RESULTS

1. Subjects

Twelve healthy Thai male volunteers were enrolled into the study. The demographic characteristics of all subjects (Tables 3, 4 and 5) and the visit with sequence of drug administration are listed earlier in Table 1. The range of age (mean ± S.D.), height, weight and BMI were 18-26 y (20.83 ± 2.66), 1.63-1.76 m (1.69 ± 0.05), 48.00-64.30 kg (58.30 ± 5.37) and 18.07-24.05 kg/m^2 (20.36 ± 1.57), respectively (Table 3).

The clinical study was completed within 3 months. The three preparations of rHuEPO were well tolerated during the clinical trial with no reported serious adverse events. There was no drop-out, all volunteers continued the study to the end and were discharged in good health.

Table 3 Demographic characteristics of 12 male volunteers in this study.

Subject No.	Age (y)	Height (m)	Weight (kg)	BMI (kg/m^2)
1	20	1.72	58.30	19.71
2	19	1.63	48.00	18.07
3	26	1.70	61.00	21.11
4	20	1.68	59.30	21.14
5	20	1.76	63.60	20.53
6	20	1.65	53.50	19.77
7	21	1.74	57.80	19.09
8	26	1.70	62.10	21.49
9	18	1.63	49.20	18.52
10	18	1.64	64.30	24.05
11	22	1.72	60.50	20.57
12	20	1.75	62.00	20.24
Mean	**20.83**	**1.69**	**58.30**	**20.36**
SD	**2.66**	**0.05**	**5.37**	**1.57**

Table 4 Demographic characteristics (hematology) of 12 male volunteers in this study.

Subject No.	Hb	Hct	WBC	Differential Leukocytes/100 cells					Pletelets
	13-18 gm%	40-54%	4,400-11,000 /mm^3	neutroplils 40-75%	lymphocytes 20-50%	monocytes 2-10%	eosiniphils 1-6%	basophils 0-1%	
1	16.5	46	6,150	55	36	2	6	0	adequate
2	15.9	49	6,800	57	36	5	1	1	adequate
3	16.5	48	9,150	60	36	3	1	0	adequate
4	13.5	40	8,050	44	50	0	6	0	adequate
5	15.3	41	9,350	67	30	2	0	0	adequate
6	17.1	46	7,600	52	45	1	2	0	adequate
7	14.3	45	4,500	57	32	6	0	1	adequate
8	16.3	48	4,400	55	40	4	0	1	adequate
9	14.1	46	10,000	50	44	0	6	0	adequate
10	16.4	48	6,400	45	48	3	4	0	adequate
11	14.7	42	8,250	48	50	0	2	0	adequate
12	14.9	43	6,200	49	50	1	0	0	adequate

Table 5 Demographic characteristics (blood chemistry) of 12 male volunteers in this study.

Subject No.	FBS (40-115 mg/dL)	BUN (7-17 mg/dL)	Cr (0.5-1.5 mg/dL)	Albumin (3.5-5.5 g/dL)	Globulin (2.0-3.5 g/dL)	SGOT (up to 35 U)	SGPT (up to 45 U)	Alk phosphatase (85-240 U/L)	Cholesterol (140-250 mg/dL)	Direct bilirubin (0.0-0.3 mg/dL)	Total bilirubin (0.3-1.1 mg/dL)
1	93	12	0.9	4.5	3.5	35	45	194	181	0.2	0.5
2	93	16	1.0	5.1	3.5	11	8	235	222	0.3	1.0
3	87	14	1.0	5	2.9	20	28	107	174	0.3	0.8
4	85	12	1.0	4.2	3.5	24	16	201	210	0.2	1.0
5	93	15	0.9	3.6	3.5	15	6	167	142	0.2	0.6
6	90	14	1.1	4.1	3.5	17	14	134	208	0.3	0.8
7	86	13	0.9	5.2	3.2	11	10	132	148	0.3	1.0
8	82	16	1.1	5.5	2.2	16	10	122	207	0.3	1.1
9	89	10	1.0	5.3	2.5	18	10	221	160	0.3	0.5
10	99	13	1.1	4.9	3.4	28	45	196	137	0.3	0.8
11	92	16	1.3	3.8	3.5	14	8	89	148	0.1	0.5
12	85	14	1.0	3.9	3.2	24	13	136	140	0.3	0.9

2. Pharmacokinetics of EPO in healthy volunteers

Plasma EPO concentration-time profiles

The mean baseline erythropoietin concentrations (mIU/mL) before subcutaneous dose administrations of Epokine®, Eprex® and Recormon® were 6.478 ± 2.00 (range 3.738-9.311), 6.508 ± 1.94 (range 4.135-11.358), and 6.857 ± 2.24 (range 3.459-10.907), respectively. Statistical analysis showed no significant different between these base line values ($p>0.5$).

The individual and mean plasma EPO concentrations at various sampling times from 12 subjects after subcutaneous administration of 4,000 IU of Epokine® and Eprex® as well as 2 x 2,000 IU of Recormon® are respectively presented in Tables 6, 7 and 8. Their plasma concentration-time profiles of individual subject after administrations of the three products are compared and depicted in Figures 3-14. Moreover, the composite plasma concentration-time curves of individual subject (n=12) are shown in Figures 15-17, respectively for Epokine® and Eprex® and Recormon® and their mean concentration-time profiles are presented in Figure 18.

The mean plasma concentration-time curves of Epokine® was slightly higher than those of Eprex® and both preparations had higher concentration-time profiles when compared to Recormon®. The pairwise intra-individual concentration-time profiles of Epokine®, Eprex® and Recormon® were almost identical for volunteer No. 4, 11, and 12, while volunteer No. 2, 9 and 10 showed higher profiles of Epokine® but the profiles for Eprex® and Recormon® were similar. Volunteers No. 3, 7 and 8 showed similar profiles between Epokine® and Eprex® which were higher than those of Recormon®. Only volunteer No. 1, 5 and 6 showed the concentration-time profiles which were similar to the mean value.

Table 6 Plasma EPO concentrations after subcutaneous administrations of 4,000 IU Epokine®.

Subject No.	**Plasma EPO concentration (mIU/mL)**											
Time(h) →	**0.0**	**1.0**	**2.0**	**4.0**	**8.0**	**12.0**	**15.0**	**18.0**	**24.0**	**48.0**	**72.0**	**96.0**
1	7.506	20.309	33.389	46.281	53.966	57.423	56.713	46.457	39.336	25.136	21.255	14.242
2	3.738	15.424	36.070	68.042	100.880	94.338	94.338	74.815	59.741	21.282	14.061	10.776
3	5.419	17.731	23.247	51.099	78.668	68.262	53.441	47.150	44.689	27.952	21.048	16.954
4	8.181	11.809	30.346	68.262	85.993	95.586	87.769	72.158	56.417	31.107	16.287	9.548
5	9.299	16.999	22.803	39.653	67.808	62.684	53.829	50.368	45.912	21.013	13.624	8.859
6	3.832	18.110	43.520	81.519	135.340	112.900	100.700	83.881	78.653	28.324	14.835	11.900
7	8.172	13.908	19.731	37.633	56.059	56.506	47.563	44.522	41.033	28.058	19.552	11.130
8	5.212	7.275	21.970	57.401	80.912	73.761	62.944	44.254	39.333	16.775	10.234	8.351
9	6.408	26.660	31.970	65.062	77.162	72.024	57.295	55.379	54.011	21.818	11.943	9.211
10	6.147	21.371	37.751	71.290	104.990	85.803	63.233	54.558	36.666	20.209	17.266	11.678
11	9.311	18.049	28.291	38.194	48.894	53.106	51.088	44.069	38.369	27.678	14.290	13.503
12	4.515	11.668	14.115	32.321	48.631	36.090	27.503	28.904	29.167	19.187	15.426	12.105
Mean	**6.478**	**16.609**	**28.600**	**54.730**	**78.275**	**72.374**	**63.035**	**53.876**	**46.944**	**24.045**	**15.818**	**11.521**
SD	**2.00**	**5.10**	**8.50**	**16.08**	**26.09**	**21.57**	**21.12**	**15.63**	**13.35**	**4.54**	**3.45**	**2.49**
%CV	**30.88**	**30.72**	**29.71**	**29.39**	**33.33**	**29.81**	**33.50**	**29.02**	**28.44**	**18.89**	**21.79**	**21.65**
Max	**9.311**	**26.660**	**43.520**	**81.519**	**135.340**	**112.900**	**100.700**	**83.881**	**78.653**	**31.107**	**21.255**	**16.954**
Min	**3.738**	**7.275**	**14.115**	**32.321**	**48.631**	**36.090**	**7.503**	**28.904**	**29.167**	**16.775**	**10.234**	**8.351**
Max-Min	**5.573**	**19.385**	**29.405**	**49.198**	**86.709**	**76.810**	**73.197**	**54.977**	**49.486**	**14.332**	**11.021**	**8.603**

Table 7 Plasma EPO concentrations after subcutaneous administrations of 4,000 IU Eprex®.

