First-in-human pharmacokinetic, safety, and preliminary efficacy studies of single- and multiple-dose FRSW117, a novel PEGylated recombinant factor VIII-Fc fusion protein with an extended half-life, in patients with severe hemophilia A

The treatment for severe hemophilia A involves exogenous factor VIII (FVIII) replacement, but the utilization of prophylactic treatment in China remains limited, at just 16.2% of patients, lower than the rates observed in developed nations.[1,2] The traditional goal of prophylaxis in hemophilia A is to sustain FVIII activity levels above 1 IU/dL (1%).[3] Attaining these elevated trough levels using standard half-life recombinant FVIII products remains challenging, necessitating frequent injections. Extended half-life FVIII products offer a longer duration of action,[4] mostly with biweekly injections. Notably, efanesoctocog alfa has a half-life of approximately 40 hours,[5] enabling weekly prophylactic injections. The choice of extended half-life FVIII products is limited in China, so far.

FRSW117 is the first pegylated recombinant FVIII-Fc fusion protein manufactured by random pegylation of recombinant human FVIII-Fc fusion protein. In preclinical studies, FRSW117 exhibited an extended half-life of 37 hours at a dose of 125 IU/kg in Cynomolgus monkeys, surpassing the 4.69-hour half-life of Xyntha®, and demonstrated comparable procoagulant activity, superior prophylactic efficacy, and a manageable safety profile (*unpublished data*). Here, we report results from two studies: a phase I first-in-human trial (NCT04864743) examining the safety and pharmacokinetics of FRSW117 in comparison with those of Advate® and a phase II study (NCT05265286) assessing the pharmacokinetics, safety, and initial efficacy of a repeated four-dose regimen of FRSW117, administered weekly in patients with severe hemophilia A (FVIII activity <1%) who had undergone previous treatment with FVIII for ≥150 exposure days. Informed consent was obtained from all patients and protocols were approved by the ethics committee of the Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (phase I: XY2021018-EC-1; phase II: XY2022002-EC-1) and other participating centers.

In the phase I study, the participants in the 25 IU/kg cohort received Advate® and then the same dose of FRSW117 at a 4-day interval. FVIII activity was measured over 72 hours for Advate® and 216 hours for FRSW117. Upon confirming the safety and tolerance of FRSW117 in three participants, enrollment continued for the 25 and 50 IU/kg dose cohorts (N ≥6/cohort). In the multicenter, open-label phase II study, the participants were enrolled into the 40 and 50 IU/kg cohorts (N ≥6/cohort) and received FRSW117 on days 1, 8, 15, and 22. If bleeding episodes occurred after the second and before the third FRSW117 injection, the drug was administered for breakthrough bleeding treatment determined by investigators according to guidelines and individual patients' needs.[3] The safety and tolerability were judged by the investigators via detection of adverse events (AE), anti-drug antibodies (ADA) and FVIII inhibitors. The preliminary efficacy of FRSW117 was evaluated in the phase II trial. The follow-up was until 28 days after the single dose and the dose on day 22 in the phase I and phase II study, respectively. For the statistical analyses, SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was employed. Pharmacokinetic parameters were deduced through a non-compartmental analysis method using Phoenix WinNonlin 8.3.

In the phase I study, there were six and seven participants in the 25 and 50 IU/kg cohorts, respectively. Before the study, 53.8% (7 participants) received on-demand FVIII treatment (Table 1). All 13 participants completed the study. Peak serum concentration (C_{max}) and area under the concentration curve ($AUC_{0-\infty}$) increased in a dose-dependent manner. The geometric mean elimination half-life ($t_{1/2}$) of FRSW117 was more than twice that of Advate®, being 28.4 *versus* 13.3 hours in the 25 IU/kg cohort and 30.8 *versus* 13.8 hours in the 50 IU/kg cohort, respectively (Table 2). The time to 3% and 1% FVIII activity for FRSW117 was longer, approximately 2.5 times that with Advate® (25 IU/kg cohort: 121.633 and 169.566 hours; 50 IU/kg cohort: 165.147 and 206.462 hours). The $AUC_{0-\infty}$ for FVIII activity over time with FRSW117 was more than triple that of Advate® for the corresponding doses (Table 2). The geometric mean incremental recovery of FRSW117 was 2.955 ([IU/dL]/[IU/kg]) in the 25 IU/kg cohort and 2.637 ([IU/dL]/[IU/kg]) in the 50 IU/kg cohort. Nine participants (69.2%) experienced 18 treatment-emergent AE, all grade 1 or 2 (*Online Supplementary Table S1*). Among these, five treatment-emergent AE in three participants (23.1%) were FRSW117-related. There were no serious AE or AE leading to discontinuation of the study drug. No FVIII inhibitors were detected. Four out of 13 participants developed ADA; two were identified

