CHAPTER 5

RESULTS

1. Subjects

The mean age (range) and BMI (range) for Test-Reference group and Reference-Test group were 25.6 (20-43) years, 21.6 (18.0-24.8) kg/m^2 and 24.5 (19-38) years, 21.6 (18.1-24.9) kg/m^2, respectively (Table 2A and 2B). All subjects were healthy on the basis of medical history, physical, hematological and biochemical investigations. All volunteers completed the study without any serious adverse event. However on study day 1, volunteer No. 7 felt dizziness and light headedness after being inserted an intravenous catheter in a sitting position. His fasting blood glucose was 100 mg%. His blood pressure (mmHg) and heart rate (beats per min) were 124/88 and 71 before catheter insertion and were 104/60 and 59 (regular rhythm) at the time he had symptoms. He was diagnosed as vasovagal fainting and was put in a horizontal posture. His ECG was normal sinus rhythm. After 10-20 min, he felt better and did not want to withdraw from the study. The study medication was given to him 30 min after the catheter was inserted and he had to lie down for 4 h after dosing due to light headedness and nausea. After lunch (4 h after dosing), he felt normal and continued normal activity without any symptom. Volunteer No. 17 had mild light headedness 3 h after dosing on study day 1 despite his normal blood pressure and heart rate, and his blood glucose of 73 mg%. His symptom resolved after lunch. Volunteer No. 16 had asymptomatic elevation of liver enzymes on post study visit (study day 13). His baseline AST and ALT values were 27 and 23 unit, and were elevated to 883 and 196 unit, respectively. The liver enzymes were followed up on study day 16 (AST = 202 unit and ALT = 131 unit) and returned to normal values on study day 25 (AST = 22 unit and ALT = 28 unit).

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Table 2A Demographic characteristics of subjects in group 1 (Sequence of drug administration; Test–Reference)

Subject No.	Sex	Age (y)	Height (m)	Weight (kg)	BMI (kg/m^2)
1	Male	24	1.68	70.0	24.80
2	Male	21	1.59	61.5	24.33
3	Male	21	1.77	56.5	18.03
5	Male	22	1.65	58.0	21.30
8	Male	30	1.65	56.0	20.57
11	Male	43	1.64	60.0	22.31
12	Male	22	1.63	57.0	21.45
13	Male	21	1.65	51.5	18.92
17	Male	20	1.63	65.0	24.46
19	Male	26	1.6	46.7	18.24
21	Male	23	1.68	60.0	21.26
23	Male	21	1.75	64.0	20.90
25	Male	39	1.65	67.5	24.79
Mean		**25.62**	**1.66**	**59.5**	**21.64**
SD		**7.38**	**0.05**	**6.4**	**2.41**

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Table 2B Demographic characteristics of subjects in group 2 (Sequence of drug administration; Reference–Test)

Subject No.	Sex	Age (y)	Height (m)	Weight (kg)	BMI (kg/m^2)
4	Male	19	1.75	55.5	18.12
6	Male	20	1.66	53.5	19.42
7	Male	20	1.70	62.3	21.56
9	Male	22	1.64	55.0	20.45
10	Male	32	1.73	69.0	23.05
14	Male	38	1.73	74.5	24.89
15	Male	23	1.73	61.2	20.45
16	Male	20	1.64	56.0	20.82
18	Male	20	1.68	52.5	18.60
20	Male	24	1.64	64.0	23.80
22	Male	28	1.70	59.0	20.42
24	Male	28	1.70	72.0	24.91
26	Male	25	1.68	68.0	24.09
Mean		**24.54**	**1.69**	**61.7**	**21.58**
SD		**5.65**	**0.04**	**7.3**	**2.34**

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2. Assay validation of HPLC method

2.1 Specificity and linearity

To test the specificity, blank samples of human plasma were obtained from six individuals in different conditions. Metformin and IS were well separated by the HPLC system. Retention times were approximately 7.8 min and 9.4 min for metformin and IS, respectively. There was no significant interference at the retention times of our drug and IS (Figure 1A and 1B).

The calibration curves of metformin in plasma were linear from 25.0-4,000.0 ng/mL (Table 3). Linear regression of concentrations versus peak height ratios of metformin/IS gave coefficients of determination (r^2), which were greater than 0.9900 (r^2 = 0.9997, Figure 2).

2.2 Precision, accuracy, recovery and stability

The LLQ was 25.0 ng/mL with the accuracy (average %) and precision (average CV, %) of 97.55 and 9.63, respectively (Table 3).

The accuracy (average %) and precision (average CV, %) of intra-day assay validation were 100.89 and 5.39), respectively (Table 4) and 99.49 and 3.72, respectively for inter-day assay validation (Table 5).

The mean recoveries (%) of metformin and IS from the determination procedure were 97.14 and 95.57), respectively (Table 6).

The average deviation (%) of stability test, freeze-thaw, short-term, long-term and post-preparative were 1.95, -0.91, -2.23 and –0.79, respectively (Table 7-10).
The average deviation (%) of stock-solution stability for metformin and IS were 1.77 and -0.39, respectively (Table 11).

The results of study phase validation presented by average accuracy and precision are shown in Table 12.

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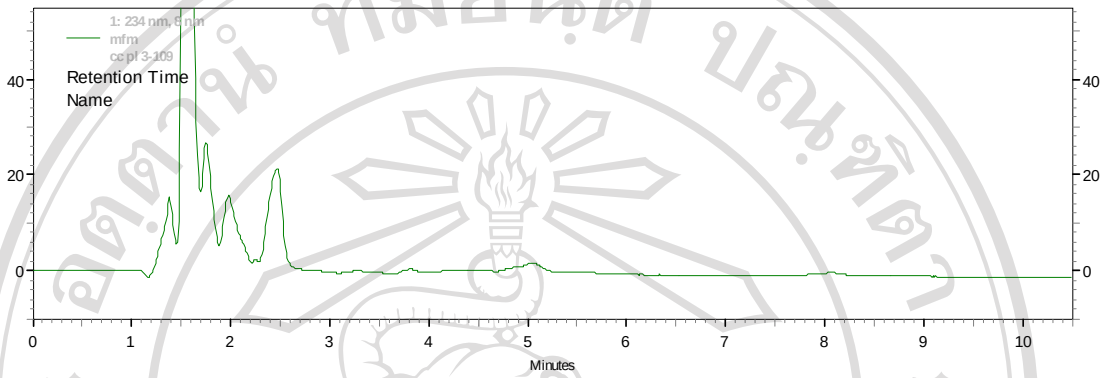
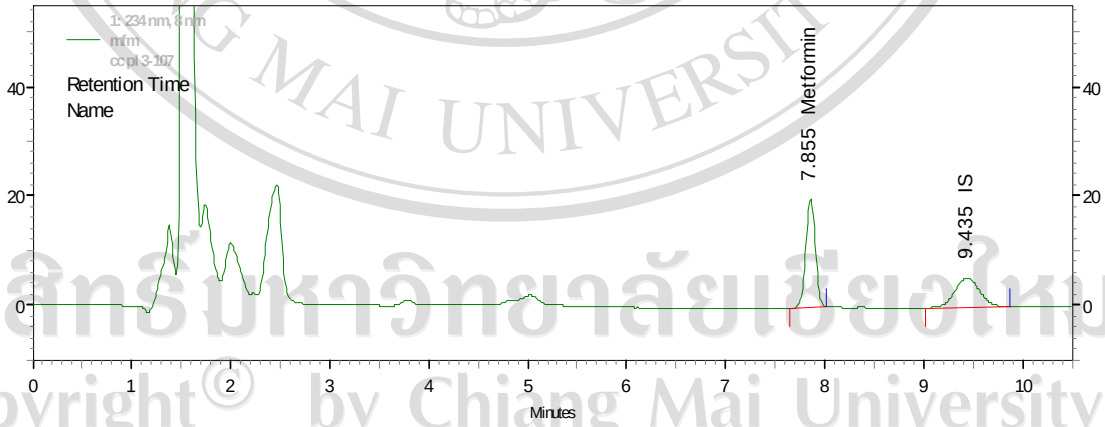


Time (min)

Figure 1A Chromatogram of blank plasma.



Time (min)

Figure 1B Chromatogram of metformin 4000.0 ng/mL and IS from human plasma sample

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Table 3 Calibration curve and LLQ of metformin in plasma

No.	Spiked concentration (ng/mL)	Metformin (peak ht)	IS (peak ht)	Metformin/IS	Calculated concentration (ng/mL)	**Accuracy (%)**
1	25	117	4309	27.1525	28.33	**113.33**
2	125	605	4588	131.8657	137.60	**110.08**
3	250	1147	4450	257.7528	268.97	**107.59**
4	500	2155	4394	490.4415	511.78	**102.36**
5	1000	4138	4525	914.4751	954.27	**95.43**
6	2000	8234	4337	1898.5474	1981.16	**99.06**
7	4000	16224	4214	3850.0237	4017.55	**100.44**

	Spiked concentration (ng/mL)	Metformin (peak ht)	IS (peak ht)	Metformin/IS	Calculated concentration (ng/mL)	Accuracy (%)
LLQ	25	79	3751	21.0611	21.98	87.90
		95	4176	22.7490	23.74	94.95
		105	4195	25.0298	26.12	104.47
		108	4098	26.3543	27.50	110.00
		89	4107	21.6703	22.61	90.45
Mean					**24.39**	**97.55**
SD					**2.35**	
Precision (CV, %)					**9.63**	

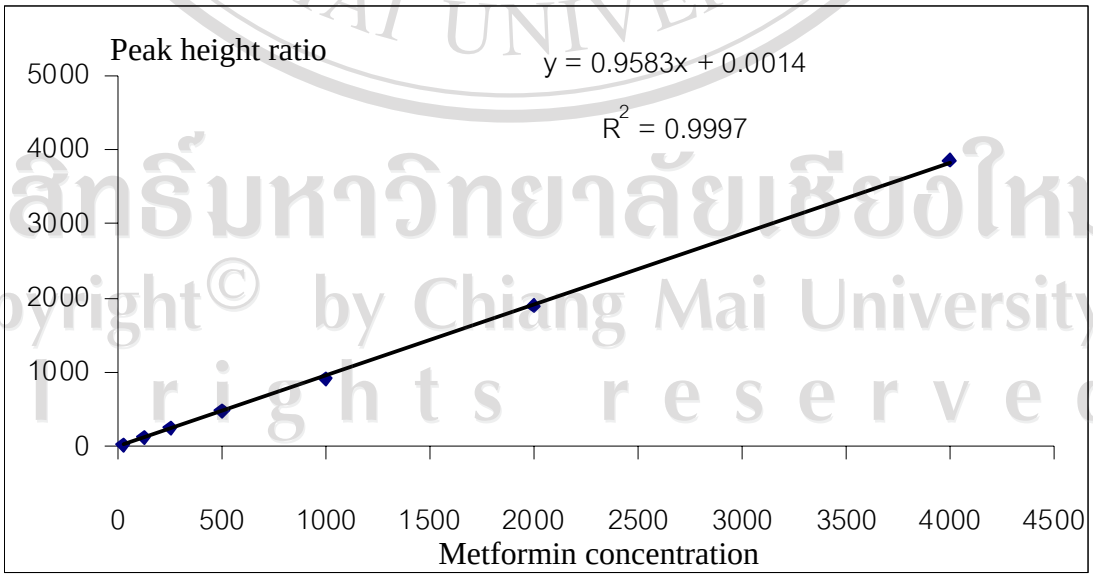

Figure 2 Calibration curve of metformin in human plasma.

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Table 4 Intra-assay validation of metformin in plasma

No.	Spiked concentration (ng/mL)	Metformin (peak ht)	IS (peak ht)	Metformin/IS	Calulated concentration (ng/mL)	Accuracy (%)
Low	75	388	4749	81.7014	85.26	113.67
		395	5107	77.3448	80.71	107.61
		414	5148	80.4196	83.92	111.89
		356	5100	69.8039	72.84	97.12
		379	5135	73.8072	77.02	102.69
Mean					79.95	106.60
SD					5.09	
Precision (CV, %)					6.37	
Medium	1900	6266	4018	1559.4823	1627.34	85.65
		7417	4460	1663.0045	1735.37	91.34
		8144	4600	1770.4348	1847.47	97.24
		7854	4543	1728.8136	1804.04	94.95
		8298	4760	1743.2773	1819.13	95.74
Mean					1766.67	92.98
SD					88.13	
Precision (CV, %)					4.99	
High	3800	19674	5656	3478.4300	3629.79	95.52
		23441	6128	3825.2285	3991.68	105.04
		24868	6320	3934.8101	4106.03	108.05
		24110	6251	3856.9829	4024.82	105.92
		23031	6271	3672.6200	3832.43	100.85
Mean					3916.95	103.08
SD					188.80	
Precision (CV, %)					4.82	
Average Precision (CV, %)					**5.39**	**100.89**

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Table 5 Inter-assay validation of metformin in plasma

Spiked concentration (ng/mL)	Calculated concentration (ng/mL)					Precision (CV, %)	Accuracy (%)
	day 1	day 2	day 3	Mean	SD		
75	78.53	79.95	76.56	78.35	1.70	2.17	104.46
1900	1849.55	1766.67	1882.08	1832.77	59.50	3.25	96.46
3800	3491.91	3916.95	3711.26	3706.71	212.55	5.73	97.54
	Average (%)					**3.72**	**99.49**

Table 6 Recovery of metformin and IS from plasma

Control sample	Spiked concentration (ng/mL)	Metformin (peak ht)	
		in mobile phase	after plasma extraction
Low	75	334 317 321 321 324	312 320 295 297 295
Mean Recovery (%)		323.40	303.80 93.94
Medium	1900	8779 8517 8833 8885 8695	7658 8661 8614 8598 8755
Mean Recovery (%)		8741.80	8457.20 96.74
High	3800	16622 16404 16976 16576 16404	14637 15560 17284 18225 17875
Mean Recovery (%)		**16596.40**	**16716.20 100.72**
Average Recovery (%)			**97.14**

Spiked concentration (ng/mL)		Internal standard (peak ht)	
		in mobile phase	after plasma extraction
	20000	4833 4718 4999 4468 4854	3985 4797 4753 4633 4647
Mean Recovery (%)		**4774.40**	**4563.00 95.57**

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Table 7 Freeze-thaw stability of metformin in plasma

Control sample	Spiked concentration (ng/mL)	Calculated concentration (ng/mL)	
		Before freeze/thaw	After freeze/thaw
Low	75	85.00 80.47 83.67	79.95 84.30 78.75
Mean **Deviation (%)**		83.05	81.00 **-2.46**
High	3800	3980.86 4094.90 4013.91	4310.52 4220.61 4328.85
Mean **Deviation (%)**		4029.89	4286.66 **6.37**
Average Deviation (%)			**1.95**

Table 8 Short-term stability of metformin in plasma

Control sample	Spiked concentration (ng/mL)	Calculated concentration (ng/mL)	
		0 h	8 h
Low	75	84.19 81.42 76.04	80.93 76.58 83.19
Mean **Deviation (%)**		80.55	80.23 **-0.39**
High	3800	3496.24 3593.21 3561.71	3388.85 3614.13 3496.54
Mean **Deviation (%)**		3550.39	3499.84 **-1.43**
Average Deviation (%)			**-0.91**

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Table 9 Long-term stability of metformin in plasma

Control sample	Spiked concentration (ng/mL)	Calculated concentration (ng/mL)	
		0 month	2 months
Low	75	82.63 84.84 82.53	77.02 83.35 78.45
Mean **Deviation (%)**		83.34	79.61 **-4.48**
High	3800	4106.67 4330.99 4349.46	4170.94 4331.16 4286.87
Mean **Deviation (%)**		4262.37	4262.99 **0.01**
Average deviation (%)			**-2.23**

Table 10 Post-prepative stability of metformin in plasma

Control sample	Spiked concentration (ng/mL)	Calculated concentration (ng/mL)	
		0 h	8 h
Low	75	83.64 80.98 80.93	86.14 76.35 80.89
Mean **Deviation (%)**		81.85	81.13 **-0.88**
High	3800	4291.09 4319.03 4378.28	4299.30 4308.05 4292.03
Mean **Deviation (%)**		4329.46	4299.80 **-0.69**
Average deviation (%)			**-0.79**

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Table 11 Stock-solution stability of metformin and IS

Control sample	Spiked concentration (ng/mL)	Metformin (peak ht)	
		0 month	2 months
Low	75	373 406 396	413 392 406
Mean **Deviation (%)**		391.66	403.67 **3.06**
High	3800	19923 21283 21275	20436 20864 21476
Mean **Deviation (%)**		20827	20925.33 **0.47**
Average deviation (%)			**1.77**

Spiked concentration (ng/mL)		Internal standard (peak ht)	
		0 month	2 months
	20000	4759 4815 4888	4803 4748 4855
Mean **Deviation (%)**		4820.67	4802.00 **-0.39**

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Table 12 Calculated concentration of QC samples of batches run in study phase

	Low (75 ng/mL)			Medium (1900 ng/mL)			High (3800 ng/mL)		
Batch No. 1	Calculate value	Deviate (%)	Status	Calculate value	Deviate (%)	Status	Calculate value	Deviate (%)	Status
	84.61	12.82	Approved	1734.69	-8.70	Approved	4407.17	15.98	Rejected
	83.86	11.82	Approved	2037.22	7.22	Approved	3774.83	-0.66	Approved
	80.53	7.38	Approved	1982.14	4.32	Approved	3768.31	-0.83	Approved
	84.28	12.37	Approved	1925.65	1.35	Approved	3910.43	2.91	Approved
	84.86	13.15	Approved	1747.44	-8.03	Approved	3727.39	-1.91	Approved
	78.70	4.94	Approved	2144.26	12.86	Approved	3805.55	0.15	Approved
Mean	82.81			1928.57			3898.95		
CV (%)	**3.09**			**8.41**			**6.58**		
Accuracy (%)	**110.41**			**101.50**			**102.60**		

	Low (75 ng/mL)			Medium (1900 ng/mL)			High (3800 ng/mL)		
Batch No. 2	Calculate value	Deviate (%)	Status	Calculate value	Deviate (%)	Status	Calculate value	Deviate (%)	Status
	78.70	4.94	Approved	2144.26	12.86	Approved	3805.55	0.15	Approved
	76.94	2.59	Approved	1823.86	-4.01	Approved	3716.02	-2.21	Approved
	79.17	5.56	Approved	1732.78	-8.80	Approved	3594.36	-5.41	Approved
	78.90	5.20	Approved	1721.02	-9.42	Approved	3419.39	-10.02	Approved
	84.34	12.46	Approved	2067.59	8.82	Approved	3549.87	-6.58	Approved
	80.83	7.77	Approved	1837.53	-3.29	Approved	3472.00	-8.63	Approved
Mean	79.81			1887.84			3592.86		
CV (%)	**3.18**			**9.37**			**4.07**		
Accuracy (%)	**106.42**			**99.36**			**94.55**		

	Low (75 ng/mL)			Medium (1900 ng/mL)			High (3800 ng/mL)		
Batch No. 3	Calculate value	Deviate (%)	Status	Calculate value	Deviate (%)	Status	Calculate value	Deviate (%)	Status
	76.81	2.42	Approved	1890.35	-0.51	Approved	3790.71	-0.24	Approved
	78.16	4.21	Approved	1822.47	-4.08	Approved	3695.74	-2.74	Approved
	79.66	6.21	Approved	1758.56	-7.44	Approved	3551.75	-6.53	Approved
	73.47	-2.04	Approved	1680.05	-11.58	Approved	3284.69	-13.56	Approved
	64.55	-13.93	Approved	1625.71	-14.44	Approved	3435.27	-9.60	Approved
	70.38	-6.17	Approved	1684.42	-11.35	Approved	3475.50	-8.54	Approved
Mean	73.84			1743.60			3538.94		
CV (%)	**7.65**			**5.70**			**5.17**		
Accuracy (%)	**98.45**			**91.77**			**93.13**		

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Table 12 Calculated concentration of QC samples of batches run in study phase (continued)

	Low (75 ng/mL)			Medium (1900 ng/mL)			High (3800 ng/mL)		
Batch No. 4	Calculate value	Deviate (%)	Status	Calculate value	Deviate (%)	Status	Calculate value	Deviate (%)	Status
	79.62	6.17	Approved	1793.23	-5.62	Approved	3566.56	-6.14	Approved
	83.30	11.07	Approved	1749.92	-7.90	Approved	3917.92	3.10	Approved
	84.79	13.05	Approved	2038.26	7.28	Approved	4109.23	8.14	Approved
	67.92	-9.44	Approved	2350.01	23.68	Rejected	3652.46	-3.88	Approved
	85.27	13.70	Approved	1732.99	-8.79	Approved	3912.05	2.95	Approved
	74.38	-0.83	Approved	1804.20	-5.04	Approved	4403.28	15.88	Rejected
Mean	79.32			1927.40			3826.37		
CV (%)	**8.55**			**12.25**			**5.15**		
Accuracy (%)	**105.76**			**101.44**			**100.69**		

	Low (75 ng/mL)			Medium (1900 ng/mL)			High (3800 ng/mL)		
Batch No. 5	Calculate value	Deviate (%)	Status	Calculate value	Deviate (%)	Status	Calculate value	Deviate (%)	Status
	73.57	-1.90	Approved	1975.46	3.97	Approved	3384.14	-10.94	Approved
	65.25	-13.00	Approved	1778.12	-6.41	Approved	3825.61	0.67	Approved
Mean	69.41			1876.79			3604.87		
CV (%)	**8.48**			**7.44**			**8.66**		
Accuracy (%)	**92.55**			**98.78**			**94.87**		

Batch No.	Subjects in the batch	Batch sized
1	1-6	234
2	7-12	234
3	13-18	234
4	19-24	234
5	25-26	78

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3. Pharmacokinetics and bioequivalence of metformin in healthy volunteers

3.1 Plasma metformin concentration-time profiles

The plasma concentrations of metformin versus time following a single oral dose of 850 mg the test product and the reference product are showed in Tables 13A and 13B, respectively. Their means, SD, % CV, maximum and minimum values are also respectively shown in Tables 14A and 14B. Tables 15A and 15B illustrate metformin pharmacokinetic parameters including T_{max}, C_{max}, AUC_{o-t}, $AUC_{o-\infty}$, $t_{1/2}$ and K_e as well as their means, SD, % CV, maximum and minimum values of the test product and the reference product, respectively. The concentration-time profiles are presented using three types of standard plots (39). Figure 3 depicts the pairwise of individual concentration-time curves of the test and the reference product. Figures 4A and 4B show a plot of 26 individual plasma concentration-time profiles while Figure 5 illustrates their mean plasma concentration-time profiles of the test product and the reference product, respectively.