Subject No.	**Plasma EPO concentration (mIU/mL)**											
Time(h) →	**0.0**	**1.0**	**2.0**	**4.0**	**8.0**	**12.0**	**15.0**	**18.0**	**24.0**	**48.0**	**72.0**	**96.0**
1	6.591	18.166	27.734	35.222	47.780	49.457	45.400	43.552	38.109	17.481	13.563	10.520
2	5.814	10.696	22.567	32.933	49.188	63.206	61.110	50.477	47.498	24.976	13.741	9.654
3	6.230	24.673	35.871	52.377	64.147	59.704	51.525	46.081	39.214	24.125	17.731	11.809
4	11.358	34.575	50.139	63.090	99.017	97.770	96.314	89.438	65.731	23.138	12.709	10.115
5	4.135	8.710	19.731	36.560	45.416	46.400	50.783	42.554	31.280	15.790	7.993	7.096
6	5.672	15.898	34.869	67.293	79.496	81.688	76.294	70.235	56.053	26.588	14.672	16.062
7	7.544	11.847	22.507	39.691	53.198	48.010	41.480	40.675	33.607	23.671	16.238	9.427
8	6.288	34.770	50.336	67.504	82.521	70.275	54.897	40.586	25.820	14.804	9.069	8.262
9	5.189	1.358	29.358	35.310	56.128	58.481	58.299	55.379	54.467	17.622	9.914	5.537
10	6.059	11.236	16.376	21.282	35.491	37.842	35.943	33.955	35.762	21.461	18.781	10.707
11	8.612	21.637	27.590	33.723	51.000	49.333	43.368	36.703	27.678	25.576	14.639	12.192
12	4.602	15.339	19.624	33.285	46.175	43.280	37.580	32.847	28.204	21.199	11.494	9.573
Mean	**6.508**	**18.409**	**29.725**	**43.189**	**59.128**	**58.787**	**54.416**	**48.540**	**40.285**	**21.369**	**13.379**	**10.079**
SD	**1.94**	**8.88**	**11.27**	**15.40**	**18.66**	**17.38**	**17.35**	**16.47**	**12.85**	**4.02**	**3.35**	**2.65**
%CV	**29.86**	**48.26**	**37.92**	**35.65**	**31.56**	**29.56**	**31.88**	**33.94**	**31.89**	**18.79**	**25.03**	**26.34**
Max	**11.358**	**34.770**	**50.336**	**67.504**	**99.017**	**97.770**	**96.314**	**89.438**	**65.731**	**26.588**	**18.781**	**16.062**
Min	**4.135**	**8.710**	**16.376**	**21.282**	**35.491**	**37.842**	**35.943**	**32.847**	**25.820**	**14.804**	**7.993**	**5.537**
Max-Min	**7.223**	**26.060**	**33.960**	**46.222**	**63.526**	**59.928**	**60.371**	**56.591**	**39.911**	**11.784**	**10.789**	**10.525**

Table 8 Plasma EPO concentrations after subcutaneous administrations of 2 x 2,000 IU Recormon®.

Subject No.	**Plasma EPO concentration (mIU/mL)**											
Time(h) →	**0.0**	**1.0**	**2.0**	**4.0**	**8.0**	**12.0**	**15.0**	**18.0**	**24.0**	**48.0**	**72.0**	**96.0**
1	5.433	15.177	22.977	23.667	32.342	35.397	37.584	29.297	25.915	21.341	11.532	11.110
2	5.894	15.424	24.816	44.841	50.718	59.176	47.981	40.978	38.322	23.129	10.455	7.894
3	6.691	11.809	21.268	32.300	48.325	50.033	47.257	44.154	33.817	23.357	17.953	12.597
4	10.907	18.507	26.096	46.829	69.105	76.360	79.087	70.264	49.819	20.165	14.390	11.471
5	5.767	10.455	14.502	22.479	32.951	33.925	36.735	33.276	24.016	14.726	11.471	9.888
6	5.752	21.889	29.482	37.693	46.856	46.022	51.869	50.447	38.940	18.356	12.225	10.356
7	7.454	10.682	17.492	23.671	37.633	38.618	31.101	31.548	30.206	20.000	12.654	9.965
8	4.853	8.262	16.596	23.313	34.054	33.249	32.354	28.058	20.448	12.654	9.517	8.620
9	3.459	10.090	21.192	42.916	55.652	59.212	53.191	47.184	32.872	10.707	5.798	4.063
10	7.719	11.236	15.399	16.554	32.421	36.847	33.955	30.618	24.506	16.554	11.325	12.297
11	10.882	25.138	30.656	28.992	47.227	47.140	43.368	35.625	24.876	15.776	10.620	11.581
12	7.478	14.115	17.787	25.051	39.947	43.718	34.161	29.693	24.701	20.149	13.416	9.485
Mean	**6.857**	**14.399**	**21.522**	**30.692**	**43.936**	**46.641**	**44.054**	**39.262**	**30.703**	**18.076**	**11.780**	**9.944**
SD	**2.24**	**5.16**	**5.41**	**10.08**	**11.27**	**12.96**	**13.48**	**12.34**	**8.46**	**4.03**	**2.91**	**2.33**
%CV	**32.62**	**35.80**	**25.14**	**32.83**	**25.64**	**27.78**	**30.59**	**31.43**	**27.55**	**22.32**	**24.67**	**23.46**
Max	**10.907**	**25.138**	**30.656**	**46.829**	**69.105**	**76.360**	**79.087**	**70.264**	**49.819**	**23.357**	**17.953**	**12.597**
Min	**3.459**	**8.262**	**14.502**	**16.554**	**32.342**	**33.249**	**31.101**	**28.058**	**20.448**	**10.707**	**5.798**	**4.063**
Max-Min	**7.448**	**16.876**	**16.154**	**30.275**	**36.763**	**43.111**	**47.986**	**42.206**	**29.371**	**12.650**	**12.155**	**8.534**

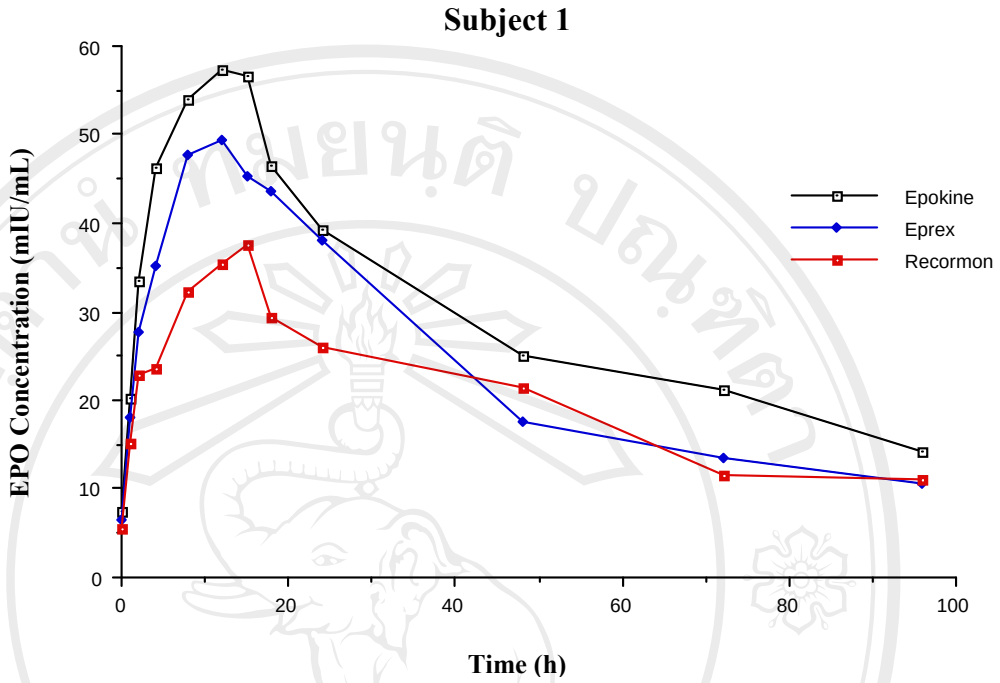

Figure 3 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 1.

