13. 試験の終了、中止または中断

13.1 試験の終了

試験が終了した場合、研究責任者は臨床研究機関の長に、試験が終了した旨を文書で報告する。臨床研究機関の長は、研究統括責任者および倫理（治験）審査委員会にその旨を文書で報告する。

13.2 試験全体の中止または中断

13.2.1 試験全体の中止または中断基準

研究統括責任者は、以下のいずれかの項目に該当する場合、本試験全体を中止または中断する。

1) 被験者の安全性確保等、倫理上あるいは医療上やむを得ない事情が発生した場合
2) 本試験を実施する科学的妥当性が失われた場合

13.2.2 臨床研究機関での中止または中断

研究責任者または臨床研究機関の長は、以下のいずれかの項目に該当する場合、当該臨床研究機関における試験を中止または中断する。

1) 研究責任者、研究者等または臨床研究機関による重大または継続した不遵守が発見された場合
2) 臨床研究機関の倫理（治験）審査委員会が、実施中の試験の継続審査等において、試験の中止または中断の決定を下した場合
3) 研究責任者、研究者等の異動により、試験の継続が不可能な場合
4) 選択基準に適合する被験者が見込めなくなった場合
5) 当該臨床研究機関が、試験を適切に実施するために求められる要件を満たさなくなった場合
6) 研究責任者が試験を中止または中断した場合

14. 症例報告書の作成

研究責任者は症例報告書を作成し、研究統括責任者に提出する。
症例報告書の記録および報告、変更または修正については以下の通りに行う。

1) 研究責任者は、必要に応じて協力者リスト等により予め指名された者の協力を得て、黒のボールペン、コンピューター出力等の消えない方法で症例報告書を作成する。症例報告書に検査結果等を貼付する場合は研究者が当該ページに確認の署名を行う。
2) 研究責任者は、記載事項の変更または修正がある場合は変更前の記載事項が判別できるように修正または追記し、症例報告書作成日以降の変更については変更年月日も記入して署名する。重大な変更または修正についてはその理由も記入する。
3) 研究責任者は、症例報告書およびその他すべての報告書のデータが正確かつ完全で読み易く、提出の時期が適切であることを保証する。

4) 研究責任者は、症例報告書の内容を点検し、問題がないことを確認した上で署名し、研究統括責任者に提出する。

5) 研究責任者は、症例報告書の写しおよび変更修正の記録の写しを保管する。

6) 研究責任者は、症例報告書に記載されたデータと原資料に何らかの矛盾が生じた場合には、研究統括責任者にその理由を説明する。

15. 記録等の保管

15.1 研究統括責任者

研究統括責任者は、臨床研究計画書、症例報告書、結果報告書、契約書、試験薬の品質に関する記録等を、試験の中止または終了後3年の期間保管する。

15.2 臨床研究機関

臨床研究機関の長は、被験者の同意取得に関する記録、症例報告書作成の基礎となったデータ（診療録、検査データ等）、倫理（治験）審査委員会の記録、契約書、試験薬管理表等の臨床研究機関において保管すべき記録類については、それぞれの記録ごとに記録保管責任者を定めて保管する。記録保管責任者はこれらの記録類を、試験の中止または終了後3年の期間保管する。ただし、研究統括責任者がこれよりも長い期間の保管を必要とする場合には、保管期間および保管方法について臨床研究機関と研究統括責任者の協議の上、延長も可能とする。

16. 金銭の支払いおよび健康被害への対応

16.1 金銭の支払い

本試験において被験者に支払われる試験協力費は、臨床研究機関の定めによるものとする。

16.2 健康被害への対応

本試験に伴い被験者に生じた健康被害については、損害賠償保険が措置されている。

17. 公表に関する取決め

本試験の結果を公表する場合には、事前に研究統括責任者の承認を得るものとする。公表の方法は、協議の上で決定する。

18. 実施体制

別紙参照

19. 試験実施期間

2010年6月 ～ 2010年11月

20. 研究に係る資金源、起こりうる利害の衝突について

本試験は厚生労働科学研究費補助金（地球規模保健課題推進研究事業）「日中韓大臣声明に基づく医薬品の民族差に関する国際共同臨床研究（H21-地球規模-指定-01）」の一環として実施され、実施に必要な研究資金は当補助金が用いられる。

厚生労働科学研究費補助金（地球規模保健課題推進研究事業）「日中韓大臣声明に基づく医薬品の民族差に関する国際共同臨床研究（H21-地球規模-指定-01）」に研究代表者および研究分担者として参加している研究者は、東邦大学所属機関の利益相反委員会によって起こり得る利害の衝突はないと判断されている。