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Table13A Plasma metformin concentrations (ng/mL) after oral administration of 850 mg metformin HCl (test product)

Volunteer No.	P 1	P 2	Plasma metformin concentration (ng/mL)																
Time (h)			0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	8.0	10.0	14.0	24.0	30.0
1	x		0.00	1125.10	2038.05	2482.76	2900.97	2914.66	2808.73	2932.88	2751.38	2506.00	2200.34	1831.96	1531.22	985.87	495.01	199.47	46.63	30.84
2	x		0.00	1203.60	2057.37	2567.70	2963.13	2950.18	2440.95	2239.82	2009.27	1643.91	1409.96	1215.20	971.16	580.85	304.37	123.96	61.12	BLLQ
3	x		0.00	431.00	1045.04	1615.39	1817.74	1923.34	2030.95	1773.65	1646.09	1574.37	1308.43	1104.59	850.91	507.05	264.25	126.47	29.91	BLLQ
4		x	0.00	360.75	1246.85	2415.20	2840.17	3033.55	3318.62	3383.23	3436.37	3295.83	2427.62	2040.11	1676.76	867.62	483.99	208.53	39.94	BLLQ
5	x		0.00	1760.00	2113.43	2671.22	3142.30	3023.34	2785.11	2635.33	2310.26	1813.78	1499.28	1146.23	934.48	552.22	273.74	97.66	41.36	BLLQ
6		x	0.00	880.21	1302.79	1817.78	2138.56	2379.93	2277.84	2045.04	1787.46	1579.20	1320.74	1164.30	927.93	512.76	271.56	131.25	46.28	29.56
7		x	0.00	747.65	1988.00	1893.68	2007.00	2031.23	1748.10	2049.82	1730.00	1519.68	1180.74	1035.16	747.78	465.02	246.89	93.27	35.15	BLLQ
8	x		0.00	693.79	1652.75	2434.84	3903.20	3419.52	2878.11	2576.55	2340.03	2015.45	1683.27	1375.01	1234.63	617.23	412.86	235.79	103.05	41.17
9		x	0.00	782.14	1775.04	3426.50	3781.51	3413.91	3461.14	2845.23	2445.47	2123.89	1998.15	1452.29	972.41	794.24	444.49	138.33	32.12	BLLQ
10		x	0.00	723.27	1667.82	1784.38	1621.16	1933.21	1770.67	1747.49	1634.98	1439.16	1233.86	953.87	800.92	452.66	233.99	110.96	30.92	BLLQ
11	x		0.00	1257.18	2866.11	3258.17	3173.14	2851.67	2558.48	2289.57	1962.59	1677.54	1363.93	1141.45	850.53	533.69	308.50	112.42	46.37	BLLQ
12	x		0.00	843.42	2051.31	2365.64	2624.16	2541.87	2576.34	2290.53	2001.57	1791.06	1517.05	1321.62	1157.78	733.90	381.94	129.86	41.78	BLLQ
13	x		0.00	2193.00	2238.59	2247.28	3063.03	2949.61	3004.95	2374.89	2021.77	1811.29	1558.25	1170.12	930.02	494.61	297.71	117.87	28.47	BLLQ

P1 = period 1 P2 = period 2 BLLQ = below lower limit of quantification

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Table 13A Plasma metformin concentrations (ng/mL) after oral administration of 850 mg metformin HCl (test product) (continued)

Volunteer No.	P 1	P 2	Plasma metformin concentration (ng/mL)																
Time (h)			0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	8.0	10.0	14.0	24.0	30.0
14		x	0.00	369.85	969.07	1343.88	2026.56	2193.87	2326.54	2015.40	1815.29	1738.01	1171.00	907.28	753.68	497.85	289.13	111.08	0.00	BLLQ
15		x	0.00	938.39	2668.46	3065.59	3255.72	3036.93	2830.33	2505.02	2289.04	1961.19	1661.85	1313.60	1094.92	583.13	348.12	139.64	50.67	BLLQ
16		x	0.00	1406.43	2675.30	3071.84	3155.91	2950.33	2869.76	2437.61	2257.38	1978.02	1554.36	1237.53	955.84	535.96	274.26	127.70	37.35	BLLQ
17	x		0.00	1007.16	2549.49	3145.31	3022.35	2574.26	2180.38	1987.03	1675.80	1466.43	1203.87	907.91	754.77	471.17	254.00	88.28	0.00	BLLQ
18		x	0.00	555.53	1858.38	1923.55	2410.47	2095.39	1851.43	1885.03	1616.51	1349.37	1094.82	880.16	730.34	451.78	217.49	81.39	34.53	BLLQ
19	x		0.00	699.18	2007.84	1905.23	1894.65	1727.95	1633.02	1516.51	1284.42	1161.57	946.82	707.69	569.59	368.62	221.73	129.24	103.58	BLLQ
20		x	0.00	868.85	2402.93	2448.11	3022.92	2703.14	2786.00	2441.33	2088.88	1815.62	1457.16	1190.83	934.41	544.90	330.10	141.26	43.37	BLLQ
21	x		0.00	540.31	1701.38	2103.00	2836.76	2564.87	2522.52	2418.19	2234.74	1950.04	1510.68	1225.05	1031.47	658.71	323.04	126.44	65.25	BLLQ
22		x	0.00	586.45	1246.88	2176.70	2796.21	2797.57	3140.73	2850.14	2447.34	2360.17	1910.12	1544.73	1273.44	725.12	386.00	148.64	47.89	BLLQ
23	x		0.00	882.55	1544.77	1954.24	1816.26	2021.30	1941.51	1703.71	1443.21	1266.41	948.25	777.11	607.15	407.10	244.63	100.62	38.29	BLLQ
24		x	0.00	706.43	1363.10	1330.27	1461.67	1774.90	1676.99	1436.46	1301.77	1132.09	860.81	621.59	549.92	291.99	178.14	72.94	0.00	BLLQ
25	x		0.00	1594.94	3294.51	3076.42	2961.41	2772.33	2755.75	2493.06	2101.04	1860.88	1184.93	908.18	731.85	411.16	218.00	88.12	0.00	BLLQ
26		x	0.00	1543.68	2314.82	2151.42	2394.54	2255.97	2563.95	2869.90	2619.38	2651.60	1999.83	1661.34	1329.81	718.87	423.78	173.89	37.40	BLLQ

P1 = period 1 P2 = period 2 BLLQ = below lower limit of quantification

Table 13B Plasma metformin concentrations (ng/mL) after oral administration of 850 mg metformin HCl (reference product)

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Volunteer No.	P 1	P 2	Plasma metformin concentration (ng/mL)																
Time (h)			0.0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	8.0	10.0	14.0	24.0	30.0
1		x	0.00	608.05	1688.26	2117.20	2246.70	2081.90	2567.95	2410.05	2577.11	2315.49	1893.55	1651.39	1412.57	881.25	522.89	187.90	44.07	BLLQ
2		x	0.00	612.81	1093.46	1771.88	2467.75	2214.43	2392.20	1937.62	1668.69	1356.54	1119.86	994.77	807.60	487.45	281.33	110.25	54.57	BLLQ
3		x	0.00	441.63	918.99	1461.18	1541.87	1656.98	1814.12	1621.91	1457.10	1366.04	1093.20	970.25	844.32	495.50	257.03	131.50	59.32	43.82
4	x		0.00	383.29	1251.47	2314.53	2370.86	2422.47	2600.01	2604.72	2611.25	2351.48	1732.83	1378.08	1172.82	612.85	378.17	193.69	42.12	BLLQ
5		x	0.00	632.33	1641.43	2001.23	2096.69	2152.94	2280.64	2442.31	2085.16	1976.45	1664.30	1393.55	1118.82	590.17	262.00	115.27	25.03	BLLQ
6	x		0.00	1048.45	1706.84	1809.66	2478.66	2784.72	2912.74	2865.23	2559.45	2224.41	1705.43	1507.99	1145.05	674.72	365.49	181.99	50.66	27.76
7	x		0.00	1186.10	600.95	410.11	218.07	546.64	814.10	1469.63	1244.18	1325.33	1287.99	1246.34	999.91	1276.35	597.45	263.86	81.71	26.36
8		x	0.00	517.14	1262.32	1966.19	2724.86	2760.00	2523.09	2314.11	2096.35	1781.97	1535.15	1369.09	1075.20	649.18	418.98	165.64	47.30	BLLQ
9	x		0.00	526.22	2930.99	3178.12	4700.28	3625.34	3123.72	2695.30	2481.34	2106.94	1762.86	1443.82	1189.43	824.71	372.59	168.96	62.52	BLLQ
10	x		0.00	1072.95	2618.27	2556.62	2011.43	2101.95	2168.15	2149.06	1937.27	1676.71	1334.91	1039.82	747.82	501.66	273.56	102.19	32.87	BLLQ
11		x	0.00	995.49	1982.64	2652.41	2489.22	2327.30	2767.49	2334.31	1904.98	1597.09	1336.45	1077.52	866.13	561.13	301.63	105.15	33.05	BLLQ
12		x	0.00	523.18	1033.27	1536.20	2083.56	1928.82	1959.53	1812.78	1697.44	1541.90	1315.10	1125.72	967.59	729.96	354.66	160.37	57.64	BLLQ
13		x	0.00	851.51	2677.52	3293.67	3698.42	2957.26	3452.32	2177.98	2076.44	1847.86	1421.43	1139.89	925.63	506.97	266.59	111.00	42.80	BLLQ

P1 = period 1 P2 = period 2 BLLQ = below lower limit of quantification

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Table 13B Plasma metformin concentrations (ng/mL) after oral administration of 850 mg metformin HCl (reference product) (continued)

Volunteer No.	P 1	P 2	Plasma metformin concentration (ng/mL)																
Time (h)			0.00	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	8.0	10.0	14.0	24.0	30.0
14	x		0.00	531.89	906.48	1951.16	2586.58	2625.34	2609.42	2299.60	1957.97	1739.84	1372.11	1096.04	817.22	515.68	272.41	90.53	26.43	BLLQ
15	x		0.00	701.32	1295.05	2173.36	3088.12	2899.42	2691.85	2500.08	2161.03	1801.79	1515.06	1167.30	954.08	491.26	342.82	129.55	48.87	BLLQ
16	x		0.00	1013.79	1293.69	1599.56	1918.39	2208.68	2123.45	1994.43	1762.69	1521.40	1241.52	927.44	760.07	430.32	254.19	124.00	41.61	35.57
17		x	0.00	581.60	1869.03	2611.16	3055.65	2678.28	2394.63	2027.01	1687.13	1535.96	1320.44	942.58	810.62	483.36	264.96	87.07	46.40	BLLQ
18	x		0.00	975.68	1822.30	1873.30	1918.91	1635.33	1376.21	1194.36	1072.93	834.71	621.51	528.38	481.29	256.69	156.84	74.72	28.72	BLLQ
19		x	0.00	725.14	1401.22	1383.99	1397.79	1357.62	1252.47	1288.81	1148.85	851.06	984.06	674.06	559.23	366.42	196.35	87.94	37.67	BLLQ
20	x		0.00	493.42	1011.96	1655.65	2305.55	2299.80	2186.67	1720.37	1556.63	1327.59	950.26	775.96	630.52	382.23	226.16	106.86	31.96	BLLQ
21		x	0.00	732.65	1961.22	2743.32	2722.72	2288.33	2197.89	2173.40	1922.61	1722.20	1359.62	1085.49	963.73	623.80	339.14	158.89	53.84	BLLQ
22	x		0.00	1006.11	1828.07	2636.20	2811.12	2908.78	2477.62	2156.85	2011.43	1650.78	1573.98	1218.03	1295.98	611.90	307.68	116.63	36.29	BLLQ
23		x	0.00	916.16	1397.45	1826.40	2337.33	2418.95	2086.58	1649.73	1638.30	1486.52	1197.14	851.78	674.23	432.78	287.11	111.52	29.71	BLLQ
24	x		0.00	506.27	1208.74	1424.81	1629.50	1535.80	1567.58	1396.43	1193.53	1065.43	799.86	674.04	511.35	300.28	184.17	75.07	25.57	BLLQ
25		x	0.00	432.51	795.13	1349.61	1584.42	1753.64	2037.51	1793.74	1648.70	1573.88	1285.84	1017.76	798.86	515.55	264.99	115.25	33.51	BLLQ
26	x		0.00	531.89	906.48	1951.16	2586.58	2625.34	2609.42	2299.60	1957.97	1739.84	1372.11	1096.04	817.22	515.68	272.41	90.53	26.43	BLLQ

P1 = period 1 P2 = period 2 BLLQ = below lower limit of quantification

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Table 14A The means, SD, % CV, maximum and minimum concentrations of plasma metformin after oral administration of 850 mg metformin HCl (test product)

Time after administration (h)	Mean (ng/mL)	SD	% CV	Maximum (ng/mL)	Minimum (ng/mL)	Max-Min (ng/mL)
Baseline (T=0)	BLLQ	BLLQ	BLLQ	BLLQ	BLLQ	BLLQ
T1=0.5	950.03	452.33	47.61	2193.00	360.75	1832.25
T2=1.0	1947.70	583.00	29.93	3294.51	969.07	2325.44
T3=1.5	2333.70	581.04	24.90	3426.50	1330.27	2096.22
T4=2.0	2655.06	645.10	24.30	3903.20	1461.67	2441.53
T5=2.5	2570.57	492.86	19.17	3419.52	1727.95	1691.56
T6=3.0	2489.96	515.64	20.71	3461.14	1633.02	1828.11
T7=3.5	2297.82	473.51	20.61	3383.23	1436.46	1946.77
T8=4.0	2048.16	479.95	23.43	3436.37	1284.42	2151.95
T9=4.5	1826.25	481.55	26.37	3295.83	1132.09	2163.74
T10=5.0	1469.47	390.27	26.56	2427.62	860.81	1566.81
T11=5.5	1185.96	333.20	28.10	2040.11	621.59	1418.52
T12=6.0	957.84	278.93	29.12	1676.76	549.92	1126.84
T13=8.0	567.85	159.36	28.06	985.87	291.99	693.88
T14=10.0	312.60	86.04	27.52	495.01	178.14	316.87
T15=14.0	129.04	39.16	30.35	235.79	72.94	162.85
T16=24.0	40.06	25.51	63.68	103.58	0.00	103.58

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Table 14B The means, SD, %CV, maximum and minimum concentration of plasma metformin after oral administration of 850 mg metformin HCl (reference product)

Time after administration (h)	Mean (ng/mL)	SD	% CV	Maximum (ng/mL)	Minimum (ng/mL)	Max-Min (ng/mL)
Baseline (T=0)	BLLQ	BLLQ	BLLQ	BLLQ	BLLQ	BLLQ
T1=0.5	740.48	256.58	34.65	1236.75	383.29	853.47
T2=1.0	1546.48	590.13	38.16	2930.99	600.95	2330.04
T3=1.5	2024.26	630.86	31.16	3293.67	410.11	2883.55
T4=2.0	2348.55	821.70	34.99	4700.28	218.07	4482.22
T5=2.5	2255.28	619.09	27.45	3625.34	546.64	3078.70
T6=3.0	2262.97	577.36	25.51	3452.32	814.10	2638.23
T7=3.5	2045.13	438.84	21.46	2865.23	1194.36	1670.88
T8=4.0	1847.21	430.69	23.32	2611.25	1072.93	1538.31
T9=4.5	1620.21	387.76	23.93	2351.48	834.71	1516.77
T10=5.0	1336.39	299.50	22.41	1893.55	621.51	1272.05
T11=5.5	1089.57	269.70	24.75	1651.39	528.38	1123.02
T12=6.0	898.14	235.91	26.27	1412.57	481.29	931.28
T13=8.0	560.65	207.16	36.95	1276.35	256.69	1019.66
T14=10.0	306.83	97.84	31.89	597.45	156.84	440.61
T15=14.0	129.65	44.14	34.05	263.86	74.72	189.13
T16=24.0	42.32	13.83	32.68	81.71	25.03	56.68

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Table 15A Pharmacokinetic parameters of metformin after a single oral dose of 850 mg metformin HCl (test product)

Volunteer No.	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	$t_{1/2}$ (h)	*Ke* (1/h)
1	3.50	2932.88	20246.65	20470.72	3.33	0.208
2	2.00	2963.13	15632.68	15950.56	3.61	0.192
3	3.00	2030.95	12040.62	12183.96	3.32	0.209
4	4.00	3436.37	20841.72	21021.08	3.11	0.223
5	2.00	3142.30	16434.32	16625.70	3.21	0.216
6	2.50	2379.93	13497.19	13741.88	3.66	0.189
7	3.50	2049.82	12399.61	12569.90	3.36	0.206
8	2.00	3903.20	18688.37	19269.07	4.04	0.172
9	2.00	3781.51	19019.01	19158.97	3.02	0.229
10	2.50	1933.21	11794.70	11950.79	3.50	0.198
11	1.50	3258.17	16274.75	16508.90	3.50	0.198
12	2.00	2624.16	16141.05	16344.81	3.38	0.205
13	2.00	3063.03	16328.71	16456.88	3.12	0.222
14	3.00	2326.54	11465.73	11863.14	2.48	0.280
15	2.00	3255.72	17573.16	17826.44	3.46	0.200
16	2.00	3155.91	16940.39	17115.77	3.25	0.213
17	1.50	3145.31	13684.36	13980.17	2.32	0.298
18	2.00	2410.47	11971.65	12138.44	3.35	0.207
19	1.00	2007.84	11279.44	12004.15	4.85	0.143
20	2.00	3022.92	16066.67	16282.15	3.44	0.201
21	2.00	2836.76	15590.98	15946.02	3.77	0.184
22	3.00	3140.73	17408.49	17640.92	3.36	0.206
23	2.50	2021.30	11352.48	11555.24	3.67	0.189
24	2.50	1774.90	8784.72	9031.78	2.35	0.295
25	1.00	3294.51	15069.10	15348.55	2.20	0.315
26	3.50	2869.90	18288.79	18648.42	3.33	0.208
Mean	**2.33**	**2798.52**	**15184.44**	**15440.55**	**3.31**	**0.22**
SD	0.76	588.88	3119.26	3103.47	0.55	0.04
% CV	32.70	21.04	20.54	20.10	16.65	18.35
Maximum	4.00	3903.20	20841.72	21021.08	4.85	0.32
Minimum	1.00	1774.90	8784.72	9031.78	2.20	0.14
Max-Min	3.00	2128.30	12057.00	11989.30	2.65	0.17
Median	**2.00**					

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Table 15B Pharmacokinetic parameters of metformin after a single oral dose of 850 mg metformin HCl (reference product)

