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 – 189 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 – 136 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.

2. Contents of reporting to the marketing approval holder, unknown or serious adverse events that the causal relationship with study drug cannot be denied

1. Name of doctor
2. Name of the site
3. Name of study drug Averox®
4. Study Number: 14988
5. Subject number
6. Sex Male / Female
7. Age of subject
8. Adverse event1 * copy the item 9 to 19, when two or more adverse events occured
9. Name of adverse event
10. Reason why the adverse event was judged to be serious
    * only applicable ones will be described
    * two or more can be selected
    1) results in death,
    2) is life-threatening,
    3) requires inpatient hospitalization or prolongation of existing hospitalization,
    4) results in persistent or significant disability/incapacity,
    5) is a congenital anomaly/birth defect, or
    6) is any other significant medically
11. Causal relationship with study drug (Averox®) Yes/No
12. The reason of judgment above * this item must be written
13. Date of occurrence 2010/MM/DD
14. Outcome * only applicable ones will be described
    (Death/Resolved/Not resolved/Resolved/Resolved with sequelae
    /Unknown/Aggravation)
15. Date of outcome 2010/MM/DD
16. Administration of study drug (Averox®)
17. Date of study drug start 2010/MM/DD
18. Actions when the adverse event occurred
    * Drug treatment or actions taken for the adverse reaction
19. Summary of adverse event (the circumstances that adverse events occurred, symptoms, place, actions)
    * describe this item chronologically as much as possible

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

Clinical Pharmacokinetic Study of Moxifloxacin in Healthy Adult Male Subjects

Attachment

Protocol

18. Implementation Structure

Executive investigator: Shinichi Kawai
Professor of Internal Medicine, Division of Rheumatology,
School of Medicine,
Faculty of Medicine, Toho University

Ver. 0.1: Issued on December 28, 2009

18 IMPLEMENTATION STRUCTURE

1 Executive investigator

Shinichi Kawai, Professor of Internal Medicine, Division of Rheumatology,
School of Medicine, Faculty of Medicine, Toho University
Address: 6-11-1 Ohmori-nishi, Ohta-ku, Tokyo 143-8541
TEL: + 81-3-3762-4151 (ext. 6591) FAX: + 81-3-5753-8513

[Duties]

- To supervise study-related activities.
- To analyze ethnic differences using PK data collected from study sites in all the countries.

2 Study Site and principle investigators

<Japan> study site code: 00001
Kitasato University, Research Center for Clinical Pharmacology Bioiatric Center,
Director, Tomoko Hasunuma,
Address: 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan
TEL: +81-3-5791-6178 FAX: +81-3- 3440-5469

<China> study site code: 00002
Peking University First Hospital Cui Yimin
Address: No.8, Xishiku Street, Western District, Beijing, China
TEL: +86-10-6655-1122 (ext. 2043, 3456)

<Korea> study site code: 00003
Seoul National University Hospital In-Jin Jang
Addres:28 Yeongeon-dong Jongno-gu Seoul, 110-744, Korea
TEL: +82-2-2720-8290 FAX: +82-2-2745-7996

<US> study site code: 00004
SNBL Clinical Pharmacology Center, Inc. Masaru Kaneko
Address: 800 W. Baltimore St., 6th FL, Baltimore, MD21201, USA
TEL: +1-410-706-8926 FAX: +1-410-706-8964

[Duties of the investigator]

- To give explanation to volunteers using the informed consent document and form and obtain voluntary consent from them.
- To conduct a clinical study in healthy adult subjects in their countries in accordance with the protocol.
- To adjust the entire study.