21. 参考文献

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8) 「医薬品の臨床薬物動態試験について」（2001年6月1日　医薬審発第796号）

22. 付録

1) DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS (PUBLISH DATE: DECEMBER, 2004)　― 臨床検査のみ

2) 予期しない重篤な有害事象の報告様式

付録 1)

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY	*Standard International Units are listed in italics*			
Absolute CD4+ count – Adult and Pediatric > 13 years (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count – Adult and Pediatric > 13 years (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, 1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *1.55 – 1.69 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *0.39 – 0.53 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *0.54 – 0.68 mmol/L*	7.0 – 8.9 g/dL *1.09 – 1.39 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 0.69 mmol/L*	< 7.0 g/dL *< 1.09 mmol/L*
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *1.32 – 1.46 mmol/L*	7.0 – 8.4 g/dL *1.09 – 1.31 mmol/L*	6.0 – 6.9 g/dL *0.93 – 1.08 mmol/L*	< 6.00 g/dL *< 0.93 mmol/L*

* Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *1.47 – 1.63 mmol/L*	8.0 – 9.4 g/dL *1.24 – 1.46 mmol/L*	7.0 – 7.9 g/dL *1.09 – 1.23 mmol/L*	< 7.00 g/dL *< 1.09 mmol/L*
Infant*†, 1 – 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *1.86 – 2.02 mmol/L*	10.0 – 11.9 g/dL *1.55 – 1.85 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L*	< 9.0 g/dL *< 1.40 mmol/L*
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.26 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN

*Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*

*Values are for term infants.

†Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 169 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*

*Values are for term infants.

†Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
URINALYSIS	*Standard International Units are listed in italics*			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

*Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

付録 2)

（様式）

予期しない重篤な有害事象報告

平成　　年　　月　　日

厚生労働大臣　殿

以下の臨床研究に関連する予期しない重篤な有害事象について、下記の通り報告する。

1. 報告者情報

(1) 臨床研究機関名・その長の職名及び氏名：

(2) 研究責任者名：

(3) 臨床研究課題名：

(4) 臨床研究登録 ID：

（※あらかじめ登録した臨床研究計画公開データベースより付与された登録 ID 等、臨床研究を特定するための固有な番号等を記載する。当該臨床研究に係る報告は、関係する全ての研究機関において同じ番号を用いること。）

(5) 連絡先：　TEL：　FAX：

e-mail：

2. 報告内容

(1) 発生機関：　□自施設　□他の共同臨床研究機関（機関名：　　）

(2) 重篤な有害事象名・経過

（発生日、重篤と判断した理由、介入の内容と因果関係、経過、転帰等を簡潔に記入）

(3) 重篤な有害事象に対する措置

（新規登録の中断、同意・説明文書の改訂、他の被験者への再同意等）

(4) 倫理審査委員会における審査日、審査内容の概要、結果、必要な措置等

(5) 共同臨床研究機関への周知等：

共同臨床研究機関　□無し　□有り（総機関数（自施設含む）　　機関）

当該情報周知の有無　□無し　□有り

以上

（資　料　２）

日中韓大臣声明に基づく医薬品の民族差に関する国際共同臨床研究
健康成人男性を対象としたメロキシカムの薬物動態学的臨床試験

安全性に関する報告

（終了報告：2011 年 3 月 31 日）

研究統括責任者　　川合　眞一
東邦大学医学部内科学講座（大森）膠原病科　教授

要約

この試験の目的は、既に市販されているメロキシカムを用いて、日本人、中国人および韓国人の健康成人男性における薬物動態に関する民族差の有無を、同一の試験計画に基づいて 3 国間で検討するものである。また対照として、米国在住のヨーロッパ系コケージアンに対して同様の試験計画に基づく臨床試験を行った。

試験デザインは、非盲検、メロキシカム 7.5 mg の単回経口投与試験であった。北里大学臨床薬理研究所（日本）、北京大学第一医院（中国）、ソウル大学病院（韓国）、SNBL Clinical Pharmacology Center（米国）の 4 施設が試験に参加し、2010 年 11 月 16 日から 2010 年 12 月 21 日にかけて試験が実施された。