Volunteer No.	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	$t_{1/2}$ (h)	*Ke* (1/h)
1	4.00	2577.11	17711.36	17923.26	3.33	0.208
2	2.00	2467.75	12687.99	12979.09	3.70	0.187
3	3.00	1814.12	11206.23	11559.29	4.13	0.168
4	4.00	2611.25	16403.16	16614.35	3.48	0.199
5	3.50	2442.31	14480.42	14588.86	3.00	0.231
6	3.00	2912.74	17206.24	17462.42	3.51	0.198
7	3.50	1469.63	13025.23	13560.45	4.54	0.153
8	2.50	2760.00	15720.42	15959.04	3.50	0.198
9	2.00	4700.28	20036.76	20349.27	3.46	0.200
10	1.00	2618.27	13972.03	14130.70	3.35	0.207
11	3.00	2767.49	14743.56	14895.51	3.19	0.218
12	2.00	2083.56	13422.93	13747.60	3.90	0.178
13	2.00	3698.42	16758.90	16968.44	3.39	0.204
14	2.50	2625.34	13474.19	13591.19	3.07	0.226
15	2.00	3088.12	15351.97	15598.57	3.50	0.198
16	2.50	2208.68	12451.87	12666.22	3.57	0.194
17	2.00	3055.65	13968.10	14194.46	3.38	0.205
18	2.00	1918.91	9178.96	9325.56	3.54	0.196
19	1.00	1401.22	9057.39	9283.18	4.15	0.167
20	2.00	2305.55	11280.84	11437.71	3.40	0.204
21	1.50	2743.32	15305.84	15595.58	3.73	0.186
22	2.50	2908.78	15904.16	16075.14	3.27	0.212
23	2.50	2418.95	12402.04	12547.60	3.40	0.204
24	2.00	1629.50	8946.59	9074.03	3.45	0.201
25	3.00	2037.51	11435.32	11599.48	3.40	0.204
26	2.00	2577.80	13857.62	13980.29	3.26	0.212
Mean	**2.42**	**2532.39**	**13845.77**	**14065.67**	**3.52**	**0.20**
SD	0.78	688.49	2737.93	2754.49	0.34	0.02
% CV	32.33	27.19	19.77	19.58	9.67	8.80
Maximum	4.00	4700.28	20036.76	20349.27	4.54	0.23
Minimum	1.00	1401.22	8946.59	9074.03	3.00	0.15
Max-Min	3.00	3299.06	11090.17	11275.24	1.54	0.08
Median	**2.25**					

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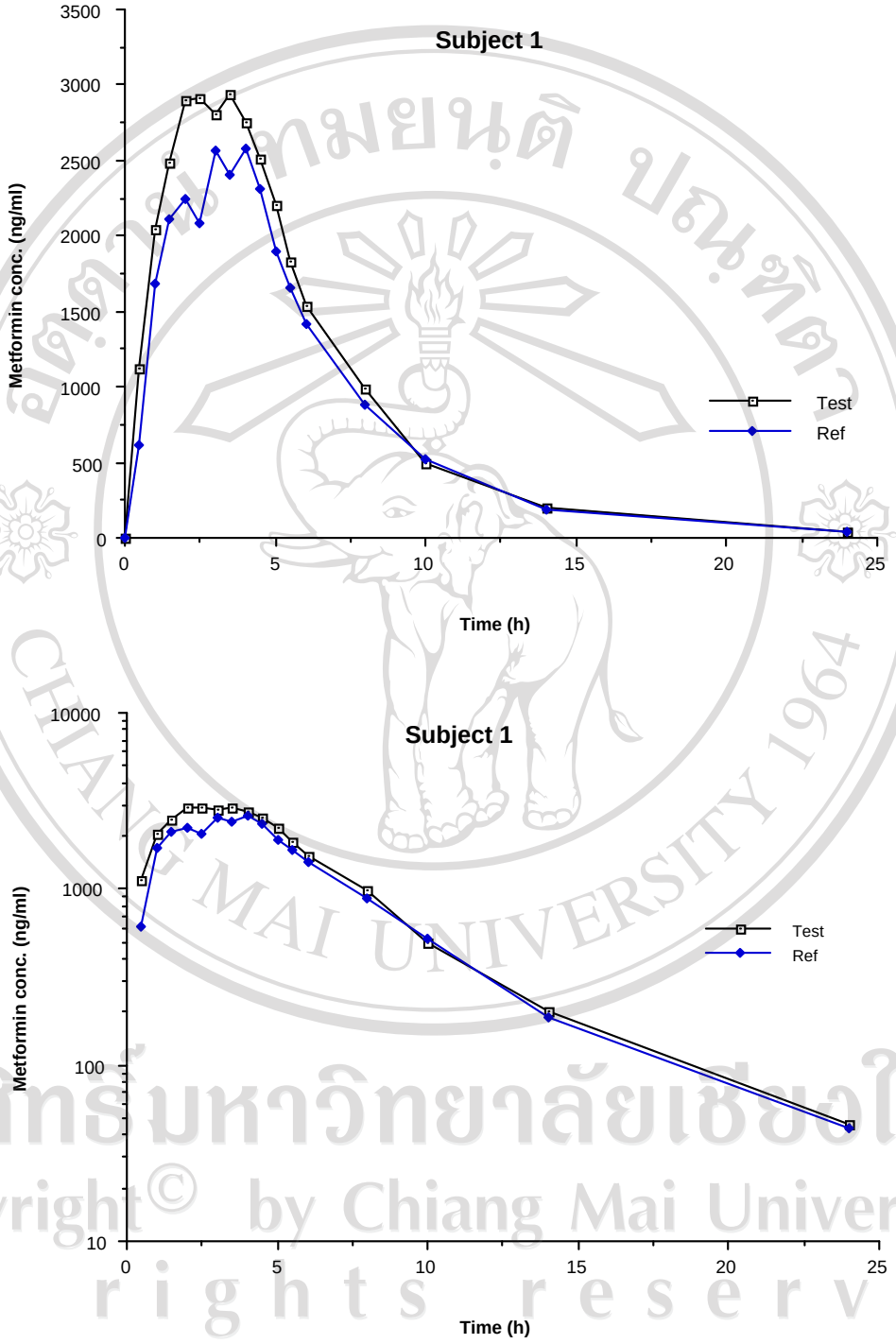

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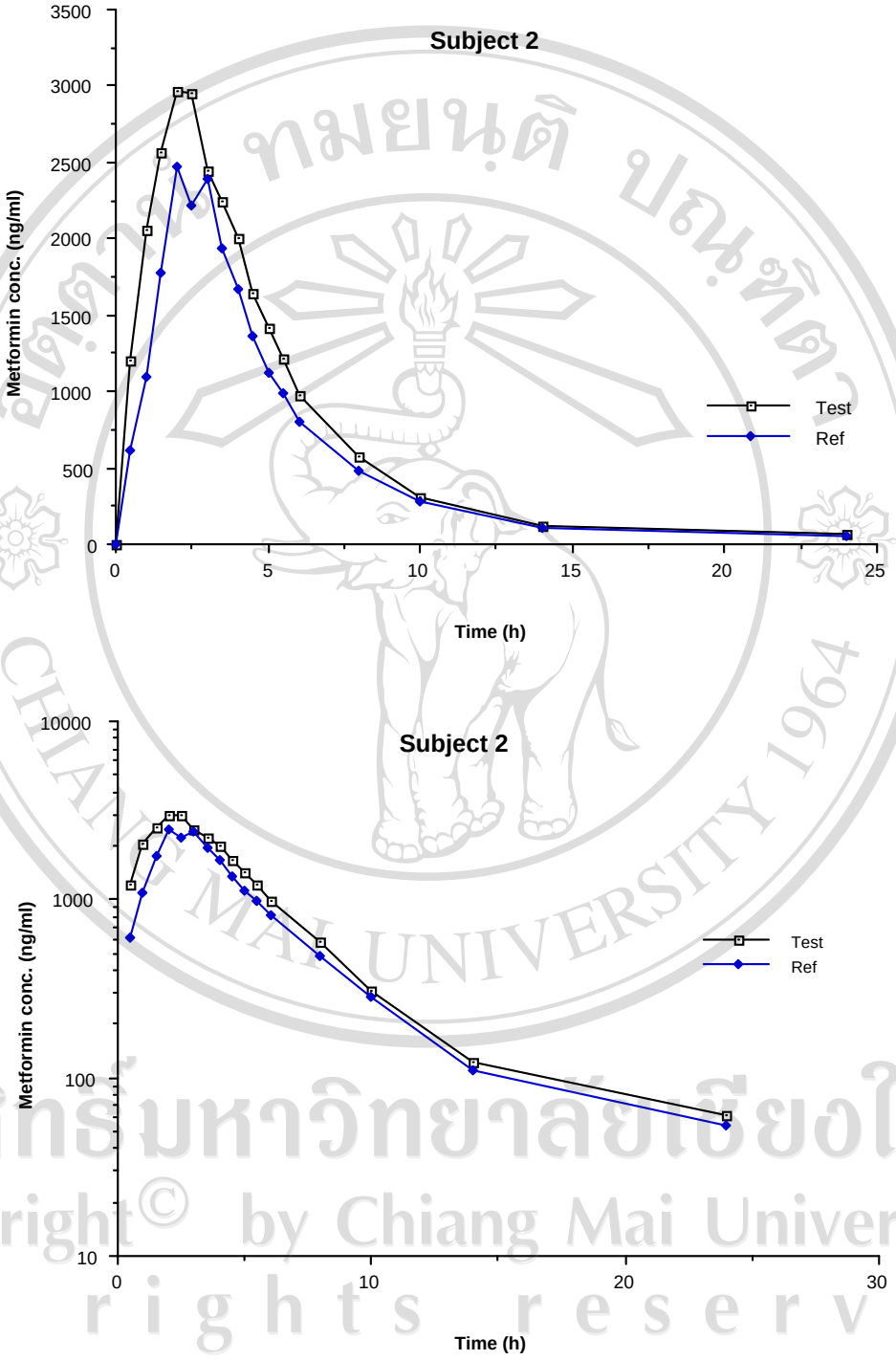
Figure 3 Pairwise plasma concentration-time profiles after single oral dose of 850 mg metformin HCl of the test and the reference products.



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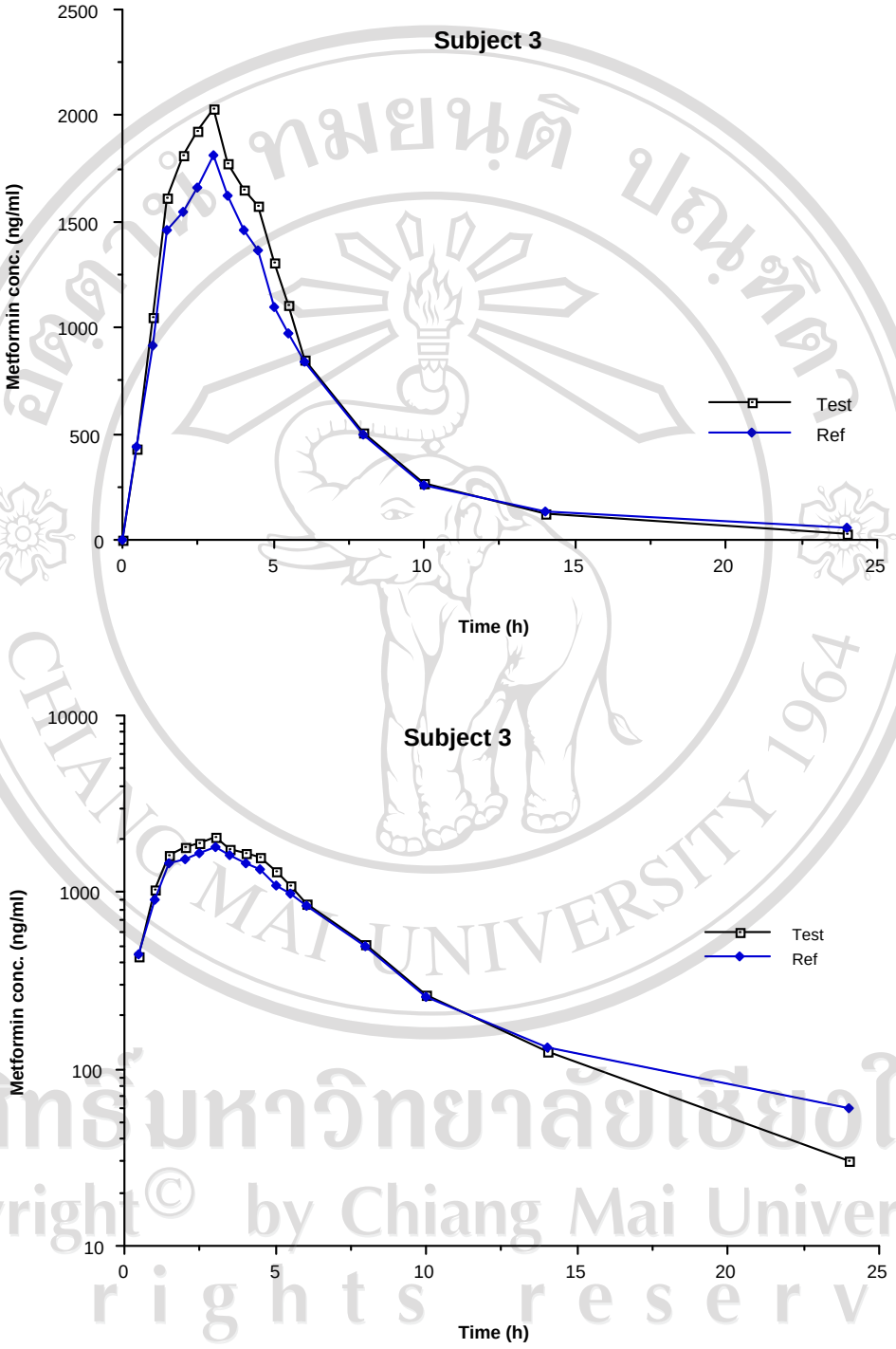

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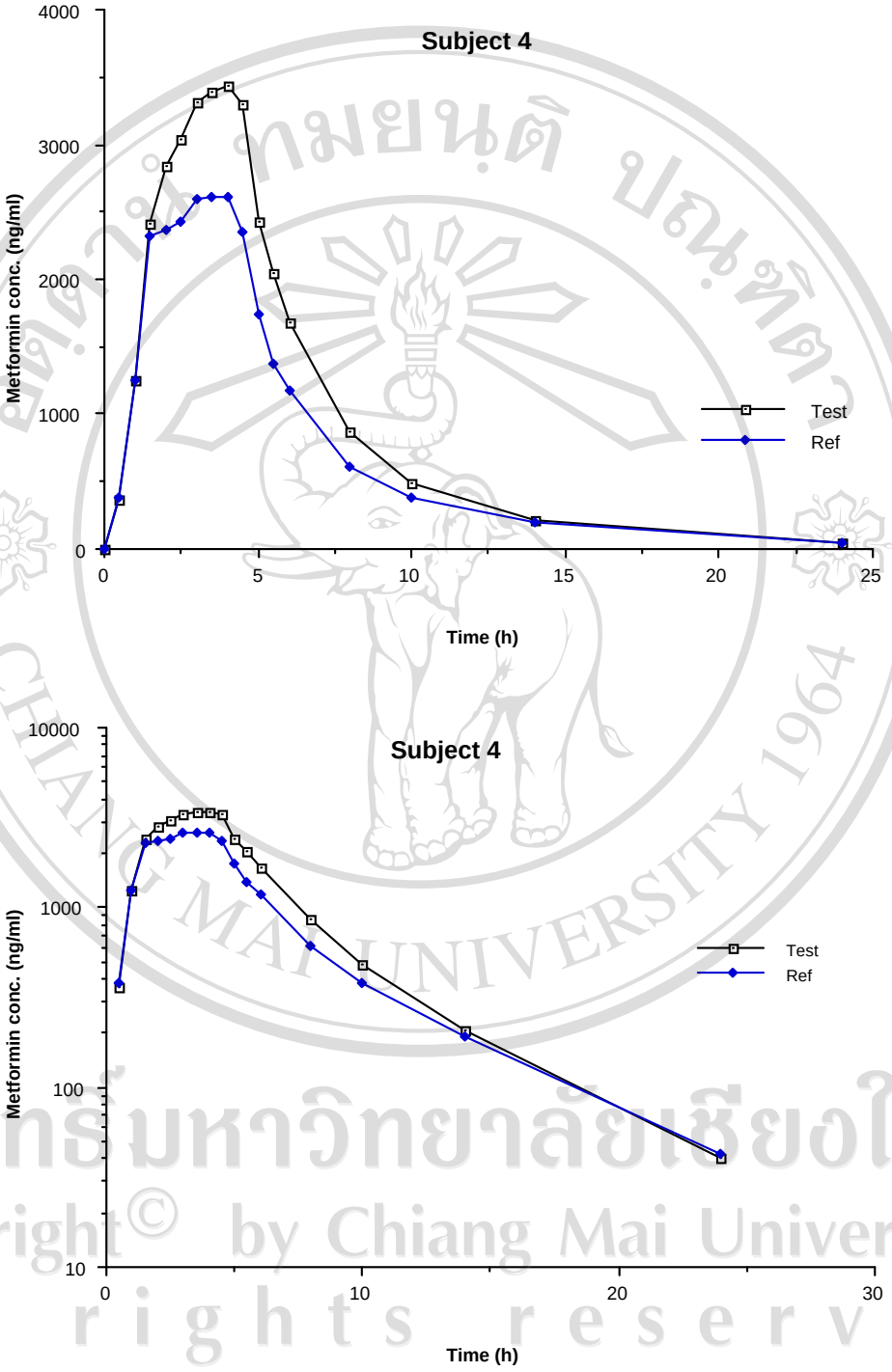

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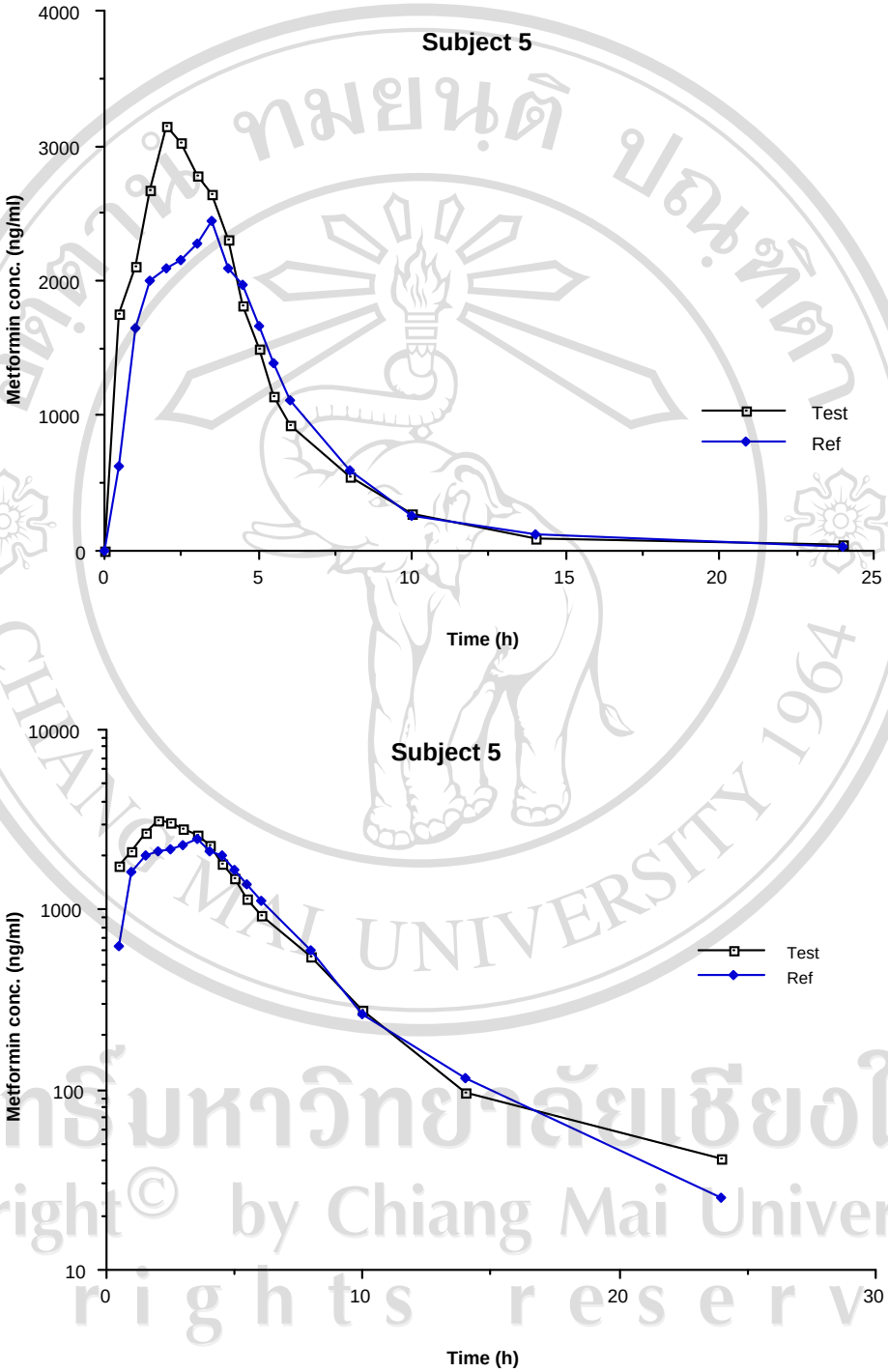

