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Blood 142 (2023) 2615–2616

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

322.DISORDERS OF COAGULATION OR FIBRINOLYSIS: CLINICAL AND EPIDEMIOLOGICAL

Pharmacokinetics, Safety and Preliminary Efficacy of Multiple Doses of Pegylated Recombinant Human Coagulation Factor VIII-Fc Fusion Protein (FRSW117) in Previously Treated Adult and Adolescent Subjects with Severe Hemophilia a: Results from an Open-Label, Multicenter, Phase 2 Study

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Introduction : Prophylaxis of severe hemophilia A (HA) with standard half-life Factor VIII (FVIII) products necessitates frequent administration, and low trough FVIII activity levels lead to higher risk of bleeds. FRSW117 is a PEGylated recombinant human coagulation factor VIII Fc fusion protein (PEGylated rhFVIII-Fc), in a phase 1 study, single-dose FRSW117 was well tolerated and provided a prominently longer t1/2 with FVIII activity maintaining at ≥ 1% for more than 7 days.
This open-label, multicenter phase 2 study (NCT05265286) aimed to evaluate the PK, safety, and preliminary efficacy of multiple 4 doses of FRSW117 in previously treated subjects with severe HA.
Methods : Severe HA (FVIII:C <1%) patients aged 12 (inclusive) to 65 years, previously treated with FVIII products ≥ 150 exposure days (EDs) were enrolled in two cohorts (M1, 40IU/kg; M2, 50IU/kg), to receive 4 once-weekly doses of FRSW117 on day 1, 8, 15, and 22 (ED1 to ED4), respectively. The PK characteristics, safety, and immunogenicity of FRSW117 were evaluated. PK samples were collected pre-dose on day 1, 8, 15, 22, and at multiple times after infusion on day 1 and day 22.
The primary endpoints were the PK parameters, the occurs of AEs, inhibitor development, and other immunogenicity profiles; the secondary endpoints were the bleeding episodes during multiple dosing. FVIII activity was determined using one-stage clotting assay. FVIII inhibitor was tested using the Nijmegen-modified Bethesda assay. PK analyses were performed using noncompartmental analysis (Phoenix WinNonlin 8.3).
Results : Between April 2022 and August 2022, a total of 15 male subjects were enrolled in cohort M1 (N=8) and M2 (N=7). 13/15 (86.7%) of the subjects were adults, 2 of them were adolescent, both in M1. The mean age was 28.1 (range: 13, 44) in M1 and 30.6 (range: 23, 36) in M2. 14 subjects completed the study, with 1 subject in M2 withdrew early after the PK sampling of ED1 due to personal reasons.
Baseline-corrected PK parameters were summarized in Table 1. Geometric mean elimination half-life ($t_{1/2}$) of M1 and M2 were 29.536h and 31.545 h, respectively, consisting with the first-in-human single dose study. Area under the activity-time curve (AUC_{0-t}), and steady-state maximum concentration (C_{max}) after 4 weekly doses for M1 and M2 were 4557.1 and 4937.9 h*IU/dL, 101.26 and 122.76 IU/dL, respectively. The mean FVIII activity at 168h after dose for M1 and M2 were summarized in Table 2, and it were 3.25 and 2.88 IU/dL on 168 h (7 day) after the dose on D22. Baseline-corrected FVIII activity over time of 2 cohorts are shown in Figure 1. The accumulation index based on AUC_{tau} were 1.008 and 1.098, respectively, indicating there was minimal accumulation after 4 once-weekly doses.
A total of 10 (66.7%,10/15) subjects reported 20 treatment emergent adverse events (TEAE) during the study. No ≥ grade 3 adverse events, serious adverse events (SAE), adverse event leading to treatment discontinuation, or AESI were reported.
No positive FVIII inhibitor was detected during the study. Pre-existing Anti-PEG-rhFVIII-Fc antibodies (ADA) were observed in 4/15 (26.7%) subjects.Pre-existing anti-PEG antibodies were observed in 3/15 (20.0%) subjects. No treatment emergent ADA and anti-PEG antibodies were observed, no treatment-boost ADA and anti-PEG antibodies were observed in subjects with pre-existing ADA and anti-PEG antibodies. No significant impact of pre-existing ADA and/or anti-PEG antibodies on PK variable, safety profile and preliminary efficacy was observed.
12/15 (80.0%) patients experienced zero bleeding episodes during the 4-week FRSW117 treatment period (from day 1 through day 28, 7 days after D22 dosing). Three of 15 (20.0%) subjects experienced 6 bleeding events among which only 1 spontaneous

bleeding episode in cohort M1. 2 bleeds episodes were treated with FRSW117 of mean dose of 30.01 IU/kg and both were controlled after one infusion, with a hemostatic response rate of 100%.