日本、中国、韓国および米国の 4 ヵ国で 121 例（日本、中国、韓国は各 30 例、米国 31 例）が試験に組み込まれた。日本、中国ではその全例に試験薬としてメロキシカム 7.5 mg が単回経口投与された。韓国では 1 例が投与前に除外基準に抵触することが判明し、コケージアンでは 1 例が投薬前に同意を撤回したため、メロキシカムを投与された被験者数はそれぞれ 29 例と 30 例であった。その結果、選択基準を満たし、除外基準に抵触しなかった被験者は合計 119 例であり、これら全例について背景（人口統計学的データ）および安全性の評価を行った。有害事象は 23 件（日本人 3 例 3 件、中国人 4 例 5 件、韓国人 8 例 11 件、コケージアン 3 例 4 件）発現した。最も多く発現した有害事象は、血中トリグリセリド増加とそう痒症（各 2 件）であった。重症度においては、高ビリルビン血症、C-反応性蛋白増加、総コレステロール増加、LDL コレステロール増加の各 1 件が中等度であった以外はすべて軽度であった。試験薬との因果関係が「多分関連あり」と判定されたのは 8 件であった。内訳は、中国人 2 例に 3 件（血中尿酸増加、白血球数減少、ヘモグロビン減少の各 1 件）および韓国人 3 例に 5 件（斑状丘疹状皮疹、全身性皮疹、そう痒性皮疹の各 1 件、そう痒症の 2 件）であった。有害事象の持続期間はフォローアップに応じなかった 2 例 3 件（C-反応性蛋白増加、総コレステロール増加、LDL コレステロール増加）を除いていずれも短く、治療や処置を必要とせずに回復した。また、臨床検査値、バイタルサインおよび

診察所見による安全性評価においては、メロキシカムの投与に起因する異常所見は認められなかった。

この試験で得られたデータから、メロキシカム 7.5 mg 経口投与は日本人、中国人、韓国人およびヨーロッパ系コケージアンの健康成人男性において安全で、忍容性が良好であることが示された。

添付資料

Clinical Study Safety Report

Study Title: Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Joint Statement by the Japanese, Chinese and Korean Ministers of Health,
Clinical Pharmacokinetic Study of Meloxicam in Healthy Adult Male Subjects

Author: Executive Investigator: Professor Shinichi Kawai, MD, PhD, Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine

1. TITLE PAGE

Clinical Study Safety Report

Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Joint Statement by the Japanese, Chinese and Korean Ministers of Health

Clinical Pharmacokinetic Study of Meloxicam in Healthy Adult Male Subjects

Division of Rheumatology, Department of Internal Medicine (Omori),
Toho University School of Medicine
6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan
Professor Shinichi Kawai, MD, PhD

EXECUTIVE INVESTIGATOR SIGNATURE

Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Joint Statement by the Japanese, Chinese and Korean Ministers of Health

Clinical Pharmacokinetic Study of Meloxicam in Healthy Adult Male Subjects

Study No ID: UMIN000004173

I, the undersigned, hereby declare that the safety part of this study was performed according to the procedures herein described and that this report represents a true and accurate record of the results obtained.

EXECUTIVE INVESTIGATOR

Division of Rheumatology,
Department of Internal Medicine (Omori),
Toho University School of Medicine
6-11-1 Omori-nishi,
Ota-ku,
Tokyo 143-8541
Japan

_____ _____

Professor Shinichi Kawai, MD, PhD Date

2. SYNOPSIS

Name of Executive Investigator: Shinichi Kawai	**Individual Study Table Referring to Part of the Dossier**	
Name of Study Drug: Meloxicam	Volume:	
Name of Active Ingredient: Meloxicam		

Study Title: Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Joint Statement by the Japanese, Chinese and Korean Ministers of Health

Clinical Pharmacokinetic Study of Meloxicam in Healthy Adult Male Subjects

Principal Investigators: <Japan> Tomoko Hasunuma
<China> Cui Yimin
<Korea> In-Jin Jang
<US> Masaru Kaneko

Study Sites: <Japan> Kitasato University, Research Center for Clinical Pharmacology Bioiatric Center
<China> Peking University First Hospital
<Korea> Seoul National University Hospital
<US> SNBL Clinical Pharmacology Center, Inc.

Publications: Not applicable

Study Period*:

	Date of first admission	Date of final follow-up
<Japan>	16 November 2010	4 December 2010
<China>	18 November 2010	29 November 2010
<Korea>	24 November 2010	17 December 2010
<US>	13 December 2010	21 December 2010

*When the study was conducted in the divided several groups, the date of the first admission of the first group and the date of final follow-up of the last group were described.