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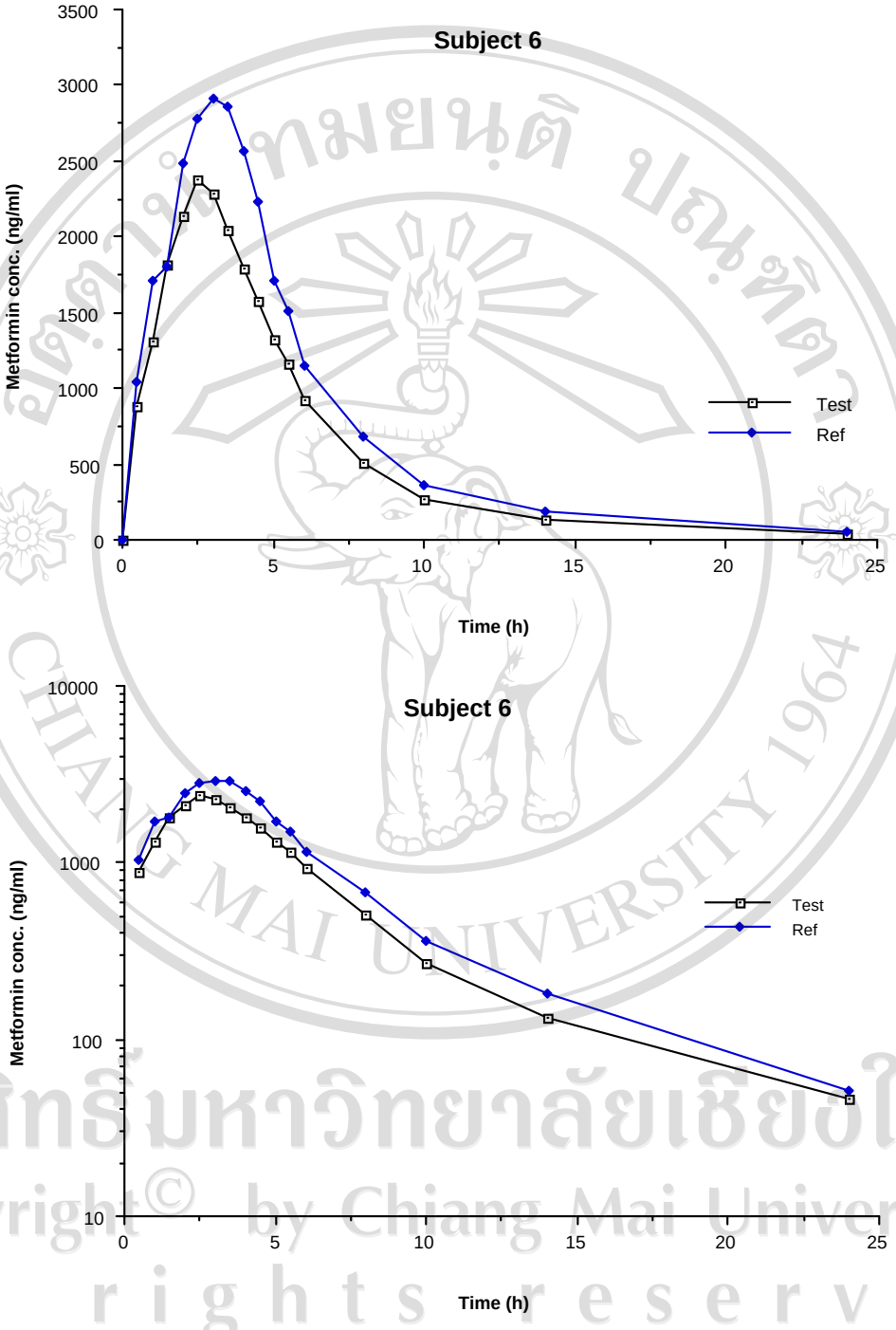

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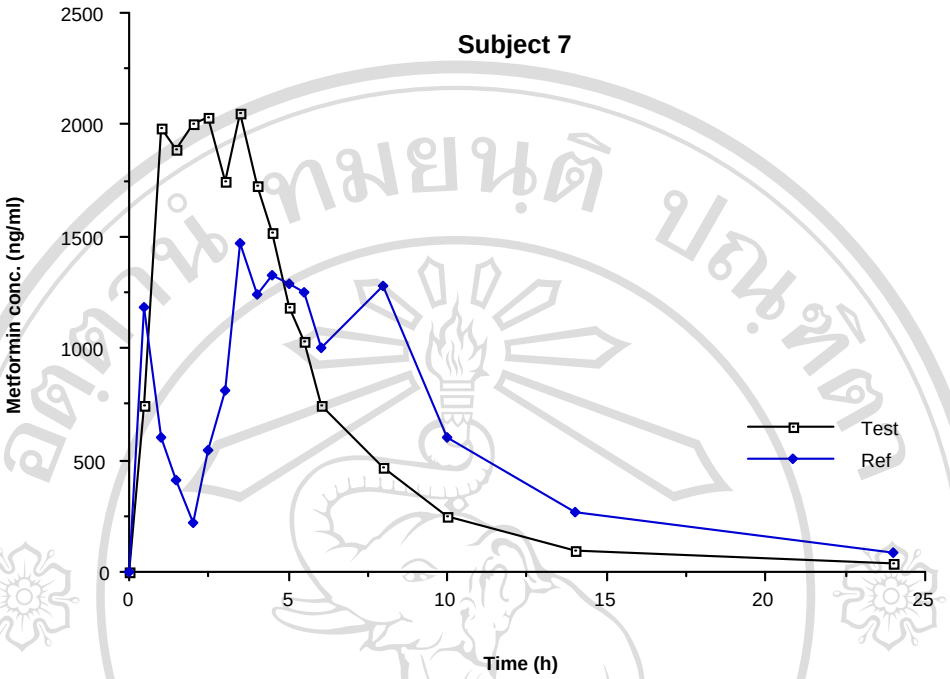

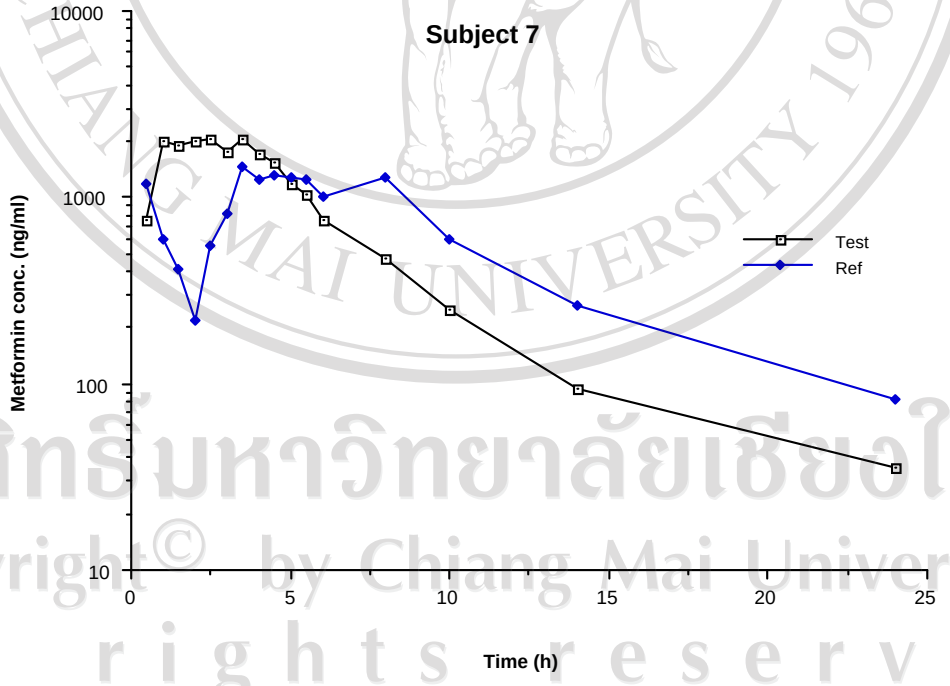

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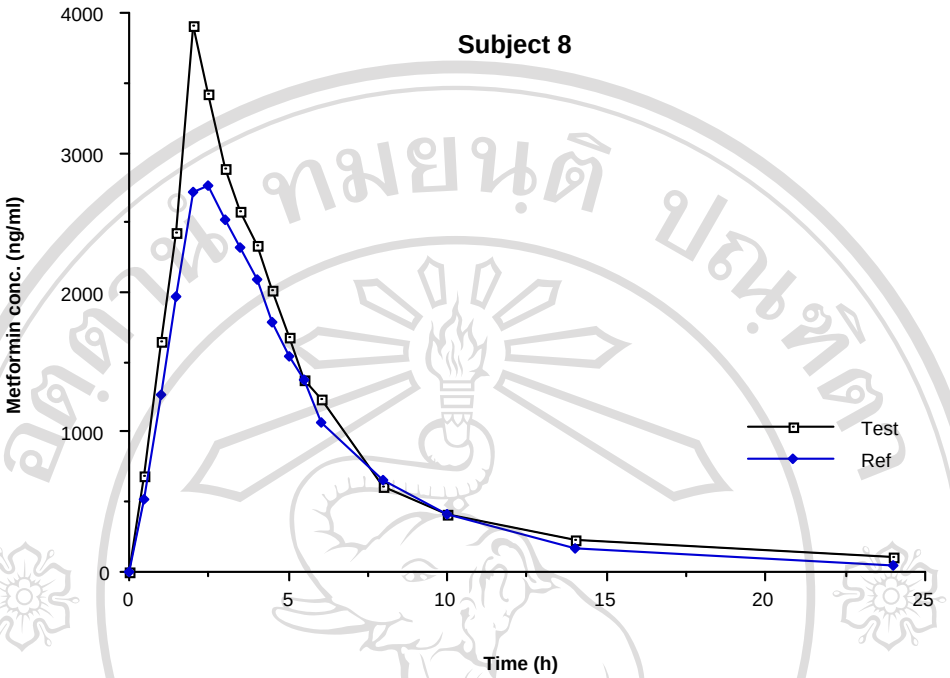

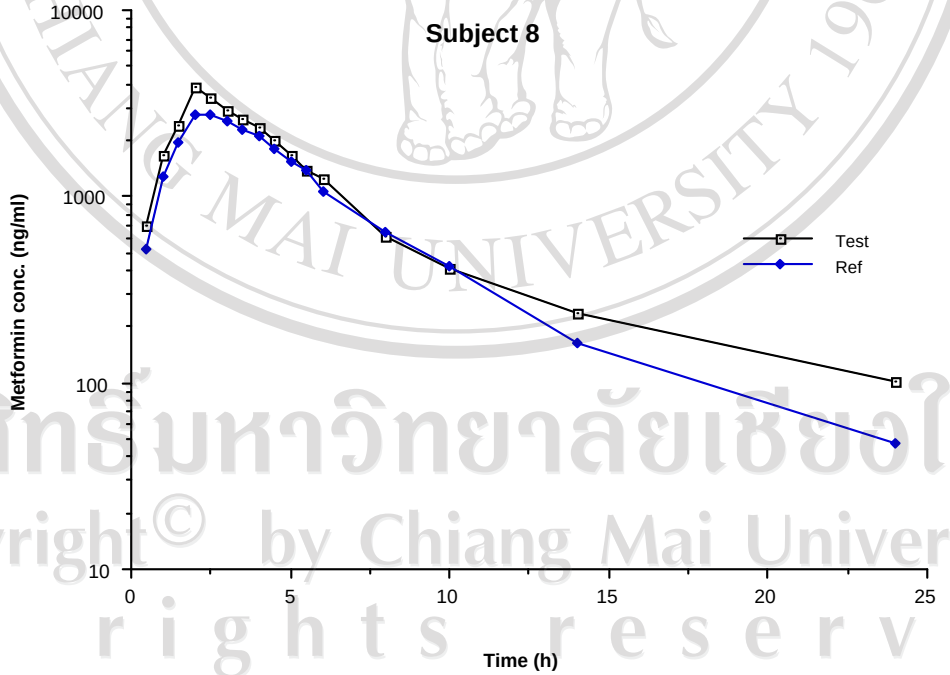

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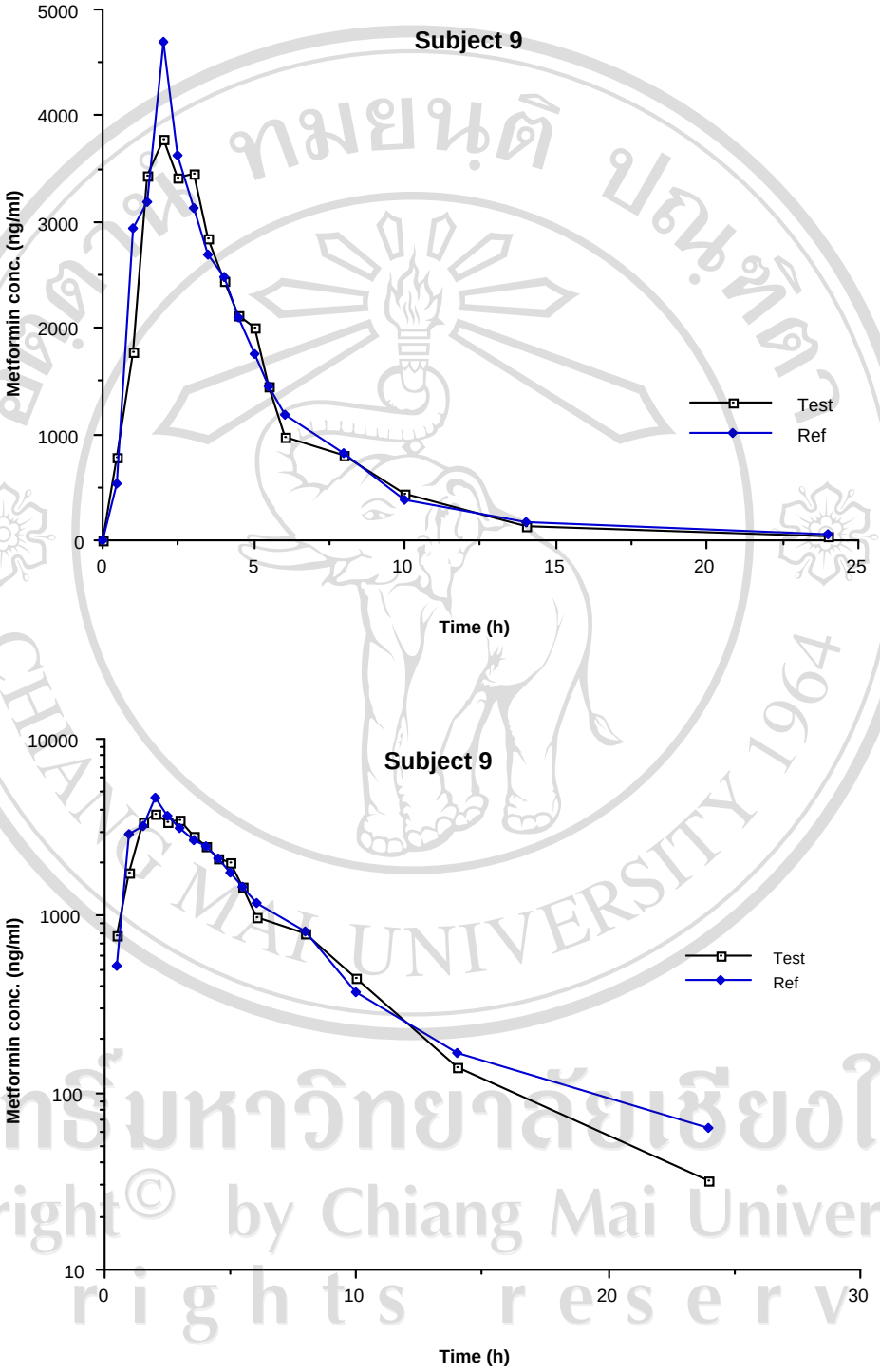

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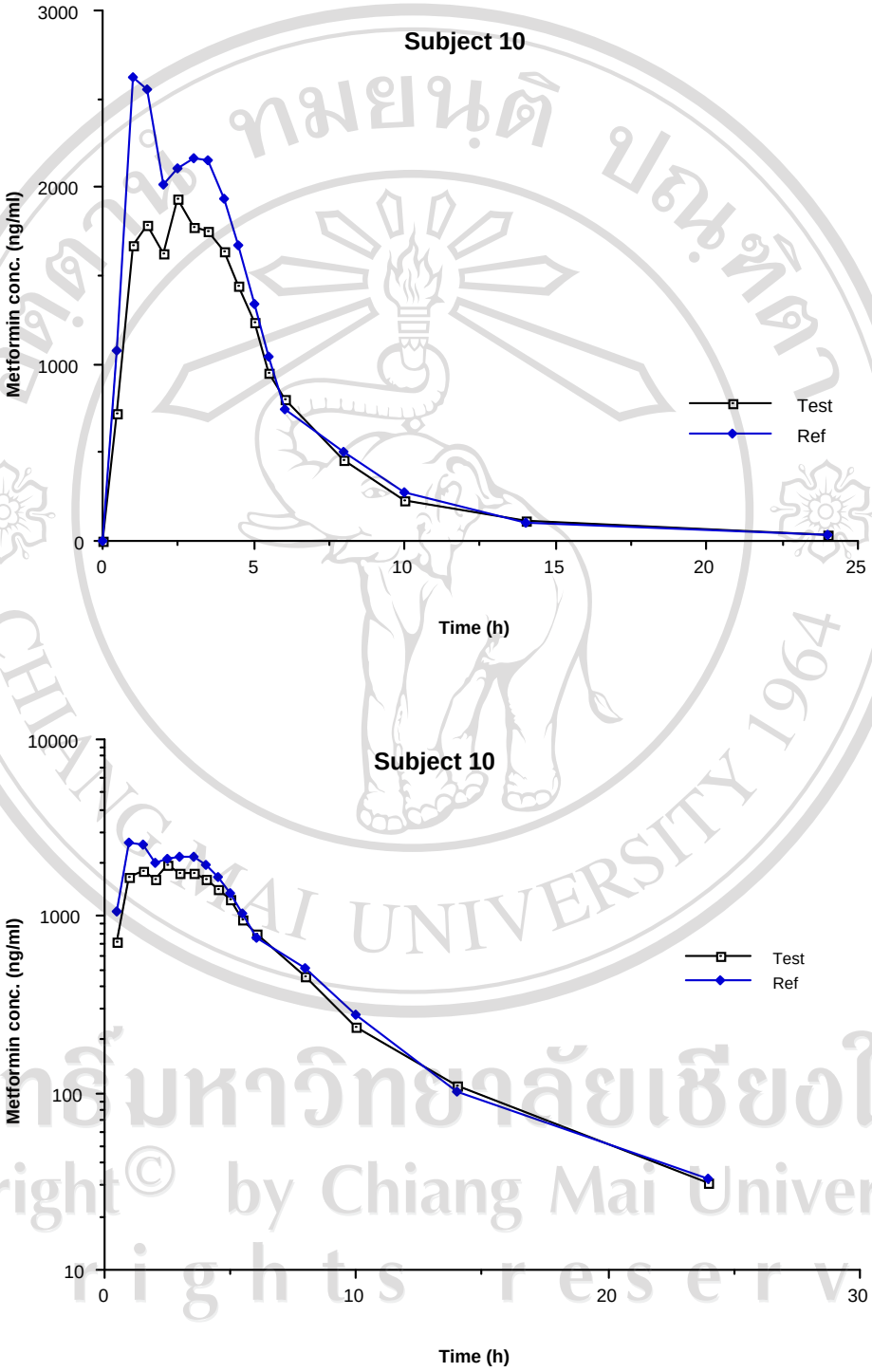