Table 1. Demographic and clinical characteristics of the participants at baseline.

Variables	Phase I, N=13			Phase II, N=15		
	25 IU/kg, N=6	50 IU/kg, N=7	Total, N=13	40 IU/kg, N=8	50 IU/kg, N=7	Total, N=15
Age, years, mean (SD)	30.3 (2.16)	34.1 (10.06)	32.4 (7.51)	28.1 (11.57)	30.6 (4.31)	29.3 (8.75)
Age <18 years, N (%)	-	-	-	2 (25.0)	0	2 (13.3)
BMI, kg/m^2, mean (SD)	23.49 (3.723)	21.86 (5.912)	22.61 (4.896)	22.43 (4.589)	21.16 (4.280)	21.83 (4.337)
Time since hemophilia diagnosis, years, median (range)	17.0 (13.0-33.3)	24.0 (13.0-34.0)	21.9 (13.0-34.0)	24.3 (10.1-37.0)	29.0 (22.0-36.7)	26.80 (10.1-37.0)
FVIII treatment in the previous 6 months, N (%)						
Prophylaxis	4 (66.7)	2 (28.6)	6 (46.2)	5 (62.5)	2 (28.6)	7 (46.7)
On-demand	2 (33.3)	5 (71.4)	7 (53.8)	2 (25.0)	2 (28.6)	4 (26.7)
Prophylaxis mixed with on-demand	-	-	-	1 (12.5)	3 (42.9)	4 (26.7)
FVIII activity, %, mean (SD)	0.58 (0.279)	0.43 (0.214)	0.50 (0.248)	0.48 (0.116)	0.41 (0.038)	0.45 (0.092)

SD: standard deviation; BMI: body mass index; FVIII: factor VIII.

as pre-existing, and two occurred after dosing (but it was not known whether these cases were due to Advate® or FRSW117). The participants did not exhibit spontaneous bleeding episodes for 168 hours following a single dose of FRSW117 (both dosages). One traumatic joint bleeding episode due to an ankle sprain was reported in a patient in the 50 IU/kg cohort 3 days after FRSW117 administration (resolved with two doses of recombinant activated factor VII to avoid interference with the pharmacokinetic analysis and FVIII activity measurements).

The phase II study enrolled eight and seven participants in the 40 and 50 IU/kg groups, respectively (Table 1). Fourteen participants completed the study. The mean FVIII activity exceeded 10% at 96 hours after dosing. At 168 hours, the activity levels were 3.25% and 2.88%, respectively (*Online Supplementary Table S2*). At steady-state, the geometric mean elimination $t_{1/2}$ was 33.0 hours for the 40 IU/kg cohort and 37.2 hours for the 50 IU/kg cohort, suggesting a dose-proportional trend of C_{max} and AUC_{0-t} (Table 3). Ten participants (66.7%) experienced 20 treatment-emergent AE. All these treatment-emergent AE were grade 1 or 2 (*Online Supplementary Table S3*). There were no serious AE or AE leading to treatment discontinuation in the study. No FVIII inhibitors were detected. Four participants (26.7%) had at least one positive ADA result but these were identified as pre-existing. Three participants had pre-existing anti-PEG antibodies of the IgM subtype, and two had pre-existing anti-PEG antibodies of the IgG subtype. None of these anti-PEG antibodies was induced or emerged due to the treatment. Twelve (80%) participants did not experience bleeding episodes. In the 40 IU/kg cohort, there was one spontaneous joint bleed (6.67%) 130.65 hours after the last FRSW117 administration and one traumatic oral bleed due to brushing teeth. Both bleeds resolved with one dose of FRSW117 (average dose: 30.01 ± 0.008 IU/kg). The response rate (excellent + good) was 100%. No spontaneous bleeding episodes were observed in the 50 IU/kg cohort. One subject in the 50 IU/kg cohort reported three instances of traumatic oral bleeding due to brushing teeth and one case of oral bleeding due to pericoronitis.