Clinical Phase:
Clinical pharmacokinetic study

Objectives:
Presence/absence of ethnicity differences in pharmacokinetics in Japanese, Chinese and Korean healthy adult males was examined between three countries, using meloxicam that had been already commercialized, based on the same protocol. As a control, a clinical study based on the similar protocol was conducted in European Caucasians residing in the US.

Methodology:
This was an open-label, single administration study in male healthy volunteers. In Japan, China (only Han people) and Korea, persons whose paternal and maternal parents and grandparents have their own country's citizenship were eligible. In the US, European Caucasians were included.
Single dose of one 7.5 mg tablet of meloxicam was administered with 150 mL of soft mineral water (less than 100 of hardness, Volvic® etc.) after 10 hours or more fasting. Water intake was prohibited within 2 hours after administration of the study drug. Food intake was prohibited within 4 hours after administration.
Calories and balance of three main nutrients (protein-fat-carbohydrate [PFC] balance) of the supper on the previous day and lunch/supper on the day of administration of the study drug were equalized wherever possible between the countries.
Safety assessments were performed at pre-determined times during the study period. Adverse events were monitored throughout the study.

Number of subjects (planned): 30 subjects for each country (Total 120 subjects)

Diagnosis and main criteria for inclusion:
Healthy adult male volunteers aged 20-35 years, with body mass index of 18.5 to <30.0 kg/m^{2}and body weight of 50.0 to 100.0 kg, having given written informed consent.

SYNOPSIS (continued)

Name of Executive Investigator: Shinichi Kawai	**Individual Study Table Referring to Part of the Dossier**	
Name of Study Drug: Meloxicam	Volume:	
Name of Active Ingredient: Meloxicam		

Study drug, dose, administration route and batch numbers:
One 7.5-mg tablet of meloxicam (Batch No.084081) was administered with 150 mL of soft mineral water (less than 100 of hardness, Volvic® etc.).

Duration of study: 5 days: hospitalization (-Day 1) to discharge (Day 4)

Reference therapy, dose, administration route and batch numbers: None

Criteria for evaluation:
Safety:
Laboratory test values (hematology, blood biochemistry and urinalysis), vital signs (body temperature, blood pressure and pulse rate), body weight and adverse events were included in the safety evaluation.

Statistical methods:
Safety parameters:
For laboratory test values (hematology and blood biochemistry), vital signs (temperature, blood pressure and pulse rate) and body weight, basic statistics (means and standard deviations) were obtained at each test period. For the laboratory safety data out of range values were flagged in the data listings and a list of clinically significant abnormal values was presented.
Adverse events were tabulated and summarised according to MedDRA (Ver.13.0), and classified by System Organ Class and Preferred Term.

SAFETY RESULTS:
A total of 121 eligible subjects that consisted of 30 subjects each for Japanese, Chinese and Koreans and 31 Caucasians were enrolled in the study in order to investigate the PK profile of single oral dose of 7.5 mg of meloxicam. Of 121 subjects, two were withdrawn from the study before administrating the study drug because 1 Korean subject did not fulfil any inclusion or any exclusion criteria and 1 Caucasian subject withdrew his consent. All other subjects fulfilled all of the inclusion criteria and none of the exclusion criteria. Consequently, 119 subjects were evaluated for safety and completed the study.

Totally, 23 AEs were reported by 18 subjects. The most frequent AEs were blood triglyceride increased and pruritus (2 events each). Eight AEs were judged as "probably related" (each 1 event of blood uric acid increased, white blood cell count decreased, haemoglobin decreased, rash maculo-papular, rash generalised and rash pruritic, and 2 events of pruritus). Four events were judged moderate in severity (each 1 event of hyperbilirubinaemia, elevated C-reactive protein, elevated total cholesterol and elevated LDL cholesterol). AEs other than 3 AEs (each 1 event of elevated C-reactive protein, elevated total cholesterol and elevated LDL cholesterol) were short lasting and resolved without concomitant medication or other intervention. No serious AE were observed in these 4 ethnic groups. There were no deaths or other serious AEs.

Laboratory measurements and clinical safety assessments (vital signs and physical examinations) did not show any clinically relevant abnormalities arising from the administration of meloxicam.

CONCLUSION:
Most of treatment-related AEs were mild in severity, and none required concomitant medication or intervention. Laboratory and other safety assessments did not appear to show any clinically relevant abnormalities arising from the administration of meloxicam. Meloxicam showed the similar safety results in these 4 ethnic groups.
The data from this study indicate that meloxicam given in oral dose of 7.5 mg is safe and relatively well-tolerated by healthy male Japanese, Chinese, Korean and Caucasian subjects.

Date of the final report: 31 March 2011

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