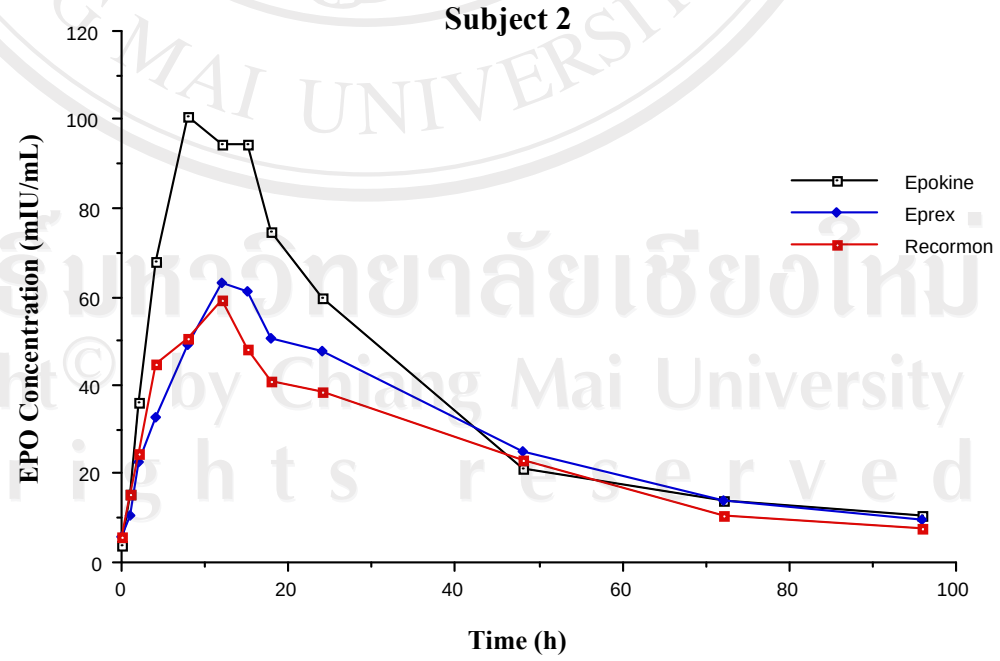

Figure 4 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 2.

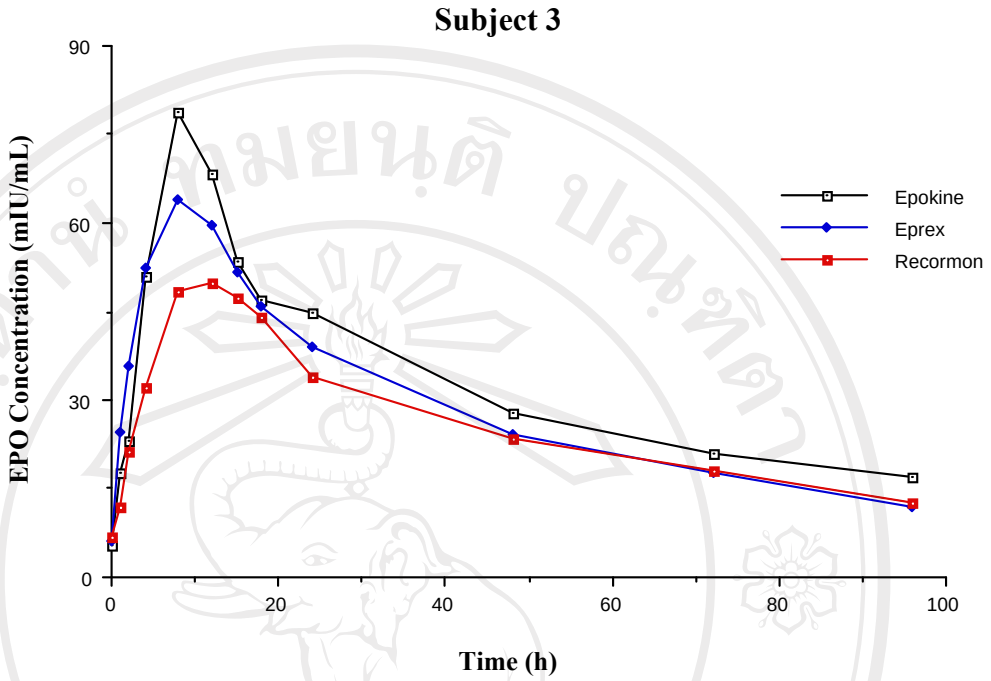

Figure 5 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 3.

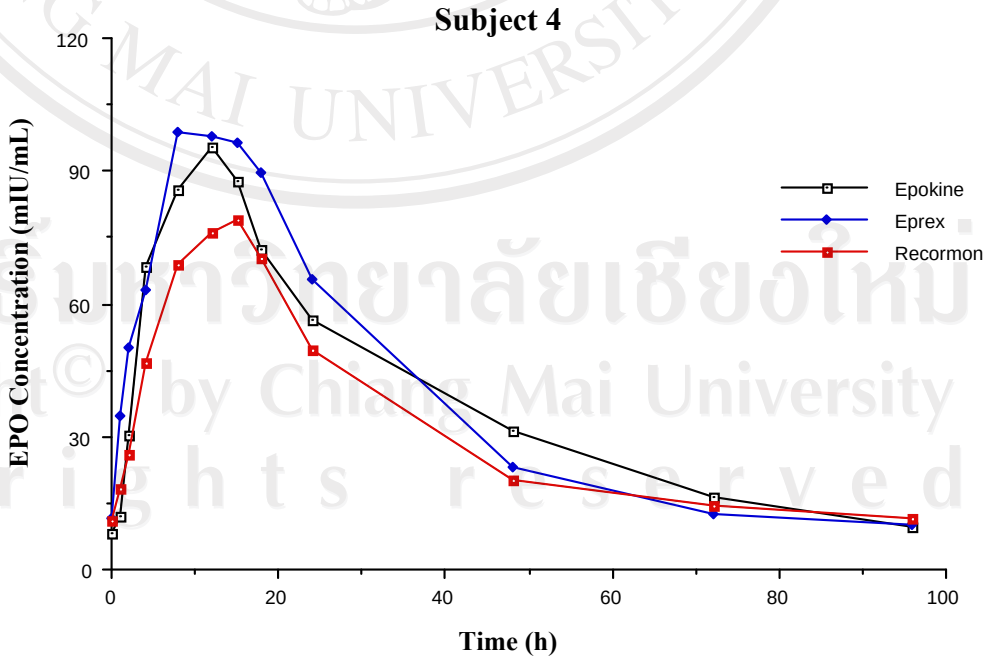

Figure 6 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 4.

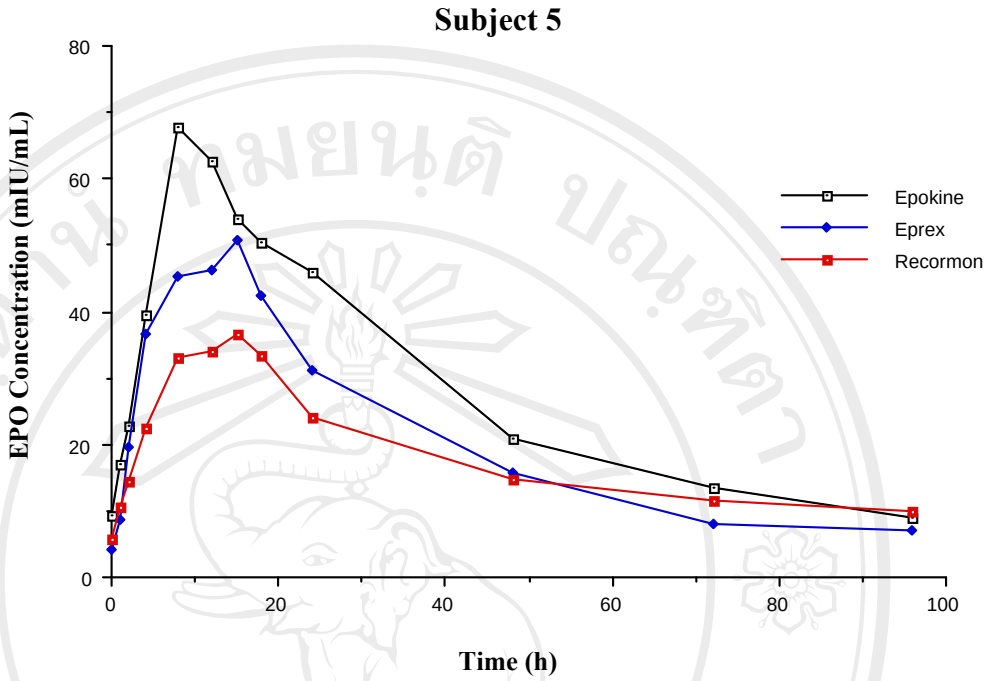

Figure 7 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 5.