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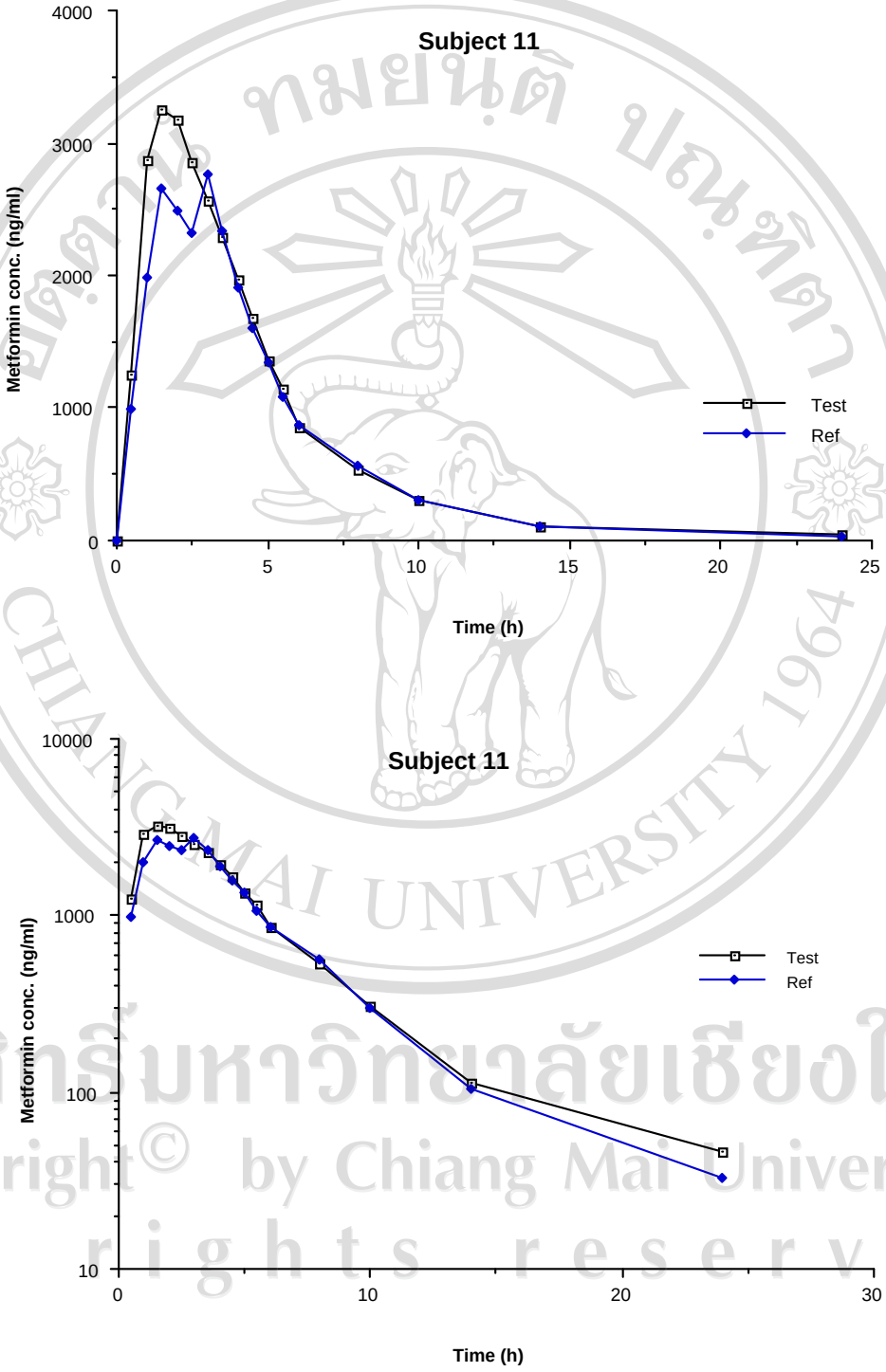

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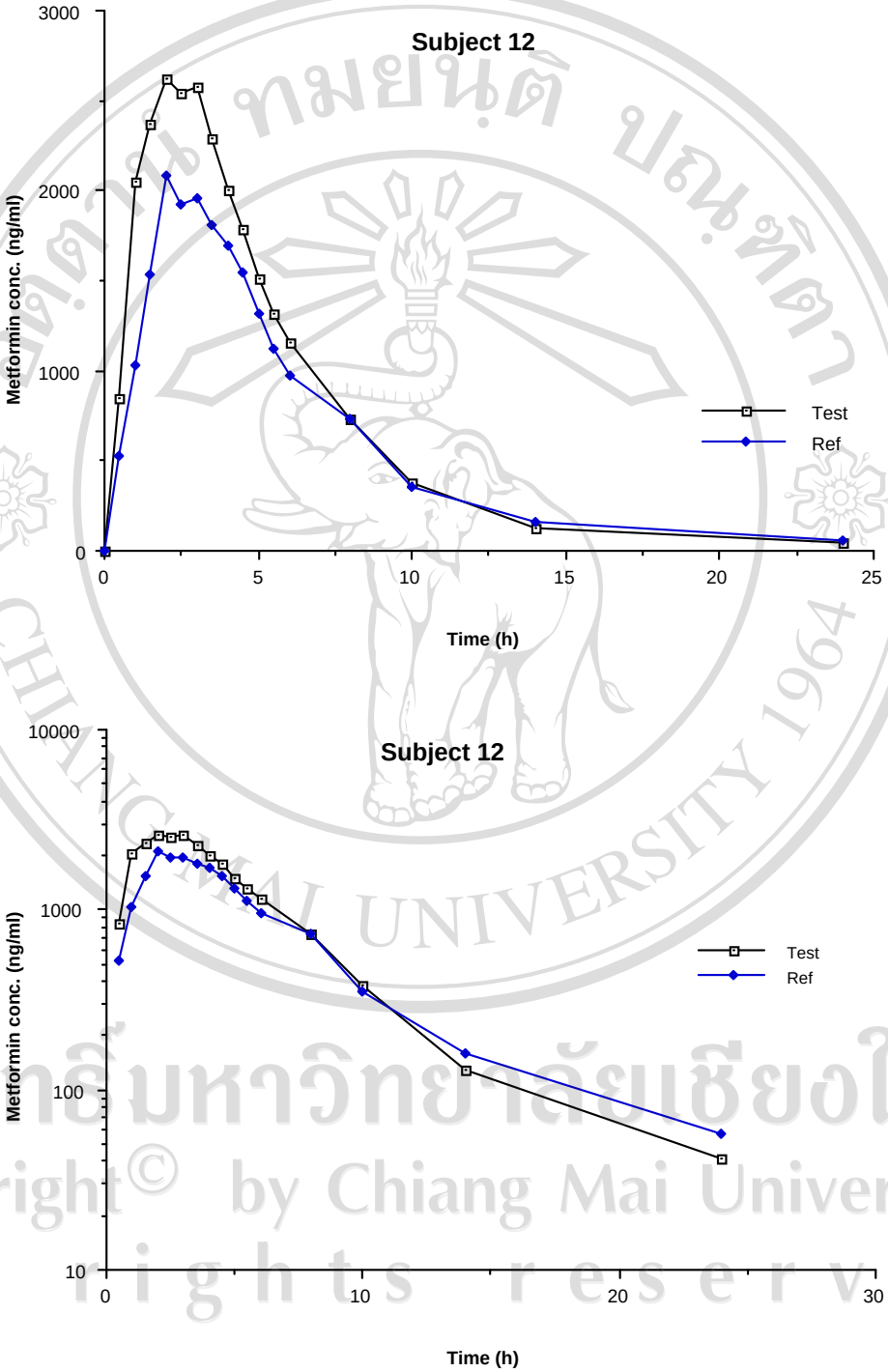

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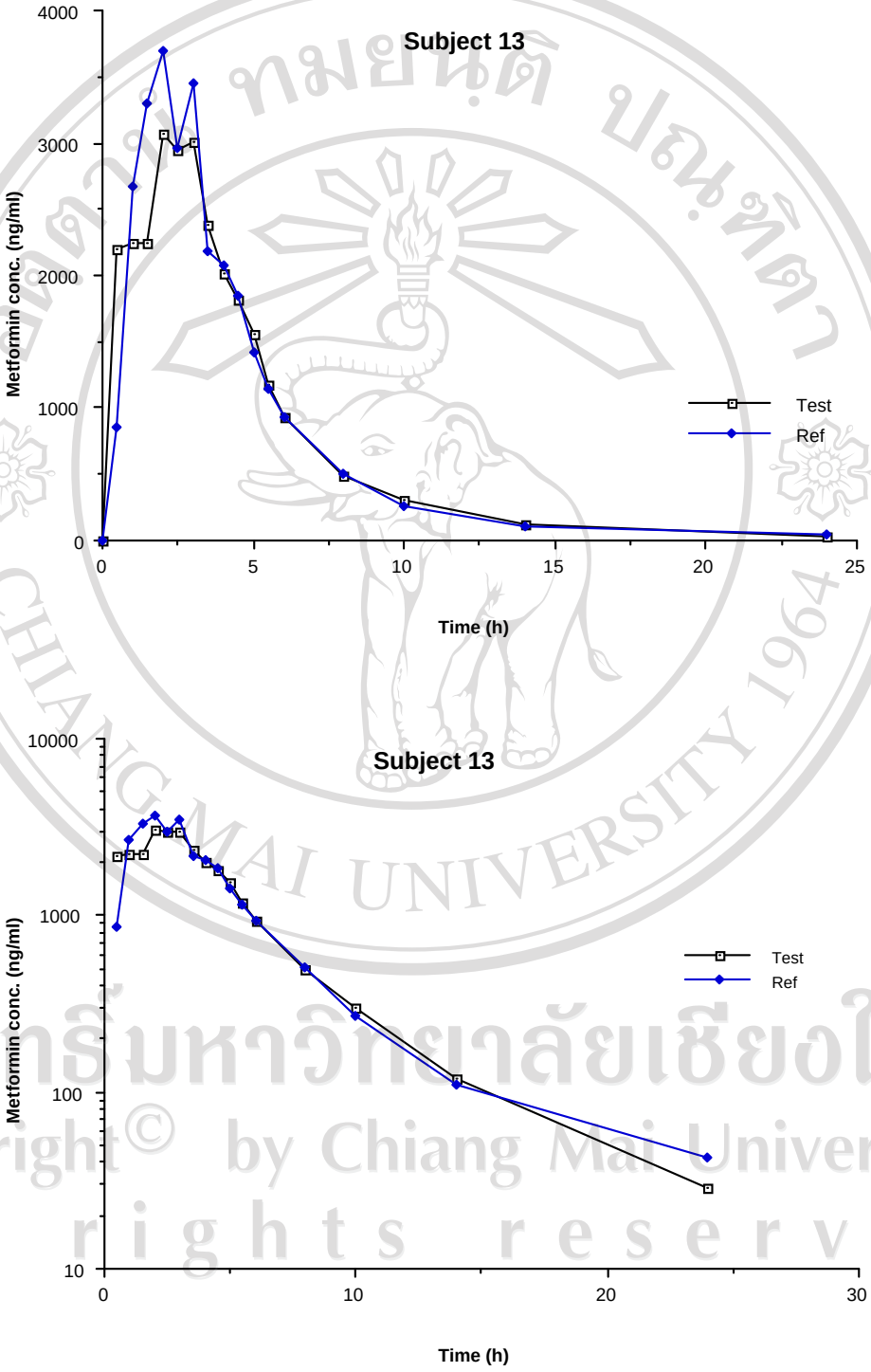

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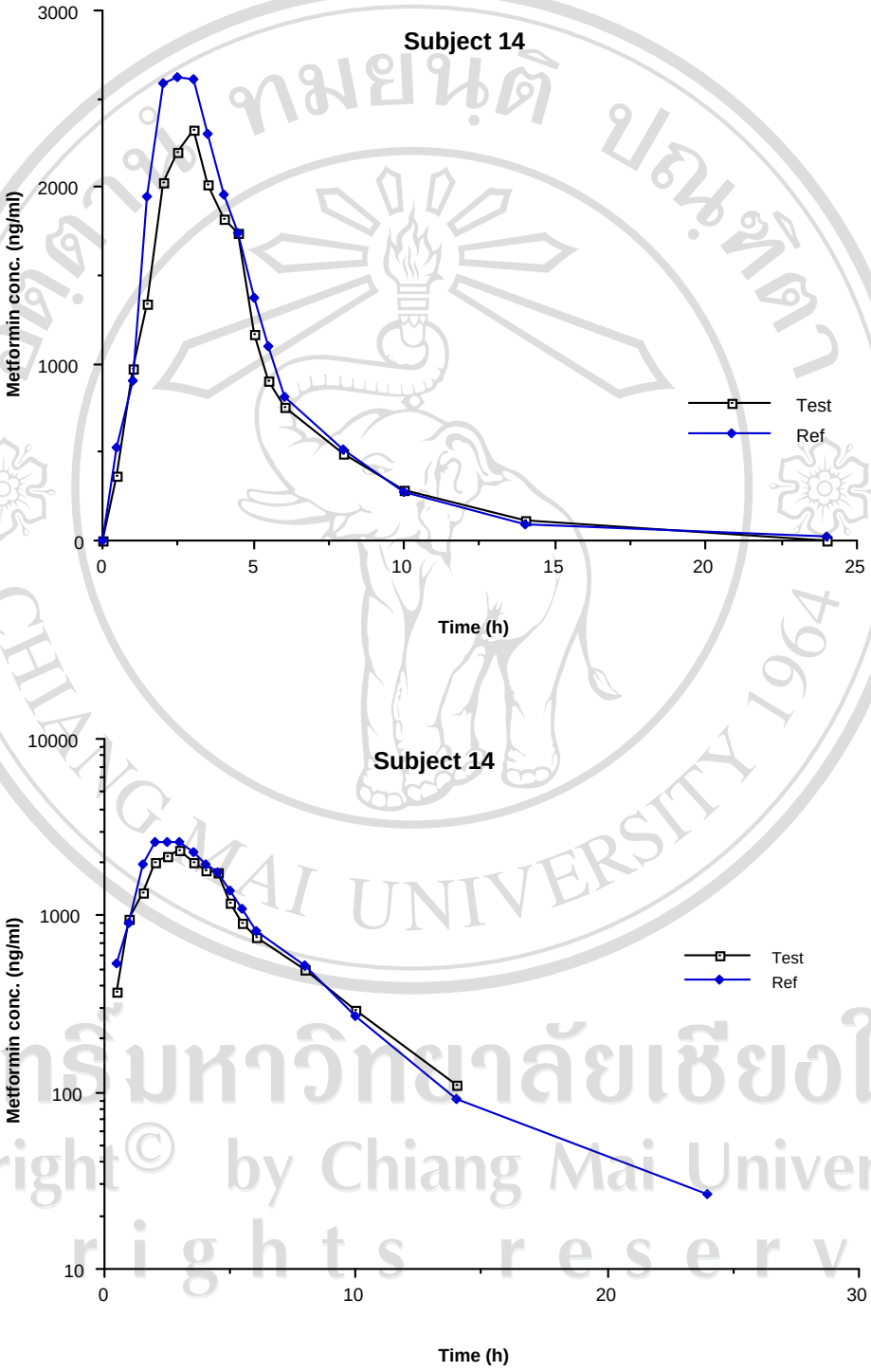

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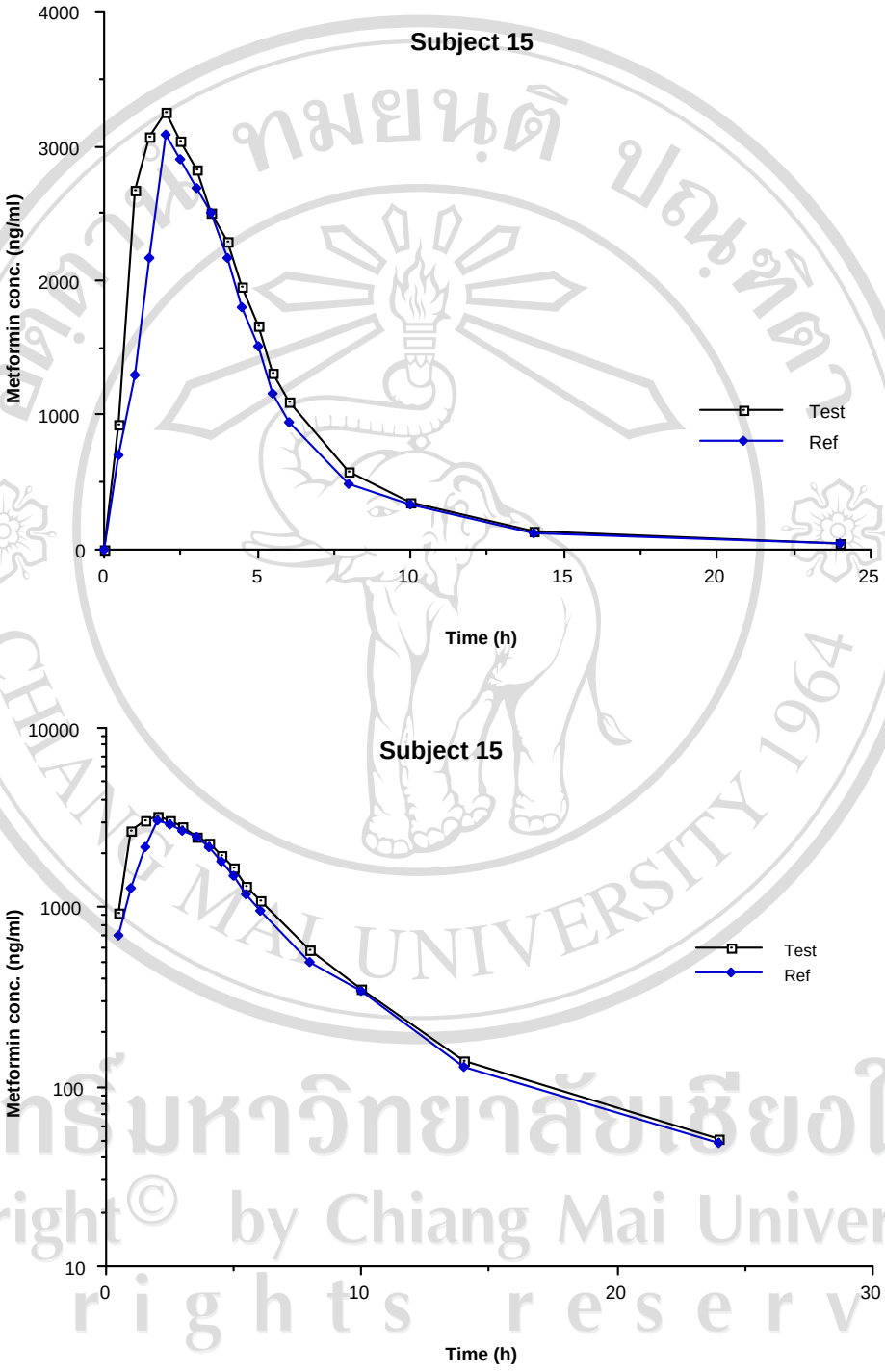