The pharmacokinetic findings from our phase I and II clinical studies of FRSW117 underscore a pivotal advancement in hemophilia A treatment, highlighting its ultra-long half-life and potential to reduce prophylactic infusion frequency. Notably, the $t_{1/2}$ of FRSW117 after single doses of 25 and 50 IU/kg was 28.4 and 30.8 hours, respectively. Comparatively, FRSW117 exhibits a longer $t_{1/2}$ than twice-weekly extended half-life products, such as efmoroctocog alfa (19.0 hours), rurioctocog alfa pegol (16.0 hours), damoctocog alfa pegol (17.0 hours), and turoctocog alfa pegol (16 hours),[6-8] yet falls short of the $t_{1/2}$ reported for efanesoctocog alfa (40 hours).[5,9] By potentially reducing the frequency of prophylactic infusions, FRSW117 would probably offer a promising avenue for improving the therapeutic landscape for patients, contingent upon further validation in future trials.

The study's findings on C_{max} and incremental recovery rate underscore the comparable hemostatic efficacy of FRSW117 to that of standard half-life products. Despite slight variations in C_{max} between FRSW117 and Advate®, the ratios indicate substantial equivalence, reinforcing the therapeutic potential of FRSW117 in achieving desired hemostatic levels with a reduced dosing frequency. This equivalence in peak plasma concentration and incremental recovery, pivotal for effective hemostasis, aligns with previous research.[10] Targeting trough levels exceeding 3%, as suggested by emerging preferences in clinical practice, could potentially optimize prophylaxis by reducing bleeding episodes and enhancing patients' quality of life,[3] corroborated by the findings of the PROPEL trial.[11] Furthermore, the relationship between FVIII exposure and bleeding frequency, is highlighted in the

Table 2. Pharmacokinetic parameters of the single-dose phase I pharmacokinetic study and comparison between Advate® and FRSW117.