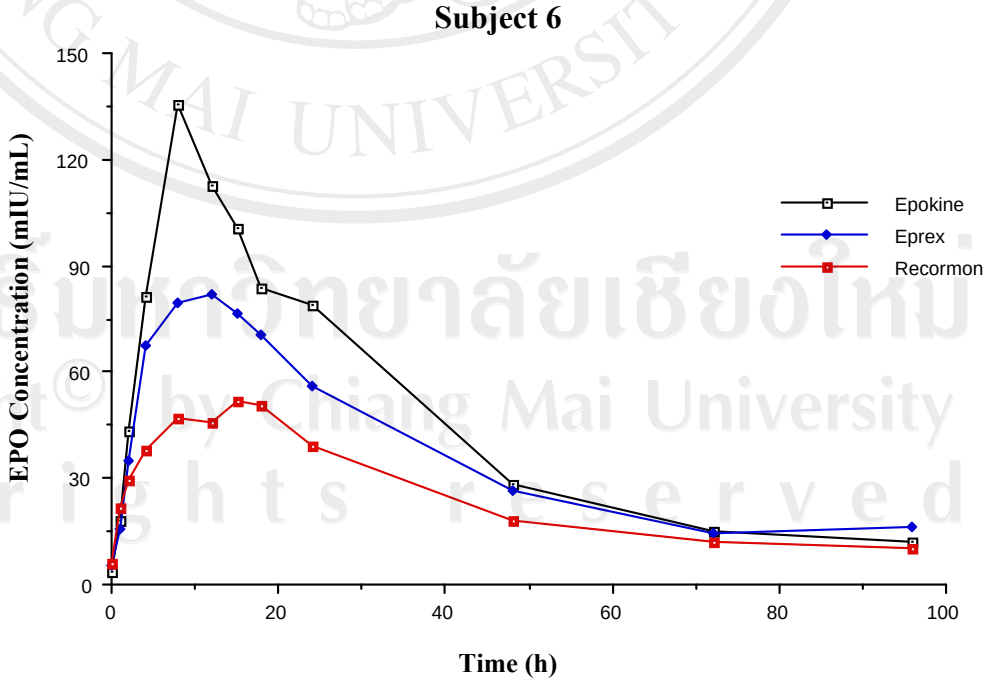

Figure 8 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 6.

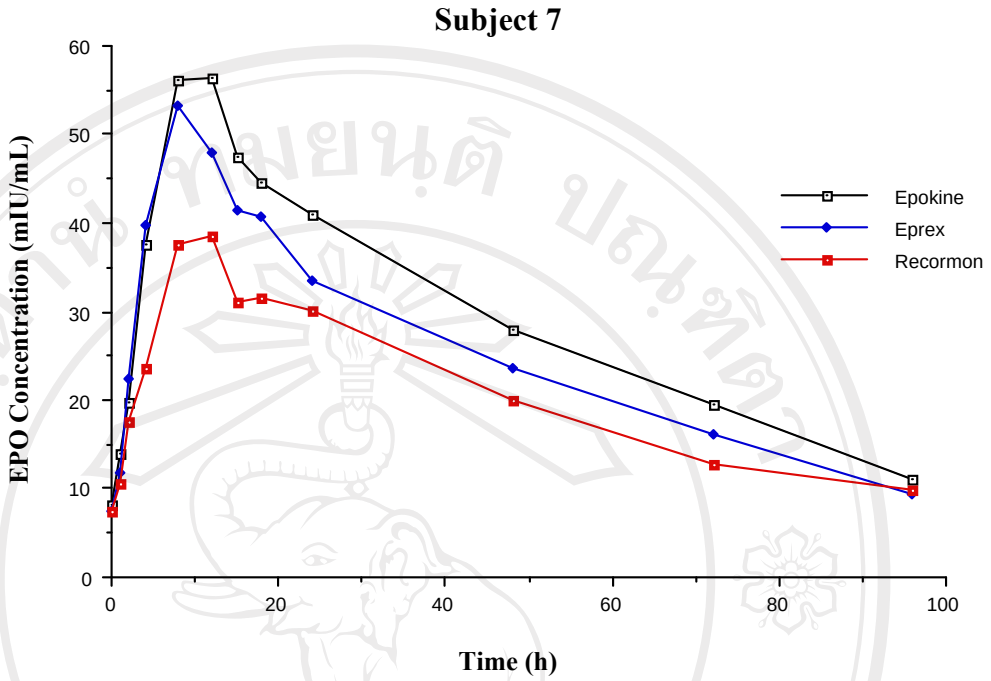

Figure 9 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 7.

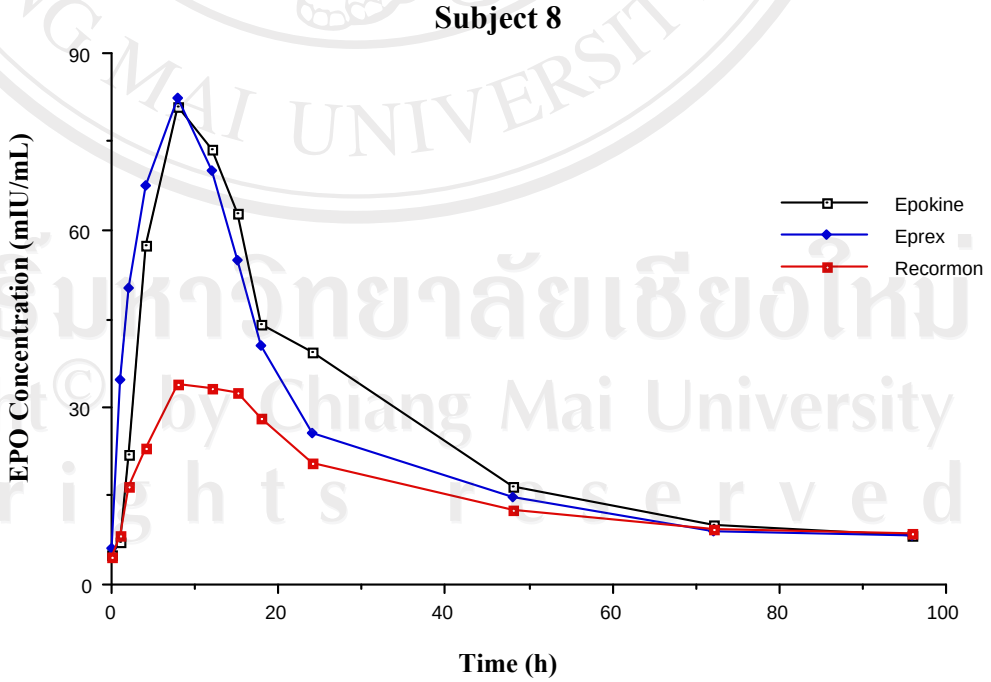

Figure 10 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 8.

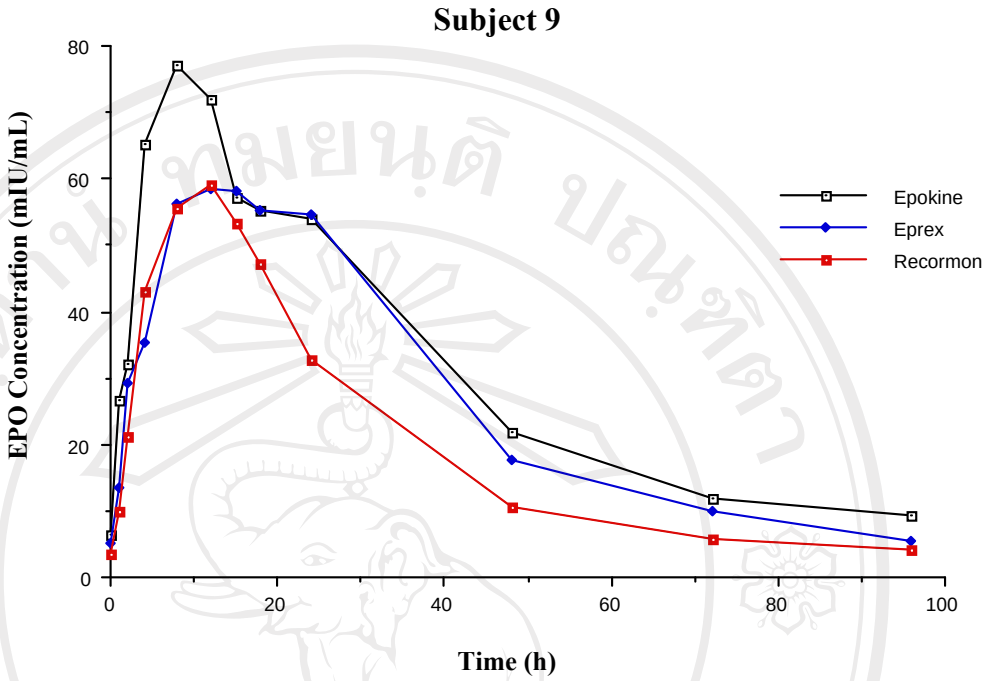

Figure 11 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 9.