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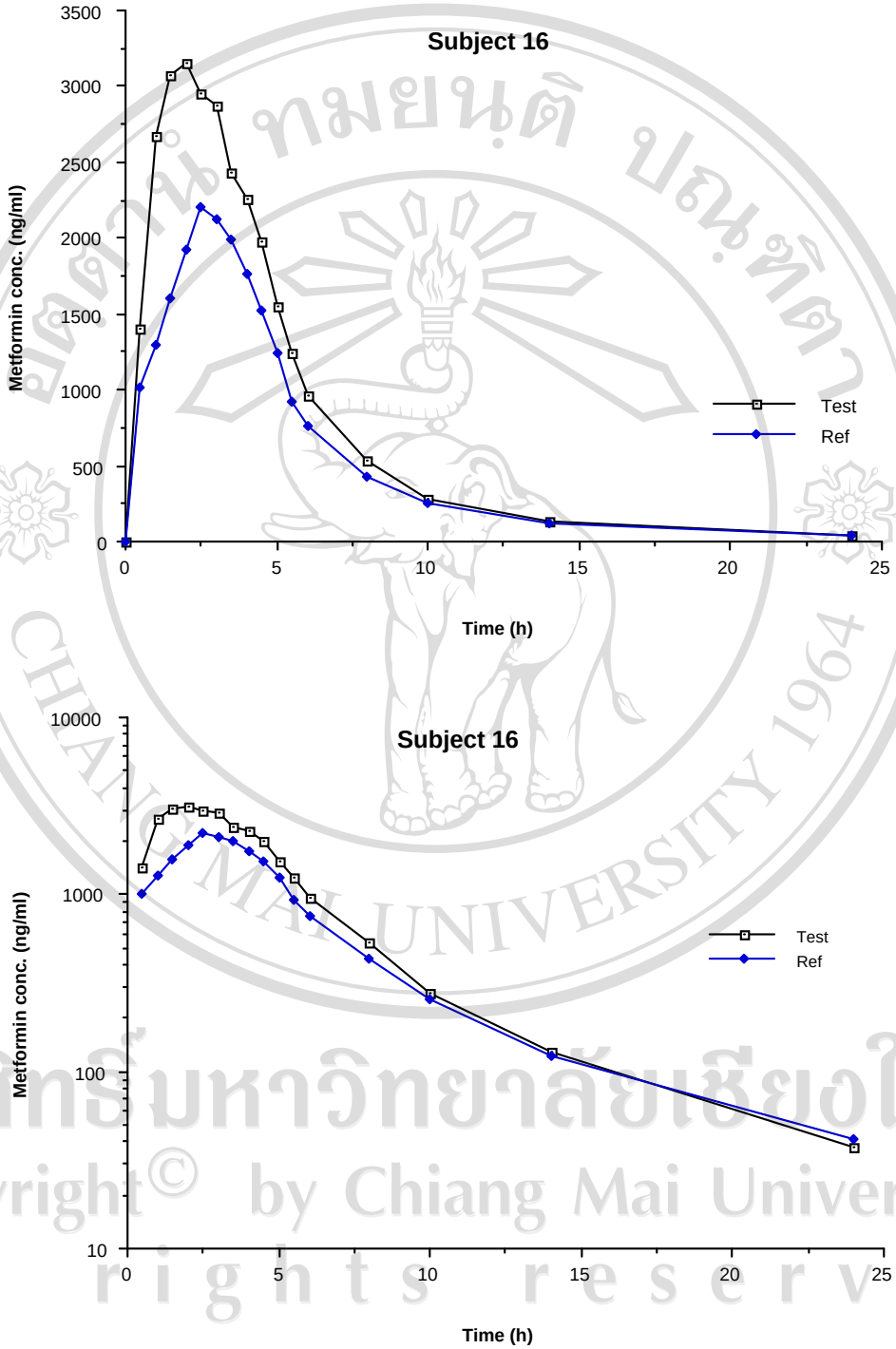

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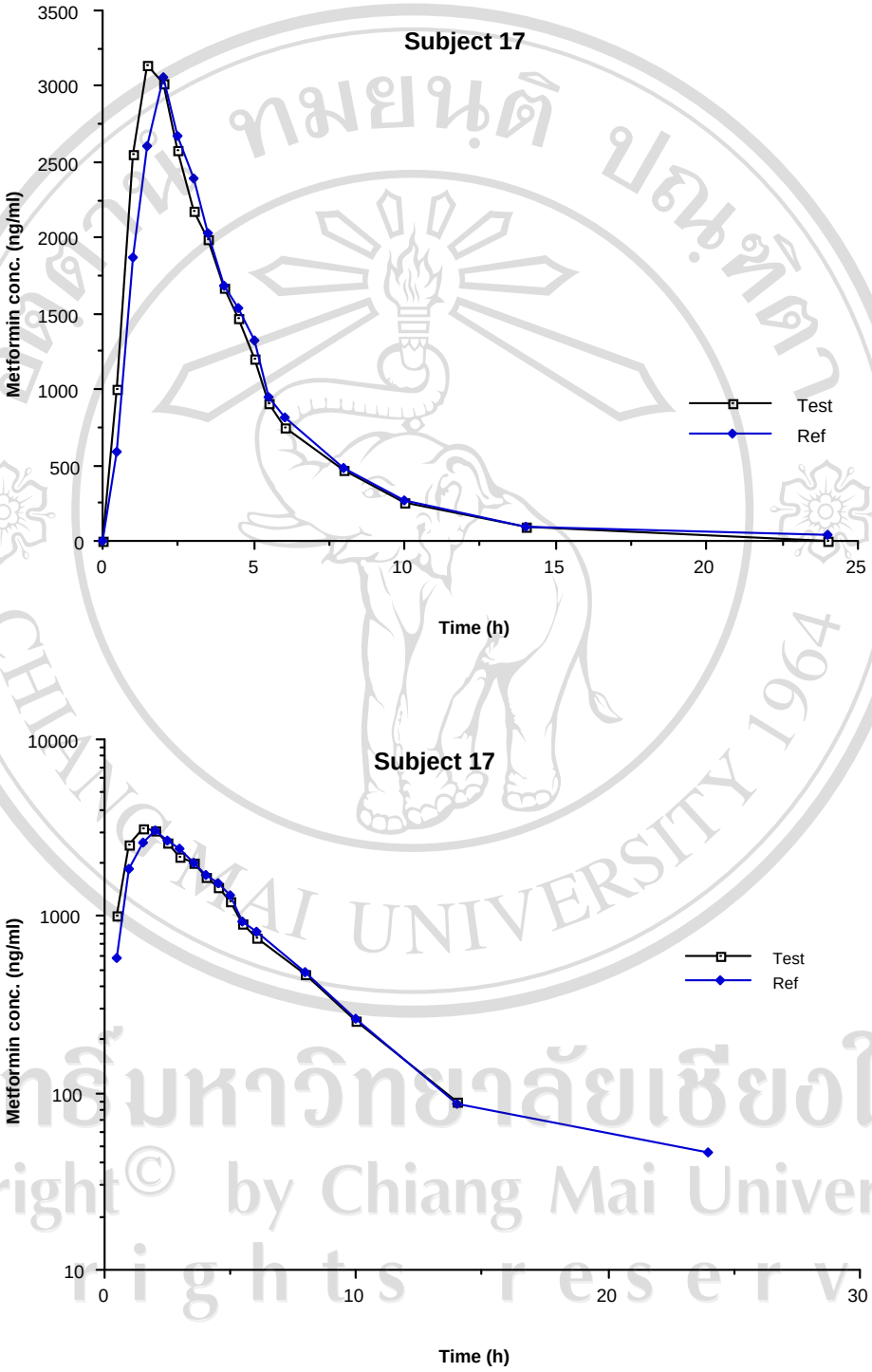

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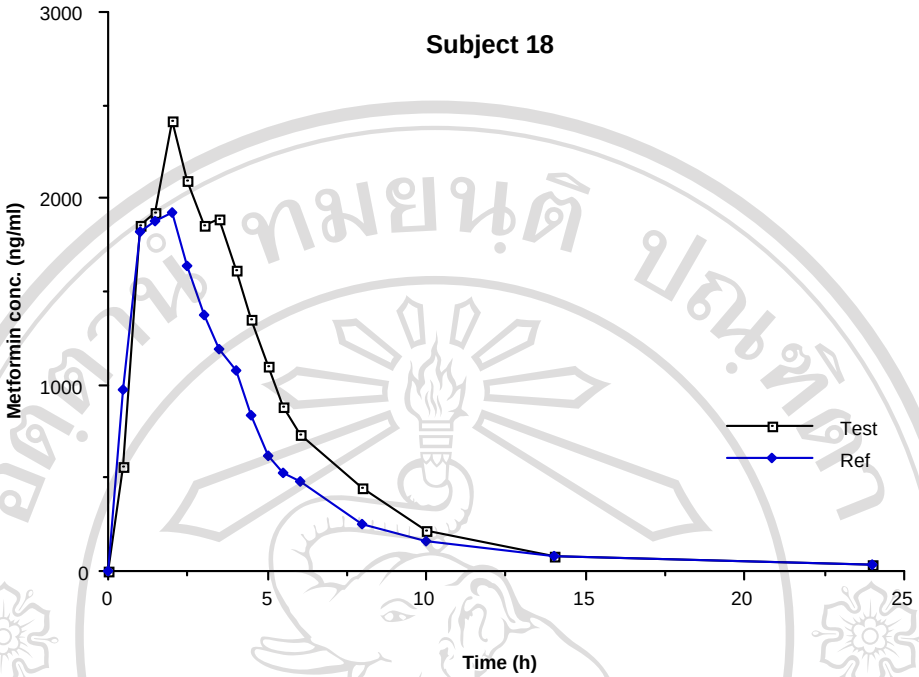

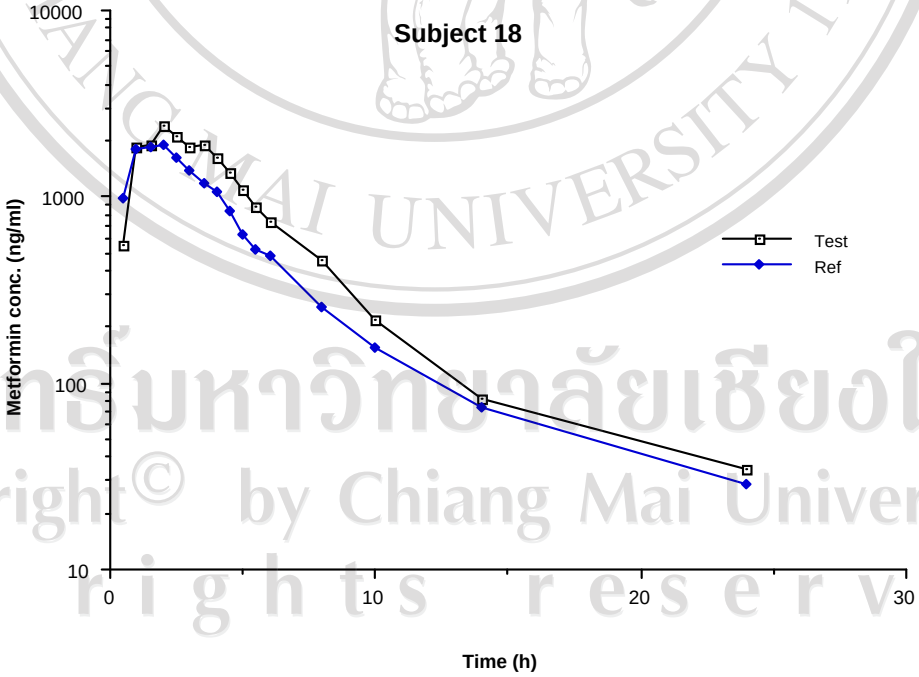

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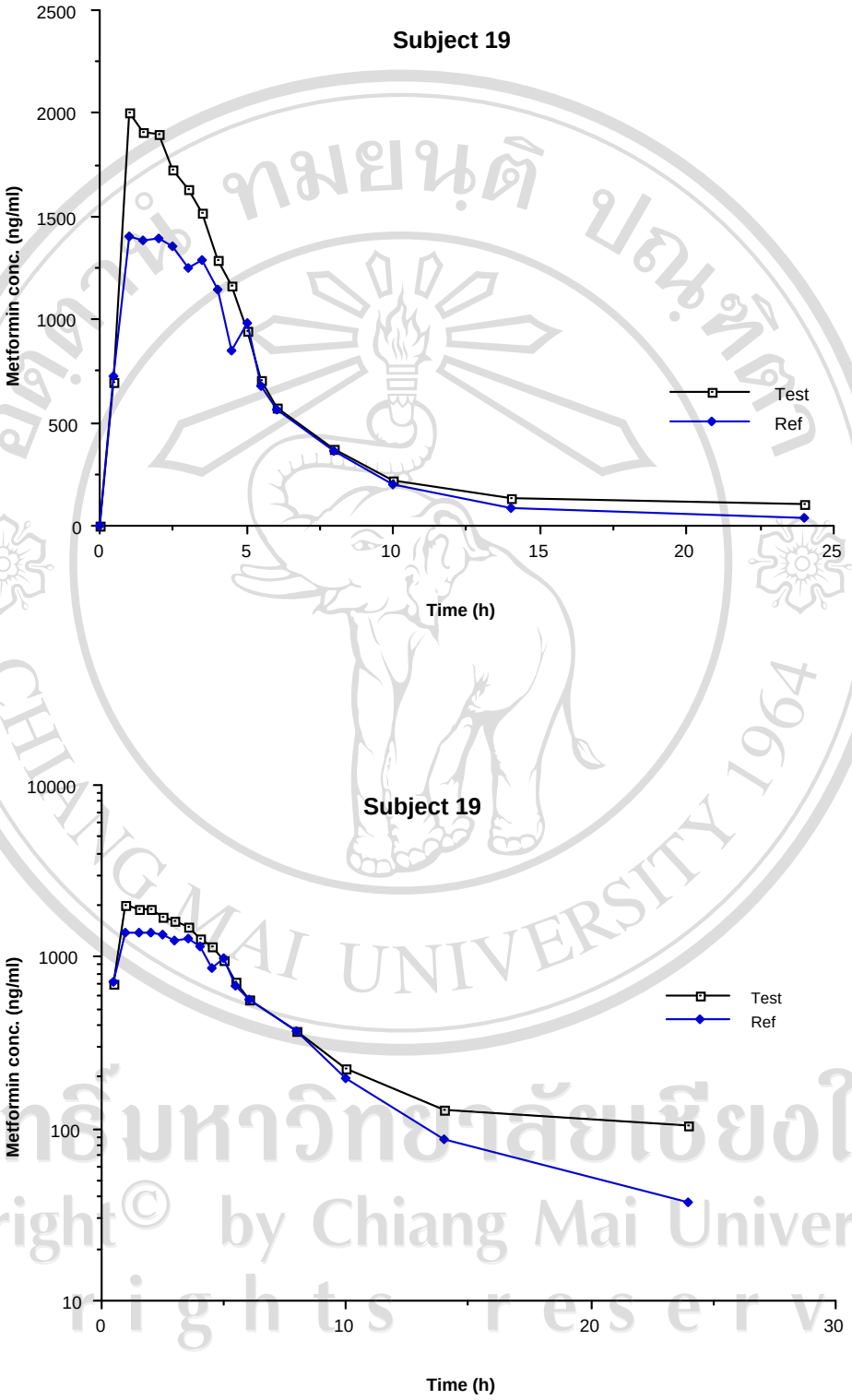

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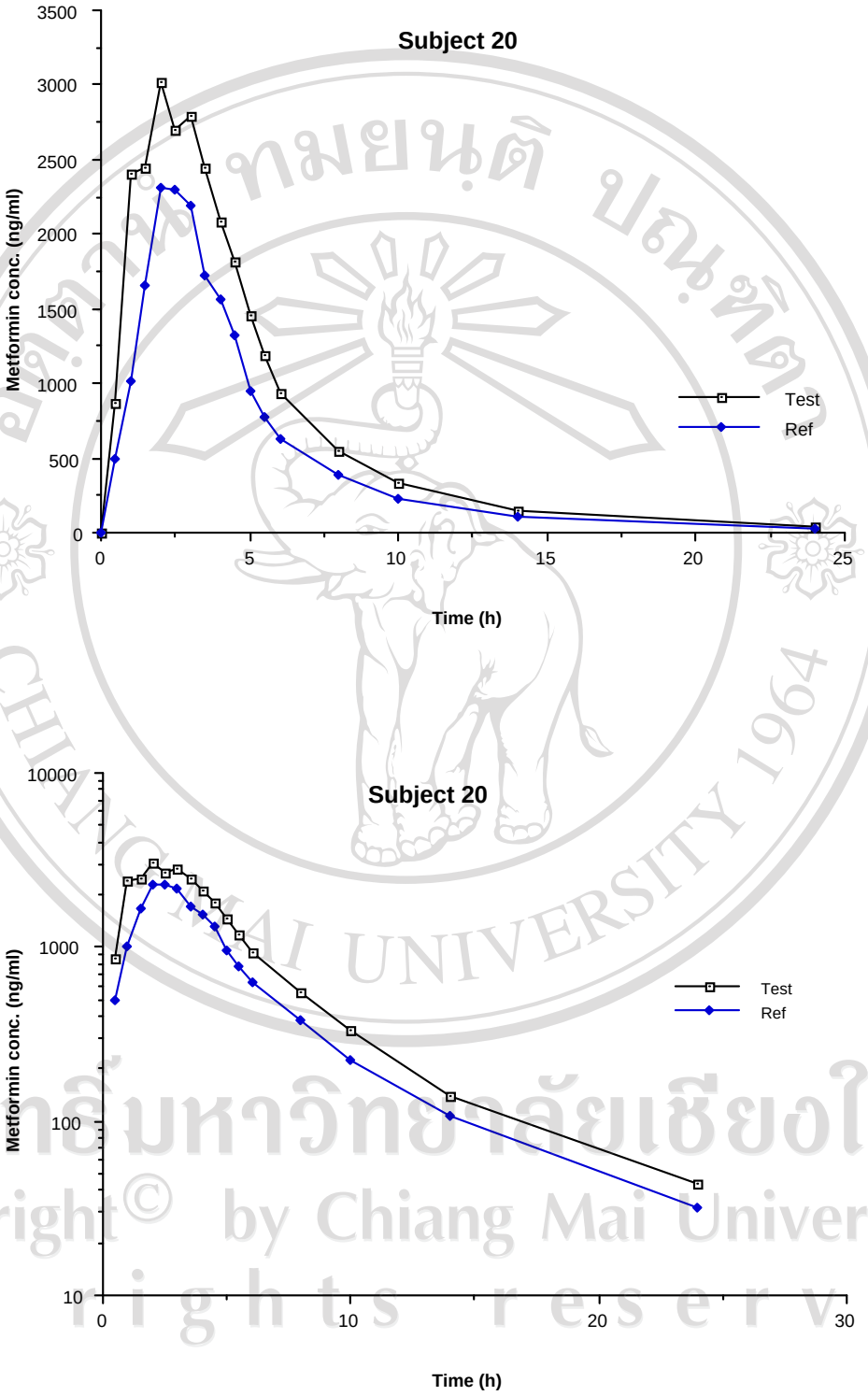

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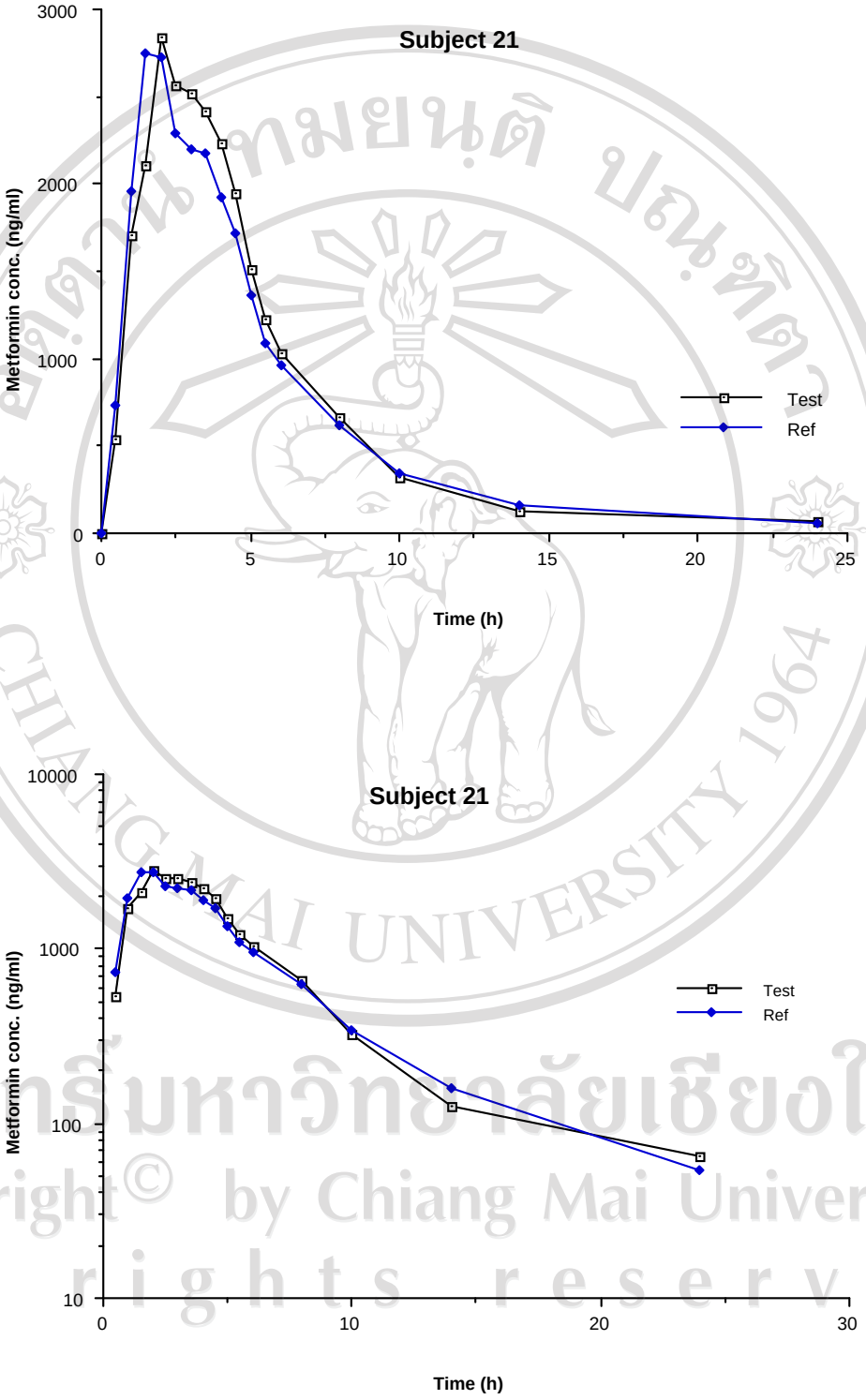

