVATE®	FRSW117	Ratio
C_{max} (IU/dL)	69.72	74.22	1.06	135.47	131.84	0.97
T_{max} (h)	0.1670	0.7940	4.7543	0.1670	0.5754	3.4453
$t_{1/2}$ (h)	13.318	28.359	2.129	13.818	30.837	2.232
$AUC_{0-\infty}$ ((h*IU/dL)	856.7	2849.3	3.3	1802.5	5569.8	3.1
CL (dL/h/kg)	0.0292	0.0088	0.3002	0.0277	0.0090	0.3237
IR ([IU/dL] /[IU/kg])	2.789	2.955	1.059	2.710	2.637	0.973

Safety

- No development of FVIII inhibitors was detected for all 13 subjects.
- 18 TEAE were reported in 9 patients (69.2%). 5 FRSW117-related TEAEs were reported in 3 patients (23.1%) including: increased thrombin-antithrombin III complex, increased blood bilirubin, hypertriglyceridemia, fever, and urinary tract infection.
- No SAEs, ≥ grade 3 TEAEs, AESIs, or AEs leading to early withdrawal or discontinuation of study treatment were reported.

CONCLUSIONS

- FRSW117 demonstrated a prominently longer $T_{1/2}$ and was able to maintain FVIII activity at ≥ 1% for more than 7 days compared with ADVATE®.
- Single dose of FRSW117 (25 IU/kg or 50 IU/kg) was well tolerated in previously treated patients with severe hemophilia A.
- Study results supported a potential weekly treatment interval of FRSW117 in the Phase 3 clinical study.

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