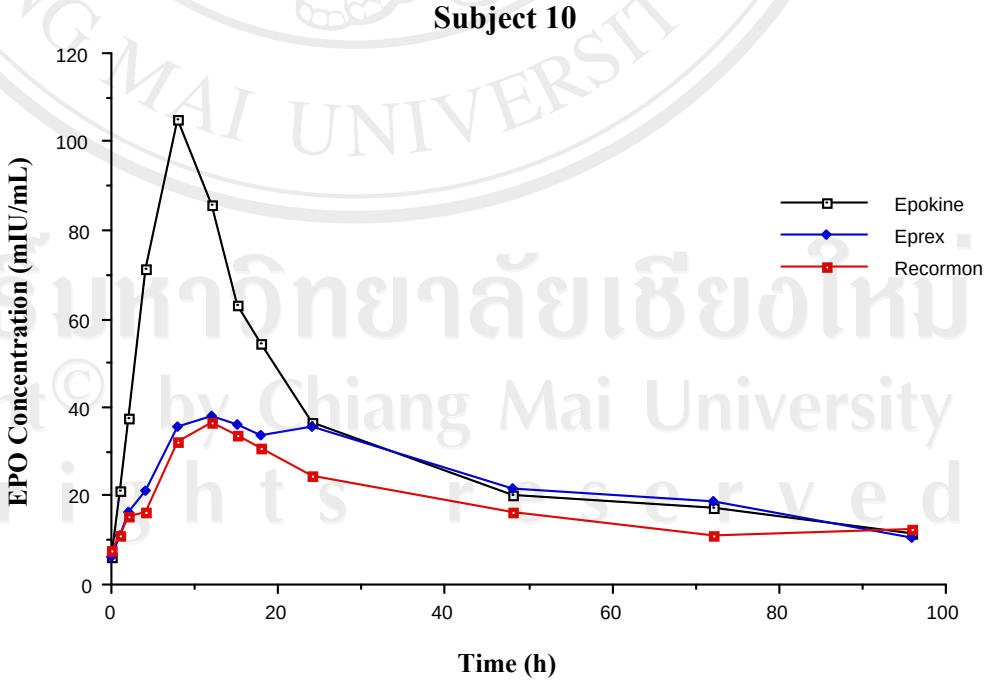

Figure 12 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 10.

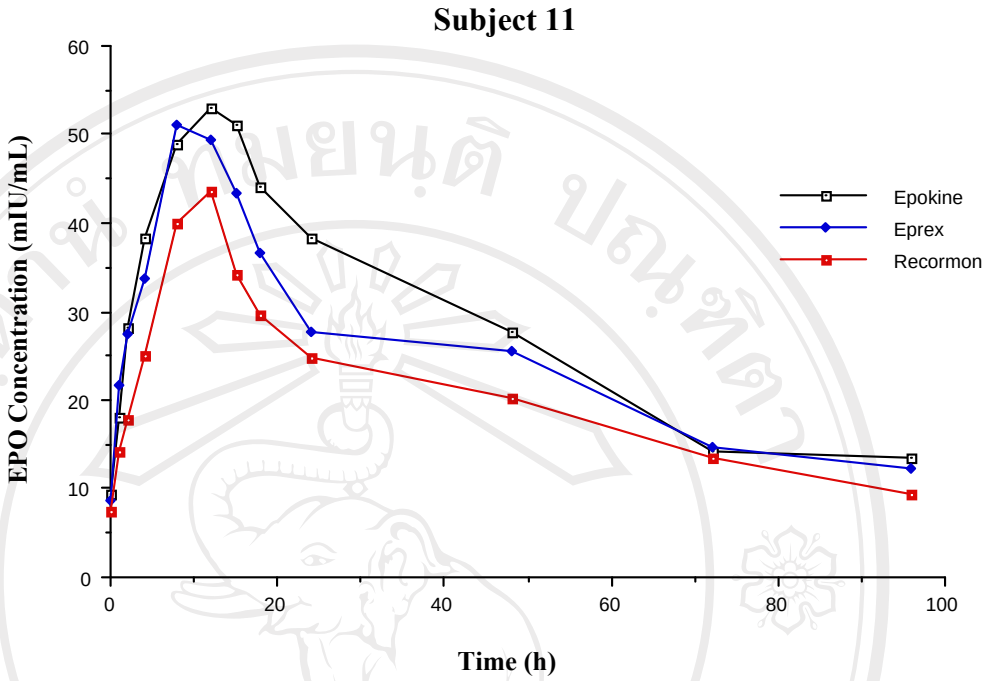

Figure 13 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 11.

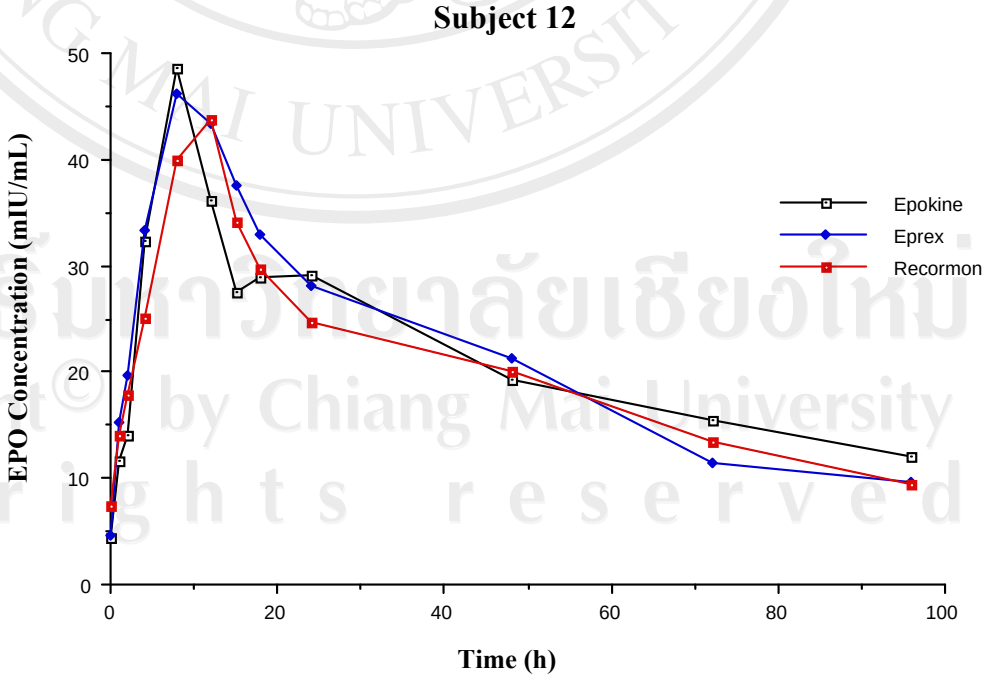

Figure 14 Plasma concentration-time curves of subcutaneous 4,000 IU administration of Epokine® Eprex® and Recormon® to subject no 12.

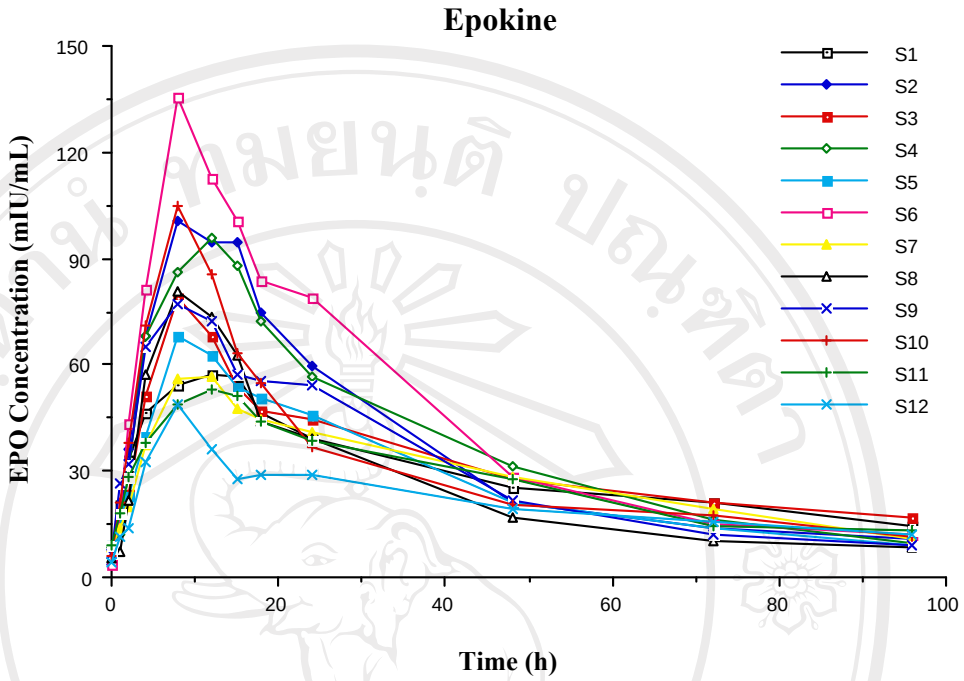

Figure 15 Plasma concentration-time curves of individual subjects (n=12) after administration of 4,000 IU Epokine®.