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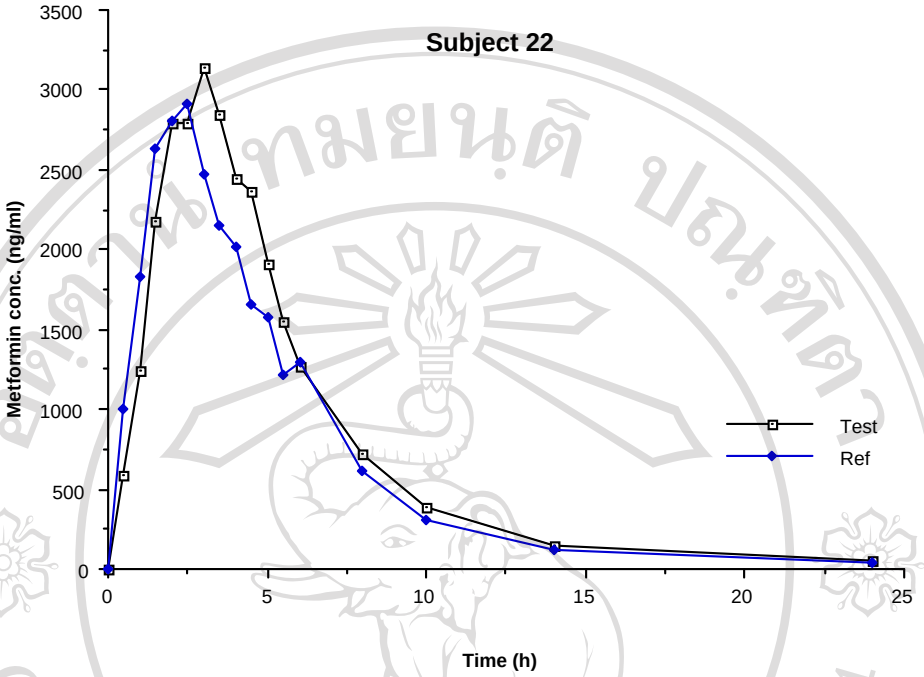

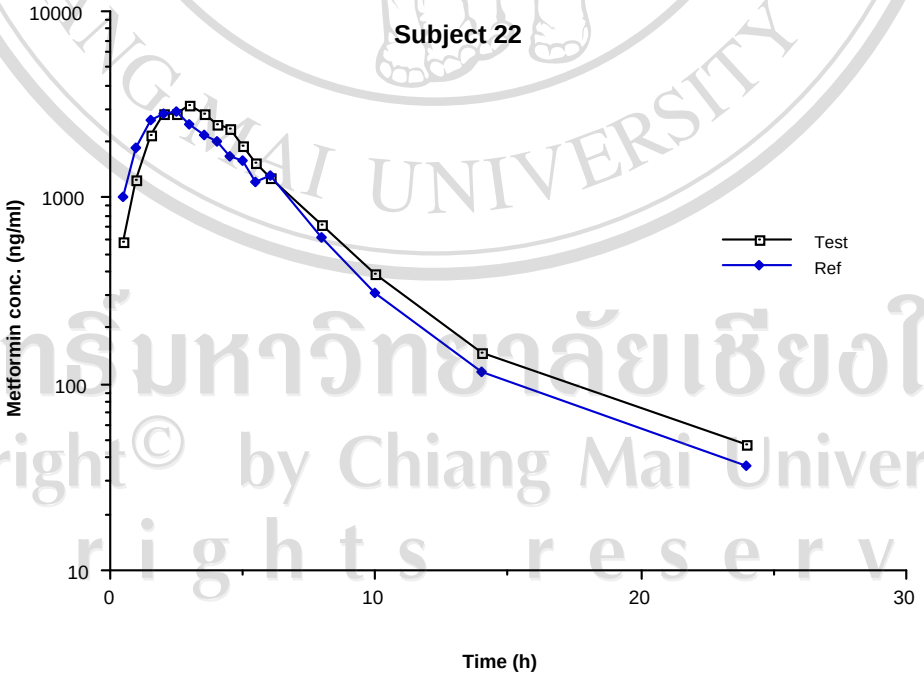

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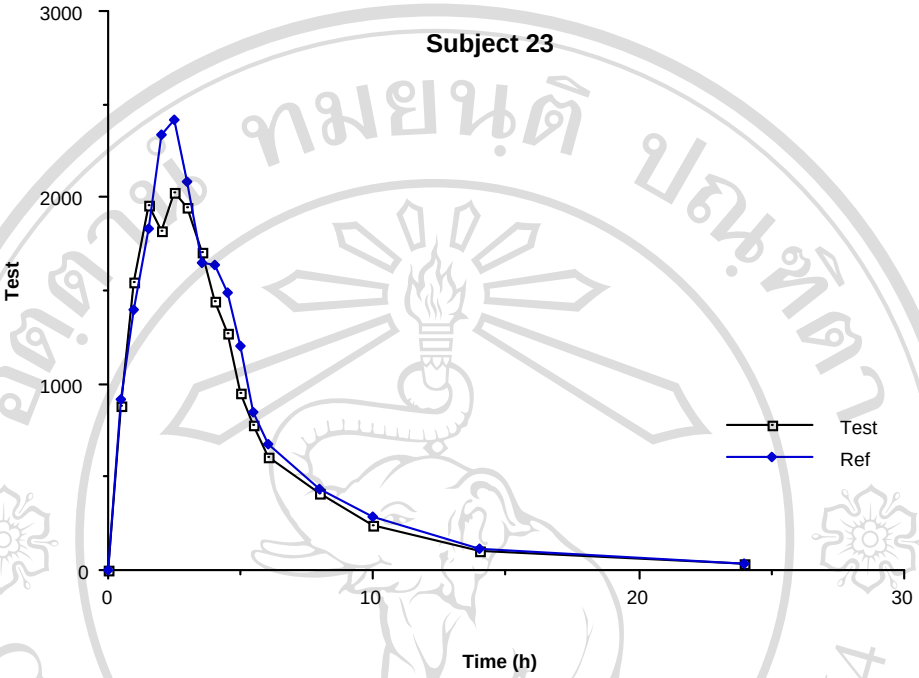

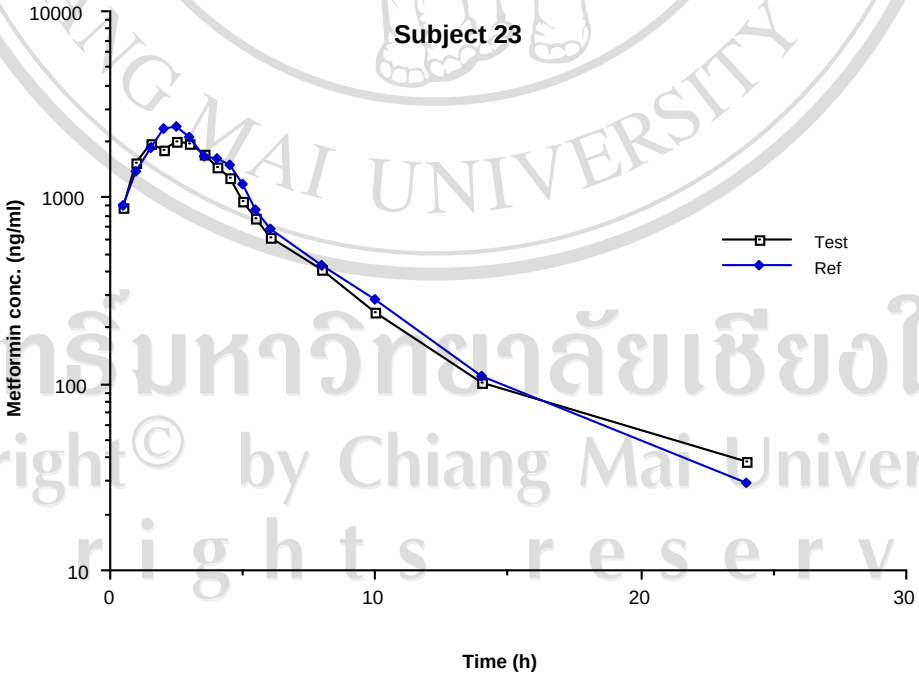

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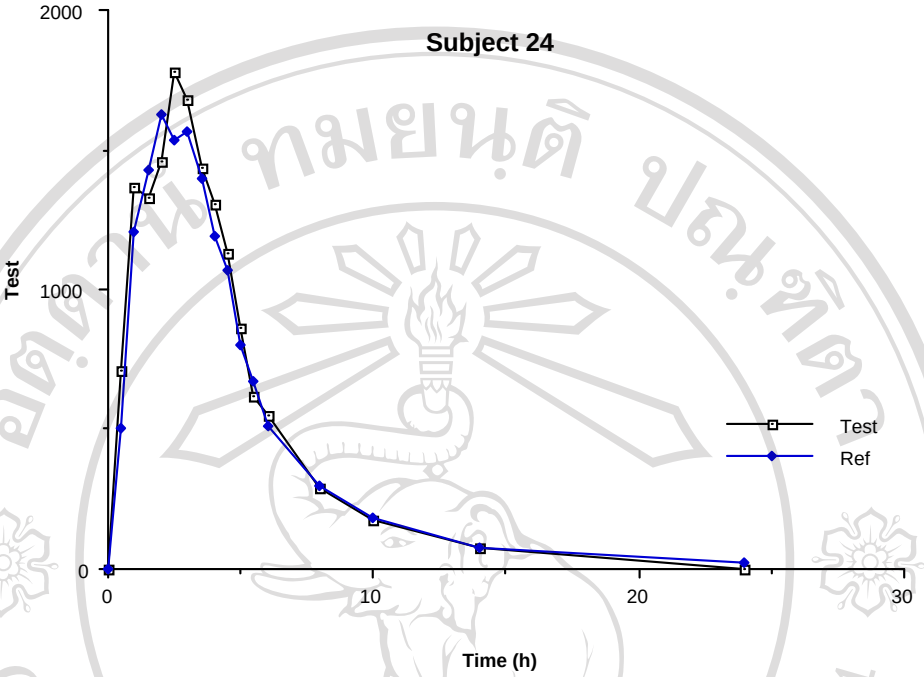

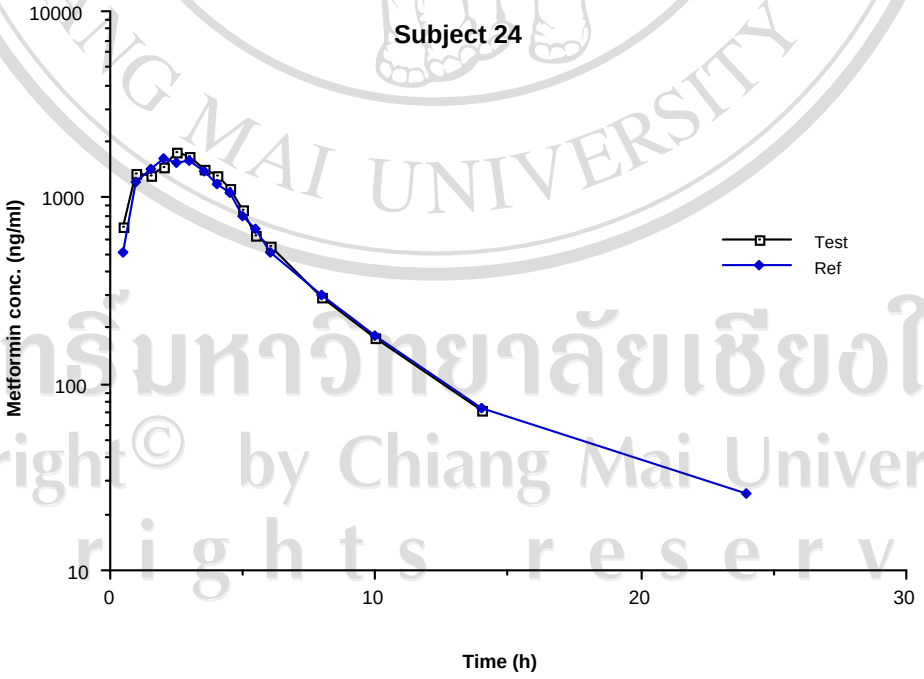

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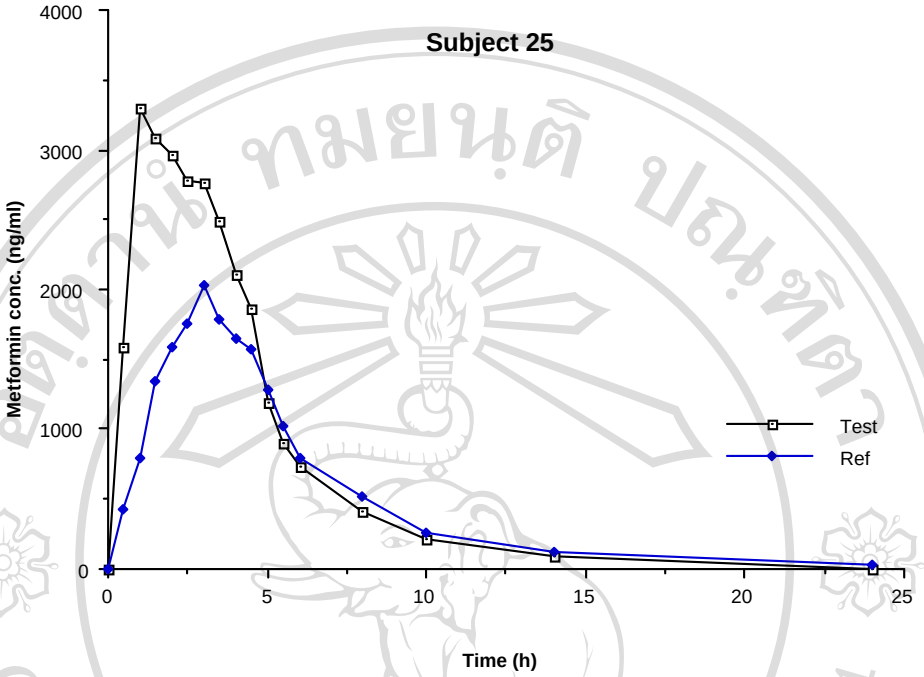

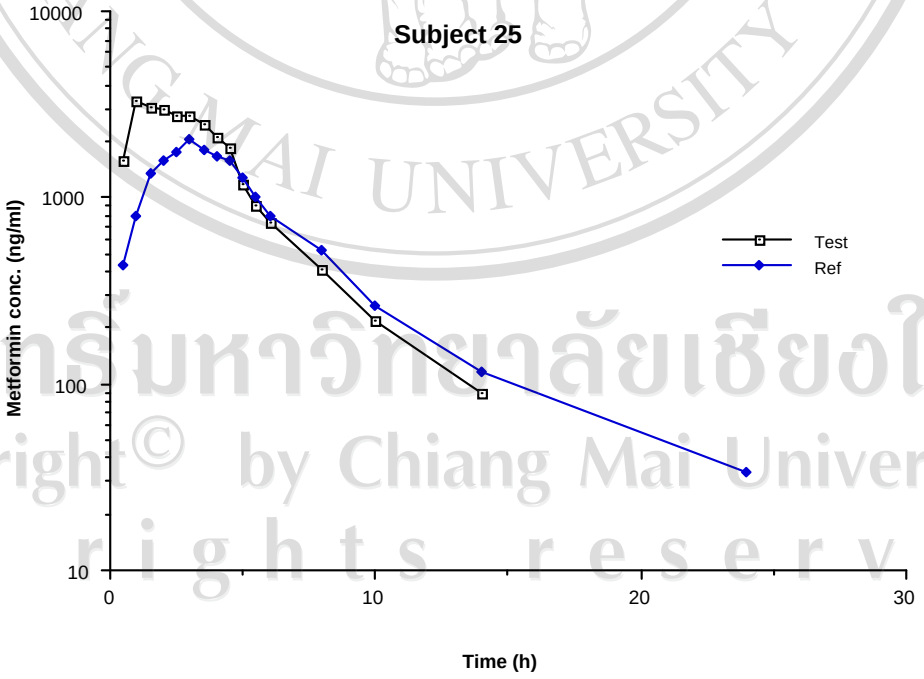

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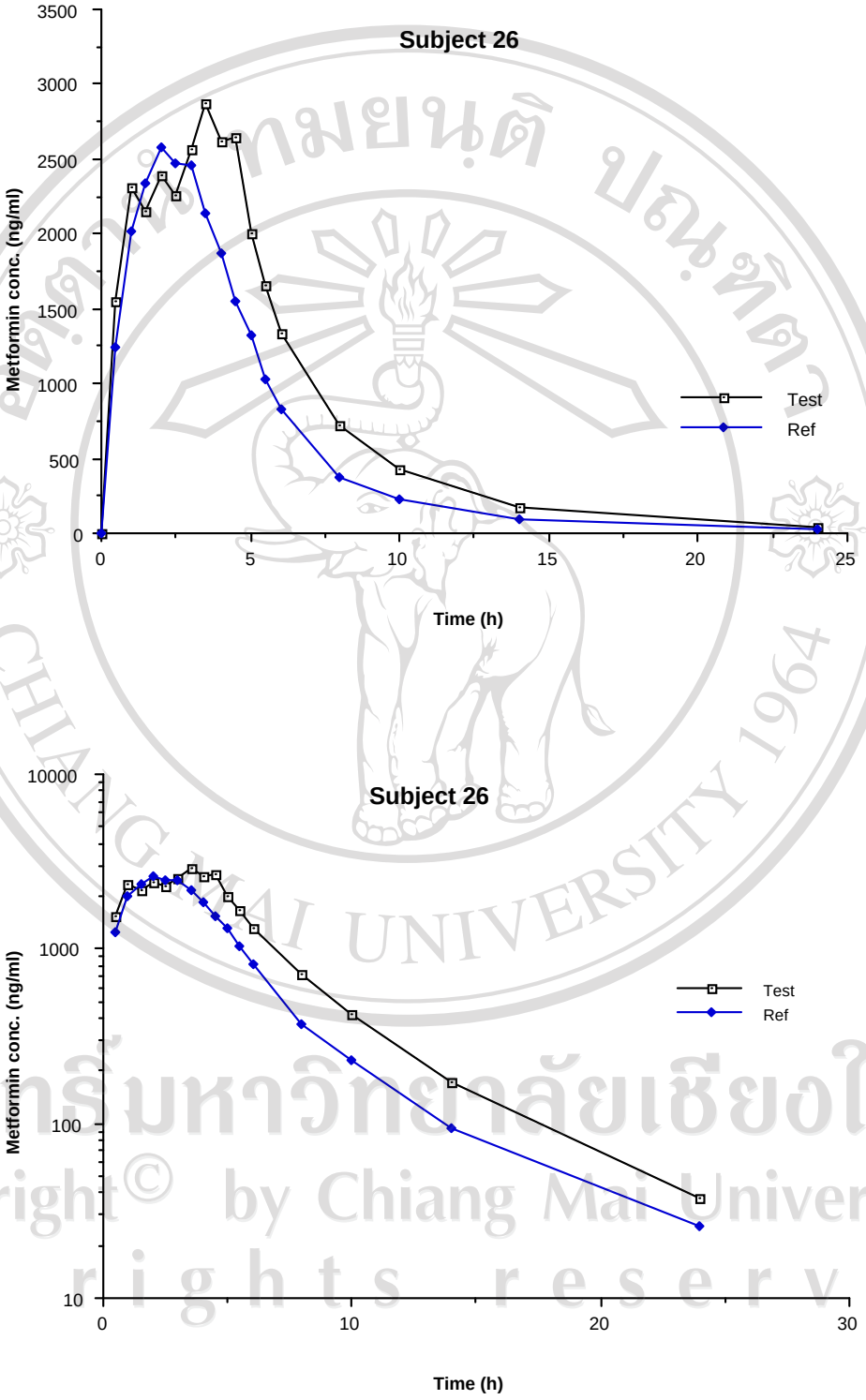