Variables	$t_{1/2}$ h	C_{max} IU/dL	$AUC_{0-\infty}$ h*IU/dL	CL dL/h/kg	V_d dL/kg	Incremental recovery rate (IU/dL)/(IU/kg)	Time to 40% of FVIII activity, h	Time to 10% of FVIII activity, h	Time to 5% of FVIII activity, h	Time to 3% of FVIII activity, h	Time to 1% of FVIII activity, h
Advate®, 25 IU/kg (N=6)											
Mean	14.0	70.62	877.3	0.0298	0.575	2.825	4.267	25.587	38.515	46.252	66.802
SD	4.8	11.729	219.44	0.0065	0.1381	0.4709	1.9694	6.1446	5.7005	6.4071	15.0256
Median	13.0	73.75	814.0	0.0312	0.575	2.950	4.440	23.640	38.245	44.440	64.000
P25	9.9	62.70	710.0	0.0259	0.460	2.510	2.165	21.500	35.790	44.210	58.670
P75	18.5	81.20	965.0	0.0352	0.690	3.250	5.899	26.370	41.190	47.110	74.940
Min	9.0	51.1	682	0.0198	0.39	2.04	1.87	20.88	30.22	39.11	48.00
Max	20.5	82.2	1239	0.0357	0.76	3.25	7.08	37.49	47.40	58.20	91.20
GM	13.3	69.72	856.7	0.0292	0.561	2.789	3.848	25.066	38.162	45.909	65.439
FRSW117, 25 IU/kg (N=6)											
Mean	28.5	76.43	2895.2	0.0089	0.372	3.042	23.111	74.287	100.302	121.837	169.687
SD	3.3	20.370	546.10	0.0019	0.1155	0.8096	7.7530	4.4271	5.0763	7.6527	7.0449
Median	28.9	75.05	2972.0	0.0084	0.345	2.955	25.071	74.675	101.700	122.145	167.000
P25	25.9	62.70	2631.0	0.0080	0.310	2.510	17.454	72.000	95.330	117.600	165.470
P75	31.3	85.60	3111.0	0.0095	0.440	3.420	27.606	78.670	102.550	128.730	176.650
Min	23.9	50.9	2021	0.0068	0.23	2.04	9.75	67.01	93.39	110.40	162.00
Max	32.3	109.3	3664	0.0124	0.56	4.37	32.92	78.69	107.14	130.00	180.00
GM	28.4	74.22	2849.3	0.0088	0.357	2.955	21.694	74.174	100.194	121.633	169.566
Ratio of GM (FRSW117/Advate®, 25 IU/kg)											
	2.1	1.06	3.3	0.3002	0.637	1.059	5.64	2.959	2.625	2.649	2.591
Advate®, 50 IU/kg (N=7)											
Mean	14.8	137.77	1842.7	0.0284	0.579	2.756	14.412	40.666	51.666	60.786	84.414
SD	6.7	27.525	413.11	0.0065	0.1811	0.5506	3.8678	4.4564	7.2924	8.6265	16.9378
Median	12.6	134.90	1824.0	0.0274	0.500	2.700	15.302	41.420	47.820	61.820	82.710
P25	10.3	111.90	1467.0	0.0219	0.480	2.240	10.661	35.310	45.220	53.540	70.630
P75	15.4	166.90	2283.0	0.0341	0.700	3.340	17.942	44.700	58.110	68.350	92.800
Min	10.1	107.0	1321	0.0212	0.35	2.14	10.01	34.94	43.76	47.29	69.33
Max	29.3	178.0	2360	0.0378	0.90	3.56	19.22	45.69	61.65	71.06	116.57
GM	13.8	135.47	1802.5	0.0277	0.556	2.710	13.953	40.452	51.232	60.239	83.080
FRSW117, 50 IU/kg (N=7)											
Mean	30.9	134.66	2816.0	0.0093	0.413	2.693	50.397	108.251	139.814	166.347	207.617
SD	2.3	28.334	1921.04	0.0027	0.1050	0.5660	15.5830	21.0568	24.1898	22.4556	24.5973
Median	31.3	144.50	5508.0	0.0091	0.390	2.890	48.194	101.200	134.050	157.460	201.730
P25	28.8	103.20	4241.0	0.0069	0.330	2.060	39.145	93.740	120.000	151.540	187.200
P75	32.8	151.40	7210.0	0.0118	0.480	3.030	65.346	116.000	151.680	174.000	216.000
Min	28.1	89.8	3832	0.0054	0.27	1.80	34.20	82.12	115.56	143.23	184.00
Max	34.4	171.1	9314	0.0130	0.59	3.42	77.18	150.46	184.94	210.95	257.61
GM	30.8	131.84	5569.8	0.0090	0.402	2.637	48.511	106.677	138.145	165.147	206.462
Ratio of GM (FRSW117/Advate®, 50 IU/kg)											
	2.2	0.97	3.1	0.3237	0.723	0.973	3.48	2.637	2.696	2.742	2.485

$t_{1/2}$: plasma half-life; C_{max}: peak plasma concentration; AUC: area under the plot of plasma concentration of drug; CL: clearance; V_d: volume of distribution; FVIII: factor VIII; SD: standard deviation; P25: 25th percentile; P75: 75th percentile; Min: minimum; Max: maximum; GM: geometric mean.

Table 3. Pharmacokinetic parameters of multiple doses of FRSW117.