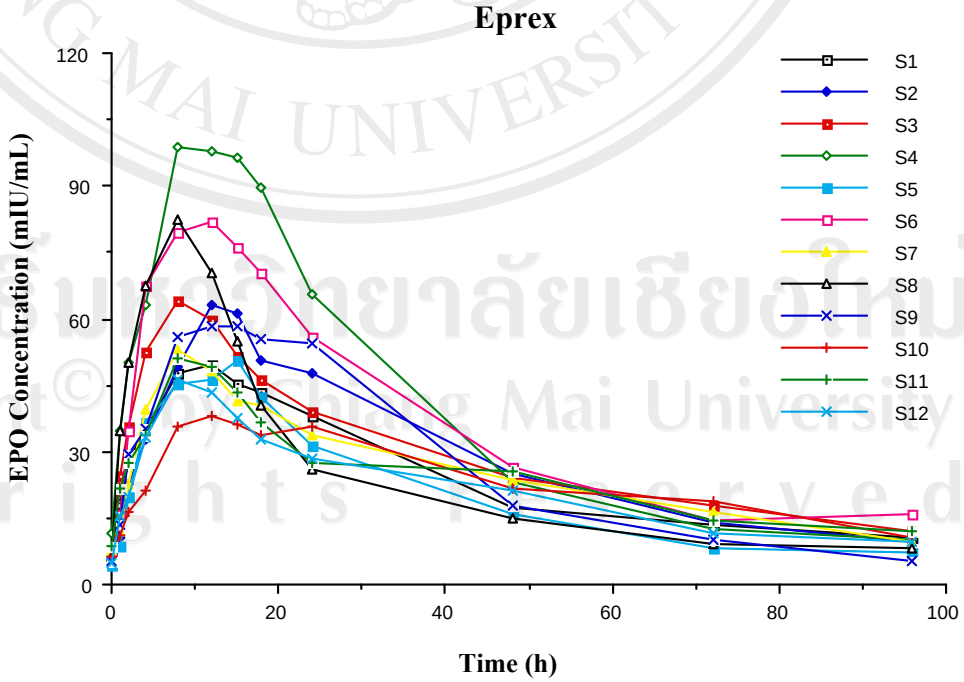

Figure 16 Plasma concentration-time curves of individual subjects (n=12) after administration of 4,000 IU Eprex®.

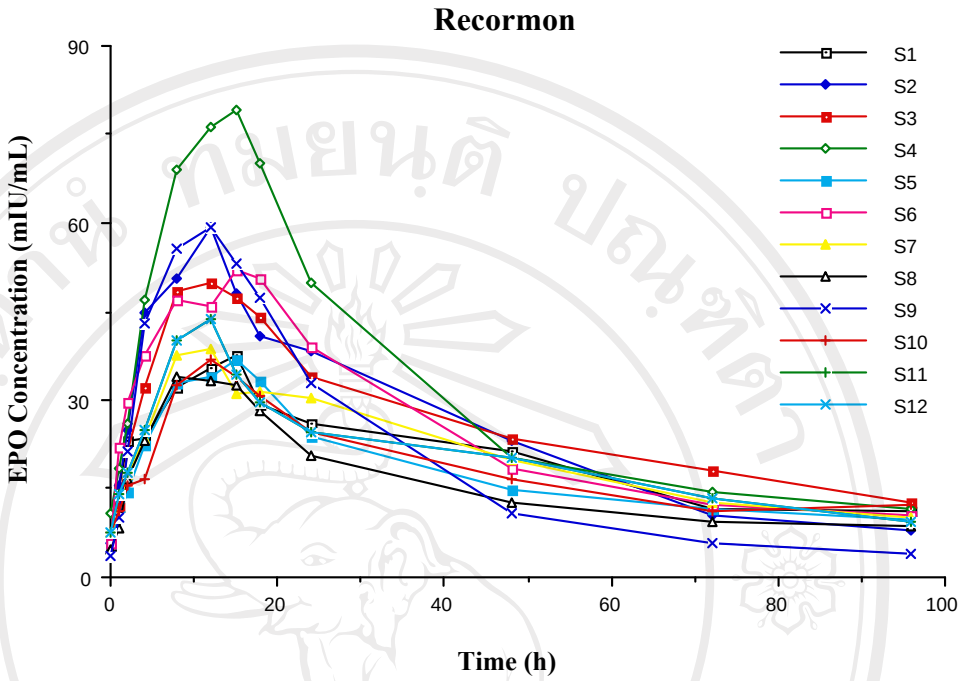

Figure 17 Plasma concentration-time curves of individual subjects (n=12) after administration of 4,000 IU Recormon®.

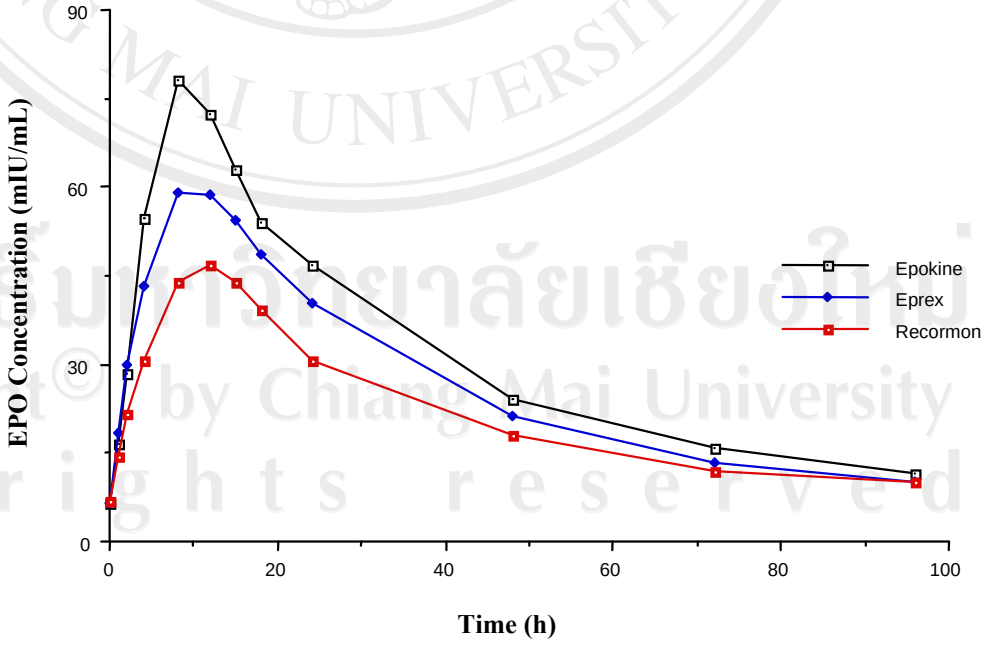

Figure 18 Mean plasma concentration-time curves of 12 subjects after administration of 4,000 IU Epokine® Eprex® and Recormon®.

Pharmacokinetic parameters of EPO and statistical analysis

The pharmacokinetic parameters derived from each subject after subcutaneous administrations of 4,000 IU Epokine®, Eprex®, and 2 x 2000 IU Recormon® are presented in Tables 9-11, respectively. The median T_{max} for Epokine®, Eprex® and Recormon® were 8.0 h, 10.0 h and 12.0 h, respectively. The range of the T_{max} for Epokine® were 8.0-12.0 h, while the range of Eprex® and Recormon® were more variable (range, 8.0-15.0 h). The mean elimination half-lives ($t_{1/2}$) for Epokine®, Eprex® and Recormon® were 34.9 h (range, 24.2-58.1 h), 33.3 h (range, 22.6-44.3 h) and 38.4 h (range, 20.5-48.9 h), respectively. The $t_{1/2}$ between Epokine® and Eprex® as well as Epokine® and Recormon® were not significantly different ($p>0.05$), however, the $t_{1/2}$ between Eprex® was statistically faster than those of Recormon® ($p<0.05$) (Tables 9-11). The average mean residence time (MRT, h) for Epokine®, Eprex® and Recormon® were 56.62±15.08 h, 51.37±10.72 and 60.56±13.88, and the clearance (CL/F, mL/h/kg) were 19.4±2.76, 23.07±3.98 and 26.75±5.48, respectively. Similar to the $t_{1/2}$, the MRT and the CL/F between Epokine® and Eprex® as well as Epokine® and Recormon® were not significantly different ($p>0.05$), however, these pharmacokinetic parameters of Eprex® was statistically different from those of Recormon® ($p<0.05$). The average Vd/F for Epokine® (56.5±20.4 L, 0.96±0.31 L/kg) was similar to Eprex® (64.4±17.2 L, 1.1±0.25 L/kg) ($p=0.7$) and were smaller than those of Recormon® (85.0±22.5 L, 1.45±0.31 L/kg) ($p<0.05$).