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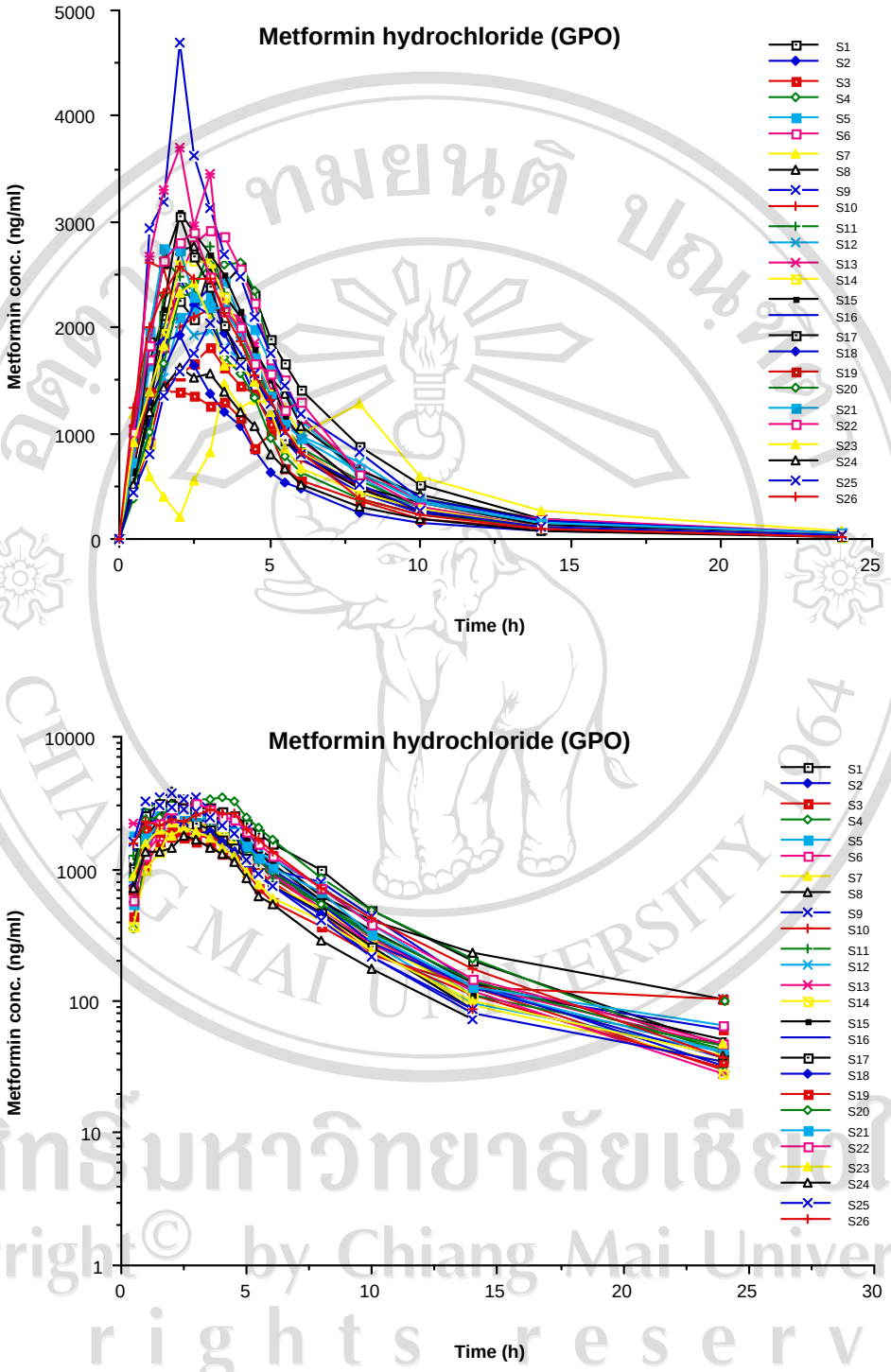

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Figure 4A Plasma concentration-time profiles after single oral administration of 850 mg metformin HCl (test product)

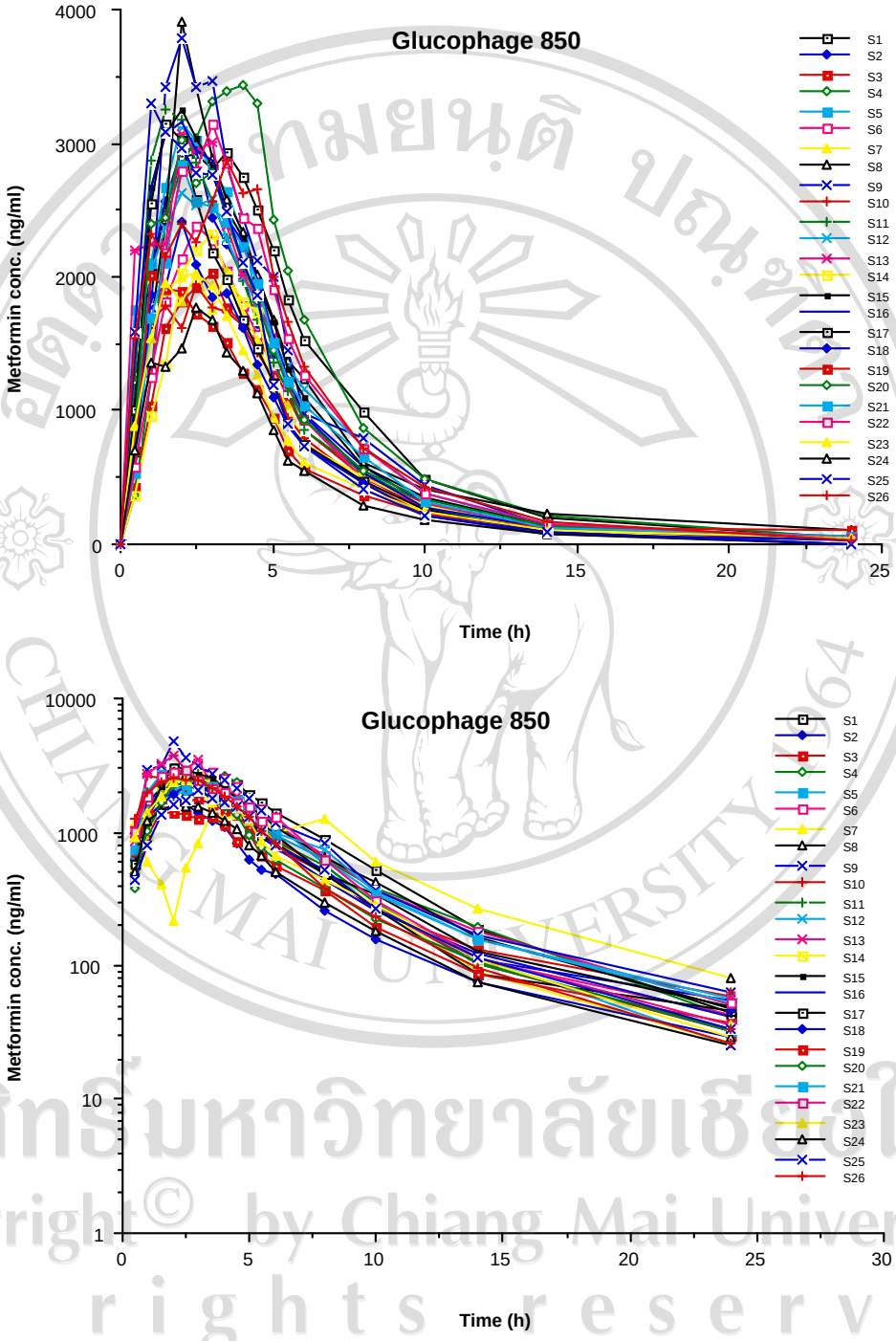

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Figure 4B Plasma concentration-time profiles after single oral administration of 850 mg metformin HCl (reference product)

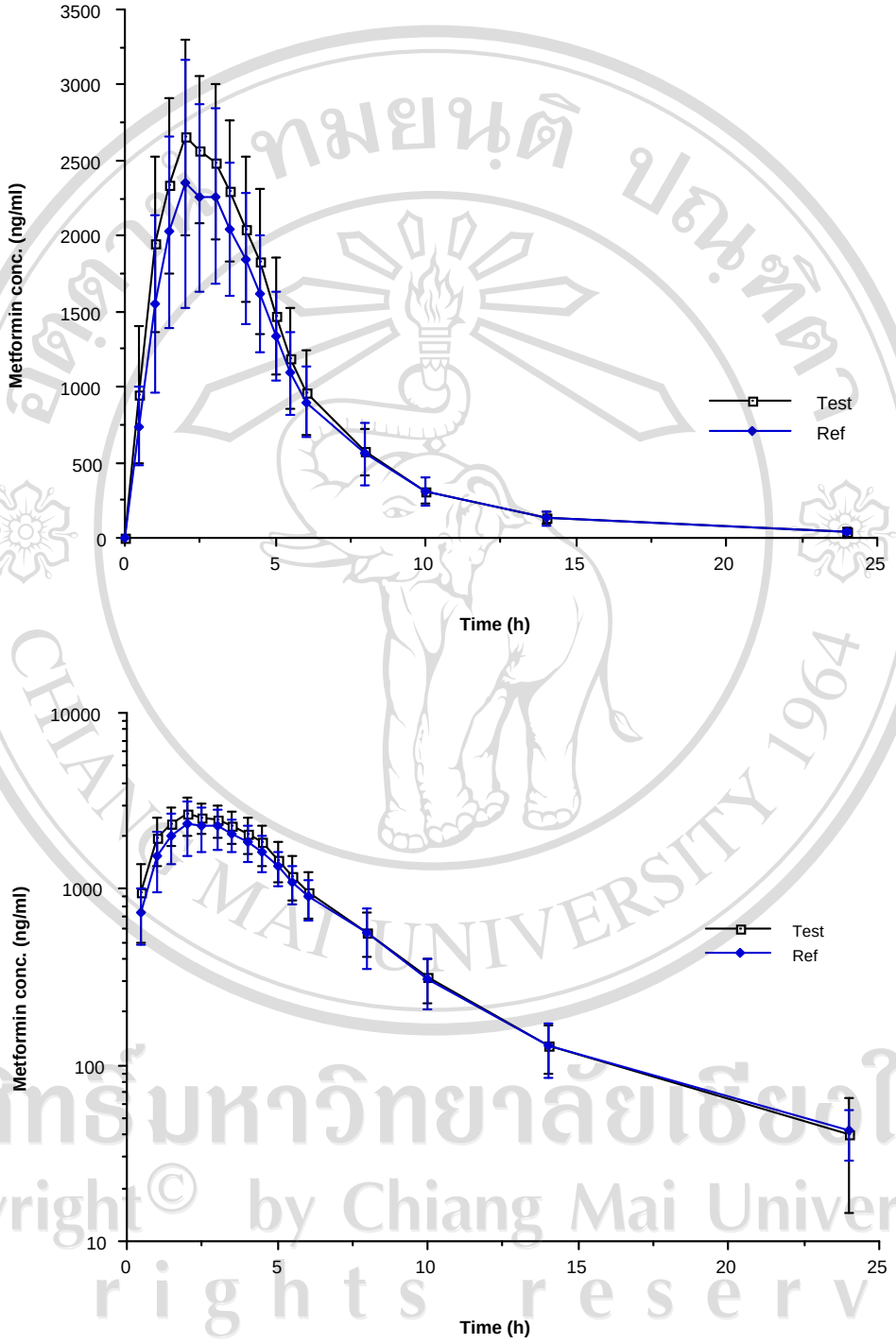

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Figure 5 Mean (± SD) of plasma concentration-time profiles after single oral administration of 850 mg metformin HCl of the test and the reference products.

3.2 Pharmacokinetics parameters of metformin and statistical analysis

The pharmacokinetics parameters derived from each subject after receiving 850-mg tablet of metformin HCl and Glucophage® are presented in Tables 15A and 15B including T_{max}, C_{max}, $AUC_{o-t,}$ $AUC_{o-\infty}$, $t_{1/2}$ and K_e as well as their means SD, % CV, maximum and minimum values of the test product and the reference product. The pharmacokinetic parameters (C_{max}, AUC_{o-t} and $AUC_{o-\infty}$) between the test and the reference products obtained from individual volunteers are compared and showned in Table 16. The means (± SD) of the C_{max}, AUC_{o-t} and $AUC_{o-\infty}$ for the test product were not significantly different from the reference product (2798.52 $\pm$ 588.88 versus 2532.39 $\pm$ 688.49 ng/mL, 15184.41 ± 3119.26 versus 13845.77 ± 2737.93 ng.h/mL, and 15440.55 ± 3103.47 versus 14065.67 ± 2754.49 ng.h/mL). The mean elimination $t_{1/2}$ of the test product (3.31 ± 0.55 h, range 2.20-4.85 h) and the reference product (3.52 ± 0.34 h, range 3.00-4.54 h) were comparable. The relative bioavailability (F_{rel}) calculated from C_{max} and AUC of $\frac{\text{Test}}{\text{Reference}}$ were 114% and 111%, respectively. T_{max} for the test product and the reference product were 2 h (mean 2.33 $\pm$ 0.76 h, range 1-4 h) and 2.25 h (mean 2.42 $\pm$ 0.78 h, range 1–4 h), respectively. All these parameters of the test product and the reference did not differ significantly.

According to the ANOVA table (Tables 17, 18, 19), the inter-subjects variability of the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were significantly high (p=0.0000, 0.0000 and 0.0002 respectively). The 90% CI for the natural log transformed data of the ratios $\frac{\text{Test}}{\text{Reference}}$ for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were 1.09 (1.04-1.16), 1.10 (1.04-1.16), and 1.12 (1.04-1.20), respectively. The T_{max} of both preparations were not significantly different since the mean [90%CI] for the T_{max} difference of -0.1 [(-0.33)-0.14] h (Table 20) was within the bioequivalence range of $\pm$ 0.48 h. Since all values were within the bioequivalence range, thus, our study demonstrates the bioequivalence of the two preparations.

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Table 16 Comparison of metformin pharmacokinetic parameters (C_{max} and AUC) in individual volunteers after single oral dose of 850 mg metformin HCl of the test product (T) and the reference products (R)

Volun-teer 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-inf} (T)	AUC_{0-inf} (R)	F_{rel} (T/R)
1	2932.88	2577.11	113.8	20246.65	17711.36	114.3	20470.72	17923.26	114.2
2	2963.13	2467.75	120.1	15632.68	12687.99	123.2	15950.56	12979.09	122.9
3	2030.95	1814.12	112.0	12040.62	11206.23	107.4	12183.96	11559.29	105.4
4	3436.37	2611.25	131.6	20841.72	16403.16	127.1	21201.08	16614.35	126.5
5	3142.30	2442.31	128.7	16434.32	14480.42	113.5	16625.70	14588.86	114.0
6	2379.93	2912.74	81.7	13497.19	17206.24	78.4	13741.88	17462.42	78.7
7	2049.82	1469.63	139.5	12399.61	13025.23	95.2	12569.90	13560.45	92.7
8	3903.20	2760.00	141.4	18688.37	15720.42	118.8	19269.07	15959.04	120.7
9	3781.51	4700.28	80.5	19019.01	20036.76	94.9	19158.97	20349.27	94.2
10	1933.21	2618.27	73.8	11794.70	13972.03	84.4	11950.79	14130.70	84.6
11	3258.17	2767.49	117.7	16274.75	14743.56	110.4	16508.90	14895.51	110.8
12	2624.16	2083.56	125.9	16141.05	13422.93	120.2	16334.81	13747.60	118.9
13	3063.03	3698.42	82.8	16328.71	16758.90	97.4	16456.88	16968.44	97.0
14	2326.54	2625.34	88.6	11465.73	13474.19	85.1	11863.14	13591.19	87.3
15	3255.72	3088.12	105.4	17573.16	15351.97	114.5	17826.44	15598.57	114.3
16	3155.91	2208.68	142.9	16940.39	12451.87	136.0	17115.77	12666.22	135.1
17	3145.31	3055.65	102.9	13684.36	13968.10	98.0	13980.17	14194.46	98.5
18	2410.47	1918.91	125.6	11971.65	9178.96	130.4	12138.44	9325.56	130.2
19	2007.84	1401.22	143.3	11279.44	9057.39	124.5	12004.15	9283.18	129.3
20	3022.92	2305.55	131.1	16066.67	11280.84	142.4	16282.15	11437.71	142.4
21	2836.76	2743.32	103.4	15590.98	15305.84	101.9	15946.02	15595.58	102.2
22	3140.73	2908.78	108.0	17408.49	15904.16	109.5	17640.92	16075.14	109.7
23	2021.30	2418.95	83.6	11352.48	12402.04	91.5	11555.24	12547.60	92.1
24	1774.90	1629.50	108.9	8784.72	8946.59	98.2	9031.78	9074.03	99.5
25	3294.51	2037.51	161.7	15069.10	11435.32	131.8	15348.55	11599.48	132.3
26	2869.90	2577.80	111.3	18288.79	13857.62	132.0	18468.42	13980.29	132.1
Mean	2798.52	2532.39	114.1	15184.44	13845.77	110.8	15440.55	14065.47	111.0
SD	588.88	688.49	23.0	3119.26	2737.93	17.4	3103.47	2754.49	17.4
% CV	21.04	27.19	20.2	20.54	19.77	15.7	20.10	19.58	15.7

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Table 17 ANOVA table (logarithmically transformed) and 90% CI of the pharmacokinetic parameter AUC_{0-t}

Source	Degree of freedom	Sum of squares	Mean squares	Computed F	*p*-values
Inter-Volunteers					
Carry-over	1	0.0021	0.0021	0.0259	0.8735
Residuals	24	1.9026	0.0793	5.9355	0.0000
Intra-Volunteers					
Drug	1	0.1063	0.1063	7.9594	0.0095
Period	1	0.0031	0.0031	0.2286	0.6369
Residuals	24	0.3205	0.0134		
Total	51	2.3345			

Significant level $\alpha = 0.05$

	Mean	90% CI
Test	9.6064	
Reference	9.5160	
Test/Reference	1.09	1.04 - 1.16

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Table 18 ANOVA table (logarithmically transformed) and 90% CI of the pharmacokinetic parameter $AUC_{0-\infty}$

Source	Degree of freedom	Sum of squares	Mean squares	Computed F	*p*-values
Inter-Volunteers					
Carry-over	1	0.0033	0.0033	0.0431	0.8373
Residuals	24	1.8265	0.0761	5.7171	0.0000
Intra-Volunteers					
Drug	1	0.1100	0.1100	8.2650	0.0083
Period	1	0.0038	0.0038	0.2846	0.5986
Residuals	24	0.3195	0.0133		
Total	51	2.2630			

Significant level $\alpha = 0.05$

	Mean	90% CI
Test	9.6241	
Reference	9.5321	
Test/Reference	1.10	1.04 -1.16

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Table 19 ANOVA table (logarithmically transformed) and 90% CI of the pharmacokinetic parameter C_{max}

Source	Degree of freedom	Sum of Squares	Mean Squares	Computed F	*p*-values
Inter-Volunteers					
Carry-over	1	0.0024	0.0024	0.0239	0.8785
Residuals	24	2.4552	0.1023	4.6492	0.0002
Intra-Volunteers					
Drug	1	0.1611	0.1611	7.3203	0.0123
Period	1	0.0196	0.0196	0.8921	0.3543
Residuals	24	0.5281	0.0220		
Total	51	3.1664			

Significant level $\alpha = 0.05$

	Mean	90% CI
Test	7.9141	
Reference	9.8028	
Test/Reference	1.12	1.04 – 1.20

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Table 20 ANOVA table and 90% CI of the pharmacokinetic parameter T_{max}

Source	Degree of freedom	Sum of Squares	Mean Squares	Computed F	*p*-values
Inter-Volunteers					
Carry-over	1	1.0817	1.0817	1.2228	0.2798
Residuals	24	21.2308	0.8846	3.6800	0.0011
Intra-Volunteers					
Drug	1	0.1202	0.1202	0.5000	0.4863
Period	1	1.7356	1.7356	7.2200	0.0129
Residuals	24	5.7692	0.2404		
Total	51	29.9375			

Significant level $\alpha = 0.05$

	Mean	90% CI
Test	2.3269	
Reference	2.4231	
Test/Reference	-0.10	(-0.33) - 0.14 BE range = $\pm$ 0.48

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