Conclusion: The therapy of 4 once-weekly doses of FRSW117 displayed favorable safety profile and provided about 3% mean FVIII activity on day 7 postdose with minimal accumulation. These results suggest that FRSW117 may offer extended bleeding protection with weekly dose interval and support further assessment of FRSW117 in phase 3 study.

Disclosures No relevant conflicts of interest to declare.

Table 1. Summary of Geometric Mean Ratios for PK Parameters of FRSW117 (Baseline Corrected, PKPS)

	Cohort M1 (40 IU/kg) (N=8)			Cohort M2 (50 IU/kg) (N=7)			Cohort M2/M1	
	ED1	ED4	ED4/ED1	ED1	ED4	ED4/ED1	ED1	ED4
$t_{1/2}$ (h)	29.536	33.025	1.12	31.545	37.215	1.18	1.07	1.13
C_{max} (IU/dL)	107.32	101.26	0.94	106.46	122.76	1.15	0.99	1.21
AUC_{0-t} (h*IU/dL)	4413.0	4557.1	1.03	4634.6	4937.9	1.07	1.05	1.08
$MRT_{0-\infty}$ (h)	41.446	44.584	1.08	43.313	44.458	1.03	1.05	1.00
Incremental recovery ([IU/dL]/[IU/kg])	2.620	2.464	0.94	2.031	2.398	1.18	0.78	0.97
CL_{ss}(dL/h/kg)		0.009			0.010			1.16
Rac		1.008			1.098			1.09
Time of FVIII activity to 5% (h)	131.470	132.367	1.01	135.145	136.889	1.01	1.03	1.03
Time of FVIII activity to 3% (h)	153.321	158.850	1.04	160.895	166.301	1.03	1.05	1.05
Time of FVIII activity to 1% (h)	197.636	216.252	1.09	207.777	225.301	1.08	1.05	1.04

Table 2. Summary of Mean FVIII:C on Day 7 After Dose During Treatment of FRSW117 (Baseline Corrected, PKCS)

FVIII:C (IU/dL)		Cohort M1 (40 IU/kg) (N=8)	Cohort M2 (50 IU/kg) (N=7)
ED1	n (missing)	8 (0)	7 (0)
	Mean±SD	2.40±1.976	2.69±1.125
ED2	n (missing)	6 (2)	6 (1)
	Mean±SD	3.08±1.482	2.23±0.656
ED3	n (missing)	6 (2)	6 (1)
	Mean±SD	2.98±1.627	2.80±0.724
ED4	n (missing)	6 (2)	6 (1)
	Mean±SD	3.25±1.596	2.88±0.637

Notes:
1. 2 Subjects receiving breakthrough therapy in Cohort M1 before ED3 administration and 1 subject withdrew early in Cohort M2 before ED2 administration were excluded for the trough FVIII: C analysis except that of ED2.
2. Baseline is FVIII activity (IU/dL) before first dose (ED1).

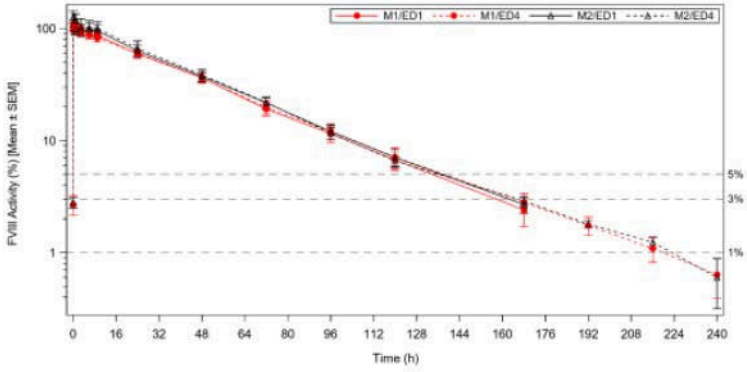

Figure 1. Mean FVIII Activity-Time Curves of FRSW117 at ED1 and ED4 (Baseline Corrected, Semi-logarithmic Curve, PKCS)

Figure 1

https://doi.org/10.1182/blood-2023-180649