The average C_{max} (mIU/mL) of erythropoietin for Epokine® (79.75, range 48.63-135.34) was the highest while the second was those of Eprex® (61.460 range, 37.842-99.017) and the lowest value was for Recormon® (47.847 range, 34.054-79.087). Similarly, the AUC_{0-t} and $AUC_{0-\infty}$ of the three biological products also followed the same order of magnitude as with the C_{max}, with Epokine® had the highest, Recormon® had the lowest and Eprex® fell in the middle values of the two. The average AUC_{0-t} (mIU·h/mL) for Epokine®, Eprex® and Recormon® were 3,024.03 (range, 2,078.95-4,304.35), 2,578.94 (range, 1,962.97-3,702.08) and 2,086.43 (range, 1,523.70-3,014.98), respectively. Likewise, the average $AUC_{0-\infty}$ (mIU·h/mL) for Epokine®, Eprex® and Recormon® were 3,619.41 (range, 2,842.09-4,720.29), 3,075.01 (range, 2,262.73-4,174.56) and 2,654.05 (range, 2,031.49-3,481.77), respectively. Individual pharmacokinetic parameters (C_{max}, AUC_{0-t} and

$AUC_{0-\infty}$) of the three biological products were compared for relative bioavailability (F_{rel}) as shown in Tables 12-14. The mean F_{rel} calculated from the ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Epokine®/Eprex® were 1.30, 1.17 and 1.18, respectively (Table 12). The corresponding F_{rel} were 1.67, 1.45 and 1.36 for Epokine®/Recormon® (Table 13) and 1.28, 1.24 and 1.68 for Eprex®/Recormon® (Table 14), respectively. The means (90% CI) for the ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, between Epokine®/Eprex® were 1.29 (1.10-1.50), 1.17 (1.11-1.24) and 1.18 (1.13-1.24), respectively (Table 15). The corresponding values for Epokine®/Recormon® were 1.64 (1.37-1.96), 1.45 (1.33-1.58), and 1.37 (1.29-1.45) (Table 16), while those values for Eprex®/Recormon® were 1.28 (1.12-1.46), 1.24 (1.17-1.13) and 1.16 (1.08-1.23), respectively (Table 17).

Table 9 Pharmacokinetic parameters of EPO after a single subcutaneous dose of 4,000 IU Epokine®.

Subject No.	T_{max} (h)	C_{max} (mIU/mL)	AUC_{0-t} (mIU·h/mL)	$AUC_{0-\infty}$ (mIU·h/mL)	$t_{1/2}$ (h)	$MRT_{0-\infty}$ (h)	CL/F (mL/h/kg)	Vd/F (L/kg)
1	12.0	57.423	2883.36	3766.32	43.0	65.6	18.22	1.13
2	8.0	100.880	3502.57	3889.38	24.9	39.1	21.38	0.77
3	8.0	78.668	3184.48	4280.36	48.8	68.3	15.34	0.99
4	12.0	95.586	3631.03	3981.53	25.4	40.0	16.90	0.62
5	8.0	67.808	2679.86	3056.54	29.5	45.3	20.57	0.87
6	8.0	135.340	4304.35	4720.29	24.2	37.3	15.81	0.55
7	12.0	56.506	2817.23	3444.96	39.1	58.0	20.14	1.13
8	8.0	80.912	2523.25	2842.09	26.5	41.0	22.71	0.86
9	8.0	77.162	2985.79	3348.04	27.3	41.3	24.27	0.96
10	8.0	104.990	3039.95	3576.58	31.9	47.9	17.36	0.80
11	12.0	53.106	2657.55	3433.37	39.8	62.7	19.24	1.11
12	8.0	48.631	2078.95	3093.48	58.1	84.9	20.90	1.74
Mean	**9.3**	**79.751**	**3024.03**	**3619.41**	**34.9**	**52.62**	**19.40**	**0.96**
S.D.	**1.97**	**25.750**	**581.80**	**540.42**	**10.9**	**15.08**	**2.76**	**0.31**
% C.V.	**21.1**	**32.288**	**19.24**	**14.93**	**31.3**	**28.67**	**14.23**	**32.14**
Median	**8.0**							
Maximum	**12.0**	**135.340**	**4304.35**	**4720.29**	**58.1**	**84.90**	**24.27**	**1.74**
Minimum	**8.0**	**48.631**	**2078.95**	**2842.09**	**24.2**	**37.30**	**15.34**	**0.55**
Max - Min	**4.0**	**86.709**	**2225.40**	**1878.20**	**33.9**	**47.60**	**8.92**	**1.19**

Table 10 Pharmacokinetic parameters of EPO after a single subcutaneous dose of 4,000 IU Eprex®.

Subject No.	T_{max} (h)	C_{max} (mIU/mL)	AUC_{0-t} (mIU·h/mL)	$AUC_{0-\infty}$ (mIU·h/mL)	$t_{1/2}$ (h)	$MRT_{0-\infty}$ (h)	CL/F (mL/h/kg)	Vd/F (L/kg)
1	12.0	49.457	2308.06	2847.65	35.6	55.7	24.08	1.23
2	12.0	63.206	2732.23	3152.23	30.2	47.9	26.38	1.15
3	8.0	64.147	2800.69	3440.93	37.6	56.3	19.08	1.03
4	8.0	99.017	3702.08	4039.91	23.2	36.5	16.69	0.56
5	15.0	50.783	1962.97	2262.73	29.3	45.3	27.83	1.17
6	12.0	81.688	3445.53	4174.56	31.5	51.2	17.94	0.81
7	8.0	53.198	2431.80	2941.10	37.4	55.8	23.56	1.27
8	8.0	82.521	2298.70	2610.41	26.2	40.4	24.64	0.93
9	12.0	58.481	2563.45	2743.88	22.6	35.9	29.63	0.97
10	12.0	37.842	2268.44	2953.44	44.3	67.5	21.09	1.35
11	8.0	51.000	2367.06	3140.66	44.0	67.3	21.02	1.34
12	8.0	46.175	2066.23	2592.65	38.1	59.0	24.87	1.37
Mean	**10.3**	**61.460**	**2578.94**	**3075.01**	**33.3**	**51.57**	**23.07**	**1.10**
S.D.	**2.5**	**17.860**	**525.92**	**571.01**	**7.4**	**10.72**	**3.98**	**0.25**
% C.V.	**24.3**	**29.063**	**20.39**	**18.57**	**22.1**	**20.79**	**17.27**	**22.48**
Median	**10.0**							
Maximum	**15.0**	**99.017**	**3702.08**	**4174.56**	**44.3**	**67.50**	**29.63**	**1.37**
Minimum	**8.0**	**37.842**	**1962.97**	**2262.73**	**22.6**	**35.90**	**16.69**	**0.56**
Max - Min	**7.0**	**61.175**	**1739.11**	**1911.83**	**21.7**	**31.60**	**12.94**	**0.81**

Table 11 Pharmacokinetic parameters of EPO after a single subcutaneous dose of 2 x 2,000 IU Recormon®.

Subject No.	T_{max} (h)	C_{max} (mIU/mL)	AUC_{0-t} (mIU·h/mL)	$AUC_{0-\infty}$ (mIU·h/mL)	$t_{1/2}$ (h)	$MRT_{0-\infty}$ (h)	CL/F (mL/h/kg)	Vd/F (L/kg)
1	15.0	37.584	1932.20	2688.59	47.2	73.5	25.52	1.73
2	12.0	59.176	2404.02	2736.03	29.2	45.2	30.50	1.28
3	12.0	50.033	2502.70	3281.59	42.9	66.2	19.97	1.24
4	15.0	79.087	3014.98	3481.77	28.8	45.5	19.33	0.79
5	15.0	36.735	1720.64	2331.38	42.8	68.8	26.98	1.67
6	15.0	51.869	2355.50	2851.46	33.2	52.6	26.24	1.26
7	12.0	38.618	1988.99	2621.63	44.0	66.9	26.37	1.68
8	8.0	34.054	1523.70	2031.49	40.8	65.7	31.69	1.87
9	12.0	59.212	1912.06	2032.14	20.5	32.0	40.00	1.18
10	12.0	36.847	1770.40	2637.92	48.9	80.7	23.61	1.66
11	8.0	47.227	1953.47	2606.13	39.1	64.1	25.39	1.43
12	12.0	43.718	1958.49	2548.42	43.1	65.5	25.35	1.57
Mean	**12.3**	**47.847**	**2086.43**	**2654.05**	**38.4**	**60.56**	**26.75**	**1.45**
S.D.	**2.5**	**13.132**	**410.86**	**428.43**	**8.6**	**13.88**	**5.48**	**0.31**
% C.V.	**20.0**	**27.447**	**19.69**	**16.14**	**22.4**	**22.91**	**20.50**	**21.22**
Median	**12.0**							
Maximum	**15.0**	**79.087**	**3014.98**	**3481.77**	**48.9**	**80.70**	**40.00**	**1.87**
Minimum	**8.0**	**34.054**	**1523.70**	**2031.49**	**20.5**	**32.00**	**19.33**	**0.79**
Max - Min	**7.0**	**45.033**	**1491.28**	**1450.28**	**28.4**	**48.70**	**20.67**	**1.08**

Table 12 Comparison of EPO pharmacokinetic parameters (C_{max} and AUC) of individual subjects after single subcutaneous administrations of 4,000 IU Epokine® (T) and Eprex® (R).