Variables	$t_{1/2}$ h	C_{max} IU/dL	$AUC_{0-\infty}$ h*IU/dL	CL dL/h/kg	V_d dL/kg	$MRT_{0-\infty}$ h	Incremental recovery rate (IU/dL)/(IU/kg)	Rac	Time to 40% of FVIII activity, h	Time to 5% of FVIII activity, h	Time to 3% of FVIII activity, h	Time to 1% of FVIII activity, h
ED1, 40 IU/kg (N=8)												
Mean	29.8	109.96	4548.4	0.009	0.383	42.124	2.688	-	41.082	133.905	155.371	200.246
SD	4.4	24.533	1163.64	0.0025	0.0888	8.0783	0.6241	-	13.2228	27.4432	27.1143	34.8863
Median	30.5	116.95	4477.0	0.0089	0.345	42.920	2.755	-	42.568	129.655	153.770	198.855
P25	25.8	91.20	3536.0	0.0067	0.320	35.435	2.225	-	27.479	111.485	131.600	165.315
P75	33.0	128.05	5752.5	0.0112	0.430	46.845	3.180	-	53.833	157.985	175.215	226.955
Min	23.8	68.8	2978	0.0065	0.31	30.74	1.72	-	22.03	100.36	122.50	163.08
Max	36.1	138.5	5878	0.0129	0.56	55.85	3.46	-	56.43	172.63	199.30	256.64
GM	29.5	107.32	4413.0	0.009	0.375	41.446	2.620	-	39.012	131.470	153.321	197.636
ED4, 40 IU/kg (N=8)												
Mean	33.4	102.53	4657.1	0.009	0.419	45.098	2.496	1.015	42.863	134.495	160.430	217.914
SD	5.5	17.174	1024.67	0.0020	0.0834	7.4512	0.4321	0.1264	11.3949	26.0520	24.5053	29.3369
Median	32.8	100.35	4811.5	0.0083	0.395	45.015	2.395	1.035	43.202	126.600	154.970	212.450
P25	29.4	92.25	3941.5	0.0078	0.355	38.755	2.260	0.925	31.838	115.585	144.160	195.000
P75	36.9	115.75	5147.0	0.0104	0.465	48.865	2.830	1.080	47.434	155.345	176.565	2366.650
Min	26.4	76.1	3295	0.0061	0.34	36.51	1.86	0.82	28.94	103.30	129.14	186.00
Max	42.5	127.4	6565	0.0121	0.58	59.00	3.14	1.22	64.80	177.60	202.91	269.11
GM	33.0	101.26	4557.1	0.009	0.412	44.584	2.464	1.008	41.582	132.367	158.850	216.252
Ratio of GM (ED4/ED1, 40 IU/kg)												
	1.1	0.94	1.03	0.99	1.10	1.08	0.94	-	1.07	1.01	1.04	1.09
ED1, 50 IU/kg (N=7)												
Mean	31.8	113.44	4850.3	0.011	0.516	43.677	2.146	-	40.882	136.374	161.780	208.911
SD	4.2	35.920	1390.12	0.0047	0.2594	6.1212	0.6319	-	19.0436	19.7166	18.5218	23.9180
Median	31.6	118.30	5051.0	0.0099	0.450	38.320	2.330		42.696	139.690	163.000	203.190
P25	28.4	95.30	4170.0	0.0081	0.380	35.520	1.910	-	40.117	114.460	142.000	192.010
P75	35.7	138.10	6143.0	0.0120	0.500	43.210	2.620	-	49.289	147.910	170.790	229.370
Min	25.9	42.9	2365	0.0076	0.33	32.99	0.86	-	1.42	110.40	140.00	179.22
Max	37.0	152.0	6620	0.0211	1.09	46.68	2.76	-	63.00	167.48	194.74	250.16
GM	31.5	106.46	4634.6	0.011	0.477	43.313	2.031	-	28.460	135.145	160.895	207.777
ED4, 50 IU/kg (N=6)												
Mean	37.3	128.08	5146.3	0.010	0.558	44.843	2.505	1.133	40.603	137.470	166.565	225.658
SD	3.3	39.317	1595.98	0.0033	0.1716	6.5951	0.7799	3006	15.5734	13.8813	10.3081	13.9055
Median	36.5	128.25	4949.0	0.0101	0.530	44.275	2.495	1.175	42.506	138.465	166.115	226.075
P25	35.1	110.60	3983.0	0.0073	0.420	38.880	2.170	0.810	23.020	124.800	156.800	212.570
P75	40.5	140.40	6886.0	0.0126	0.730	47.520	2.760	1.350	55.783	144.690	174.000	236.890
Min	33.3	70.3	3203	0.0069	0.35	38.05	1.36	0.76	21.24	120.00	155.56	211.20
Max	41.1	190.7	7254	0.0156	0.79	56.06	3.75	1.53	59.07	158.40	180.80	241.14
GM	37.2	122.76	4937.9	0.010	0.536	44.458	2.398	1.098	37.817	136.889	166.301	225.301
Ratio of GM (ED4/ED1, 50 IU/kg)												
	1.2	1.15	1.07	0.95	1.12	1.03	1.18	-	1.33	1.01	1.03	1.08

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For the pharmacokinetic analysis, blood samples were collected immediately prior to each FRSW117 injection and at specific timepoints after the injection: at 0.167, 0.5, 1, 3, 6, 9, 24, 48, 72, 96, 120, and 168 hours after the first dose, and 0.167, 0.5, 1, 3, 6, 9, 24, 48, 72, 96, 120, 168, 192, 216, and 240 hours following the last dose. $t_{1/2}$: plasma half-life; C_{max}: peak plasma concentration; AUC: area under the plot of plasma concentration of drug; CL: clearance; V_d: volume of distribution; MRT: mean residence time; Rac: accumulation ratio; FVIII: factor VIII; ED1: exposure day 1; SD: standard deviation; P25: 25th percentile; P75: 75th percentile; Min: minimum; Max: maximum; GM: geometric mean. ED4: exposure day 4.

analysis of the LEOPOLD,[12] A-LONG, and Kids A-LONG[8,13] trials and real-world studies.[14] Taken together, FRSW117 may offer a viable alternative in managing severe hemophilia A, combining efficacy with enhanced patients' convenience. FRSW117 demonstrated low potential for inducing neutralizing antibodies against FVIII. The absence of FVIII inhibitor development in all participants may suggest the safety of FRSW117 in the context of immunogenicity. Although there were instances of ADA and anti-PEG antibodies, their titers were lower than 1:80. The immunogenicity of FRSW117 was favorable,[15] although this will have to be confirmed in the context of multiple doses over a longer period since the present study lasted 28 days. Nevertheless, those results may add a layer of confidence in using PEGylation technology for hemophilia A treatment.

We acknowledge that these studies had inherent limitations, including a small cohort of participants reflective of its early-phase design focused primarily on pharmacokinetics and safety assessments. The study duration was too short to calculate annualized bleeding rates. Consequently, the long-term prophylactic efficacy and safety profiles of FRSW117 remain to be thoroughly evaluated.

In conclusion, the two studies of FRSW117 suggest the safety and tolerability of this very long half-life FVIII product over a 4-week treatment duration, alongside superior pharmacokinetics compared with those of standard half-life recombinant FVIII. These insights advocate for the potential of FRSW117 to confer extended bleeding protection with reduced dosing frequency, underscoring the need for its development. A pivotal phase III study is ongoing in China (NCT06142552).

Authors

Feng Xue,[1] Shuxia Guo,[2] Ping Liu,[2] Weizhi Chen,[3] Yun Chen,[4] Qing Wen,[4] Haiying Hua,[5] Yu Cao,[6] Xianqi Feng,[6] Jing Sun,[7] Chongyuan Xu[7] and Renchi Yang[1]

[1]State Key Laboratory of Experimental Hematology, Tianjin Laboratory of Blood Disease Gene Therapy, CAMS Key Laboratory of Gene Therapy for Blood Diseases, National Clinical Research Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin; [2]Department of Hematology, Zhengzhou People's Hospital, Zhengzhou; [3]Department of Hematology, People's Hospital of Rizhao, Rizhao; [4]Department of Hematology, Jinan Central Hospital, Jinan; [5]Department of Hematology, Affiliated Hospital of Jiangnan University, Yangzhou; [6]Department of Clinical Pharmacy, Affiliated Hospital of Qingdao University, Qingdao and [7]Department of Hematology, Nanfang Hospital of Southern Medical University, Guangzhou, China

Correspondence:
R. YANG - rcyang@ihcams.ac.cn

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No conflicts of interest to disclose.

Contributions

RY conceived and designed the clinical study. FX reviewed and revised the manuscript. All authors had access to primary clinical trial data, designed the study and/or acquired, analyzed, or interpreted data, and reviewed and approved the final version of the manuscript.

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Data-sharing statement

Deidentified individual participant data will be shared upon reasonable request to the author for correspondence.

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