Subject No.	C_{max} (T)	C_{max} (R)	F_{rel} (T/R)	AUC_{0-t} (T)	AUC_{0-t} (R)	F_{rel} (T/R)	$AUC_{0-\infty}$ (T)	$AUC_{0-\infty}$ (R)	F_{rel} (T/R)
1	57.423	49.457	1.16	2883.36	2308.06	1.25	3766.32	2847.65	1.32
2	100.880	63.206	1.60	3502.57	2732.23	1.28	3889.38	3152.23	1.23
3	78.668	64.147	1.23	3184.48	2800.69	1.14	4280.36	3440.93	1.24
4	95.586	99.017	0.97	3631.03	3702.08	0.98	3981.53	4039.91	0.99
5	67.808	50.783	1.34	2679.86	1962.97	1.37	3056.54	2262.73	1.35
6	135.340	81.688	1.66	4304.35	3445.53	1.25	4720.29	4174.56	1.13
7	56.506	53.198	1.06	2817.23	2431.80	1.16	3444.96	2941.10	1.17
8	80.912	82.521	0.98	2523.25	2298.70	1.10	2842.09	2610.41	1.09
9	77.162	58.481	1.32	2985.79	2563.45	1.16	3348.04	2743.88	1.22
10	104.990	37.842	2.77	3039.95	2268.44	1.34	3576.58	2953.44	1.21
11	53.106	51.000	1.04	2657.55	2367.06	1.12	3433.37	3140.66	1.09
12	48.631	46.175	1.05	2078.95	2066.23	1.01	3093.48	2592.65	1.19
Mean	**79.751**	**61.460**	**1.30**	**3024.03**	**2578.94**	**1.17**	**3619.41**	**3075.01**	**1.18**
SD	**25.750**	**17.862**	**1.44**	**581.80**	**525.92**	**1.11**	**540.42**	**571.01**	**0.95**

Table 13 Comparison of EPO pharmacokinetic parameters (C_{max} and AUC) of individual subjects after single subcutaneous administrations of 4,000 IU Epokine® (T) and Recormon® (R).

Subject No.	C_{max} (T)	C_{max} (R)	F_{rel} (T/R)	AUC_{0-t} (T)	AUC_{0-t} (R)	F_{rel} (T/R)	$AUC_{0-\infty}$ (T)	$AUC_{0-\infty}$ (R)	F_{rel} (T/R)
1	57.423	37.584	1.53	2883.36	1932.20	1.49	3766.32	2688.59	1.40
2	100.880	59.176	1.70	3502.57	2404.02	1.46	3889.38	2736.03	1.42
3	78.668	50.033	1.57	3184.48	2502.70	1.27	4280.36	3281.59	1.30
4	95.586	79.087	1.21	3631.03	3014.98	1.20	3981.53	3481.77	1.14
5	67.808	36.735	1.85	2679.86	1720.64	1.56	3056.54	2331.38	1.31
6	135.340	51.869	2.61	4304.35	2355.50	1.83	4720.29	2851.46	1.66
7	56.506	38.618	1.46	2817.23	1988.99	1.42	3444.96	2621.63	1.31
8	80.912	34.054	2.38	2523.25	1523.70	1.66	2842.09	2031.49	1.40
9	77.162	59.212	1.30	2985.79	1912.06	1.56	3348.04	2031.14	1.65
10	104.990	36.847	2.85	3039.95	1770.40	1.72	3576.58	2637.92	1.36
11	53.106	47.227	1.12	2657.55	1953.47	1.36	3433.37	2606.13	1.32
12	48.613	43.718	1.11	2078.95	1958.49	1.06	3093.48	2548.42	1.21
Mean	**79.751**	**47.847**	**1.67**	**3024.03**	**2086.43**	**1.45**	**3619.41**	**2654.05**	**1.36**
SD	**25.750**	**13.132**	**1.96**	**581.80**	**410.86**	**1.42**	**540.42**	**428.43**	**1.26**

Table 14 Comparison of EPO pharmacokinetic parameters (C_{max} and AUC) of individual subjects after single subcutaneous administrations of 4,000 IU Eprex® (T) and Recormon® (R).

Subject No.	C_{max} (T)	C_{max} (R)	F_{rel} (T/R)	AUC_{0-t} (T)	AUC_{0-t} (R)	F_{rel} (T/R)	$AUC_{0-\infty}$ (T)	$AUC_{0-\infty}$ (R)	F_{rel} (T/R)
1	49.457	37.584	1.32	2308.06	1932.20	1.19	2847.65	2688.59	1.06
2	63.206	59.176	1.07	2732.23	2404.02	1.14	3152.23	2736.03	1.15
3	64.147	50.033	1.28	2800.69	2502.70	1.12	3440.93	3281.59	1.05
4	99.017	79.087	1.25	3702.08	3014.98	1.23	4039.91	3481.77	1.16
5	50.783	36.735	1.38	1962.97	1720.64	1.14	2262.73	2331.38	0.97
6	81.688	51.869	1.57	3445.53	2355.50	1.46	4174.56	2851.46	1.46
7	53.198	38.618	1.38	2431.80	1988.99	1.22	2941.10	2621.63	1.12
8	82.521	34.054	2.42	2298.70	1523.70	1.51	2610.41	2031.49	1.28
9	58.481	59.212	0.99	2563.45	1912.06	1.34	2743.88	2031.14	1.35
10	37.842	36.847	1.03	2268.44	1770.40	1.28	2953.44	2637.92	1.12
11	51.000	47.227	1.08	2367.06	1953.47	1.21	3140.66	2606.13	1.21
12	46.175	43.718	1.06	2066.23	1958.49	1.06	2592.65	2548.42	1.02
Mean	**61.460**	**47.847**	**1.28**	**2578.94**	**2086.43**	**1.24**	**3075.01**	**2654.05**	**1.16**
SD	**17.862**	**13.132**	**1.36**	**525.92**	**410.86**	**1.28**	**571.01**	**428.43**	**1.33**

Table 15 The means and 90% CI of Epokine®/Eprex® ratios of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} and mean and 90% CI of the difference in T_{max} between Epokine® and Eprex®.

Pharmacokinetc parameter	Mean	90% CI
AUC_{0-t} Epokine®/Eprex®	1.17	1.11-1.24
$AUC_{0-\infty}$ Epokine®/Eprex®	1.18	1.13-1.24
C_{max} Epokine®/Eprex®	1.29	1.10-1.50
T_{max} Epokine® - Eprex® (h)	-0.92	(-2.94)-1.10

Table 16 The means and 90% CI of Epokine®/Recormon® ratios of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} and mean and 90% CI of the difference in T_{max} between Epokine® and Recormon®.

Pharmacokinetc parameter	Mean	90% CI
AUC_{0-t} Epokine®/Recormon®	1.45	1.33-1.58
$AUC_{0-\infty}$ Epokine®/Recormon®	1.37	1.29-1.45
C_{max} Epokine®/Recormon®	1.64	1.37-1.96
T_{max} Epokine® - Recormon® (h)	-3.00	(-4.69)-(-1.31)

Table 17 The means and 90% CI of Eprex®/Recormon® ratios of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} and mean and 90% CI of the difference in T_{max} between Eprex® and Recormon®.

Pharmacokinetc parameter	Mean	90% CI
AUC_{0-t} Eprex®/Recormon®	1.24	1.17-1.31
$AUC_{0-\infty}$ Eprex®/Recormon®	1.16	1.08-1.23
C_{max} Eprex®/Recormon®	1.28	1.12-1.46
T_{max} Eprex® - Recormon® (h)	-2.08	(-3.39)-0.78