3 Ethnic (Institutional) Review Committee

At study sites:

<Japan>

Ethnic (Institutional) Review Committee at Kitasato University, Research Center for Clinical Pharmacology

Address: 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan

<China>

Ethic Committee of Clinical Study, Peking University First Hospital

Address: No. 8, Xishiku Street, Western District, Beijing, China

<Korea>

Seoul National University College of Medicine / Seoul National University Hospital Institutional Review Board

Address: 28 Yeongeon-dong, Jongno-gu, Seoul 110-744, Korea

<US>

Independent Investigational Review Board, Inc

Address: 6738 West Sunrise Blvd., Suite 102 Plantation, Florida 33313, USA

At the sites of examination of polymorphism

< Japan, Korea and the US>,

Division of Medicinal Safety Science, National Institute of Health Sciences, Ethnic Review Committee

Address: 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501

<China>

Shin Nippon Biomedical Shanghai Laboratories,Ltd. Jiaxing Pharmacokinetics and Bioanalysis Center Institutional Review Board

Address: No.2, Lig Gong Tang Road, jiaxing, Zhe Jiang Province, China

[Duties]

- An advisory body of the head of the study site for investigating and reviewing requirements of a clinical research from the perspectives of dignity of individual subjects, respect of human rights, other ethical matters and science.
- To prepare a history of review and approval for study implementation.

4 Joint study site

Korea: Department of Pharmacology, College of Medicine, The Catholic University of Korea
Dong-Seok Yim

Address: 505 Banpo-dong, Seocho-gu, Seoul, Korea
TEL: +82-2-2258-7888 FAX: +82-2-2258-7859
[Duties]
・ To advise study protocol and result.

5 Collaborator

5.1 Study drug storage manager

<Japan> Kitasato University Center for Clinical Pharmacology Bioiatric Center, Department of Pharmaceutical Management, Mariko Kawashima
Address: 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan
TEL:+ 81-3-5791-6350

<China>
Peking University First Hospital Tan Zhizhen
Address: No.8, Xishiku Street, Western District, Beijing, China
TEL: +81-10-6513-9211

<Korea>
Seoul National University Hospital Min-Jung Kim
Address: 28 Yeongeon-dong Jongno-gu Seoul, 110-744, Korea
TEL: +82-2-2072-1688 FAX: +82-2-2072-1970

<US>
SNBL Clinical Pharmacology Center, Inc. Joan S. Haywood, R.Ph
Address: 800 W. Baltimore St., 6th FL, Baltimore, MD21201, USA
TEL: +1-410-706-8763 FAX: +1-410-706-8964

[Duties]
・ To be in charge of control and storage of the study drug during the study.

5.2 Document control manager

<Japan, China, Korea and US>
The principle investigators at the sites are in charge of document management
[Duties]
・ To be in charge of retention and control of essential documents to be kept at the study sites.

5.3 Monitoring

<Japan>

CMIC, Co., Ltd., CRO company, Clinical Research Dept. CRO East Japan Head Office

Address: Gotanda First Bldg. 2-8-1 Nishigotanda, Shinagawa-ku, Tokyo 141-0031
TEL: +81-3-5719-6325 FAX: +81-3-5496-9805
Responsible person: Kunimitsu Yamazaki

Monitor: Tsutomu Shibata, Hideto Ushijima, Naomitsu Takeichi, Yoshihiro Toyoda, Ryugen Kuwahata, Takanori Sando, Toru Sato

<China>

CMIC, Beijing Co. Ltd.

Address: B610-612, COFCO Plaza No.8 Jianguomennei Avenue, Beijing 100005, China

TEL: +86-10-6513-9211 FAX: +86-10-6513-9213
Responsible person: Li Lei

<Korea>

CMIC Korea Co. Ltd

Adrress:#702 Hanseong Bldg. 47-2 Seosomun-dong, Jung-gu, Seoul 100-110, Korea
TEL: +82-2-3708-3600 FAX: +82-2-3789-6900
Responsible person: YunJeong Choi

<US> To be decided

[Duties]

- To perform monitoring activities.

5.4 Clinical laboratory center

<Japan> Hosen Clinic, Kitasato University Center for Clinical Pharmacology

Address: 1-28-16 Komagome, Toshima-ku, Tokyo 170-0003, Japan

TEL:+81-3-5976-7611

Responsible person: Sayoko Morita

<China>

Peking University First Hospital

Address: No. 8, Xishiku Street, Western District, Beijing, China

TEL: +86-10-6655-1122 (ext. 2043, 3456)

Responsible person: Feng Zhenru

<Korea>

Clinical Trials Center Core Lab Clinical Research Institute, Seoul National University Hospital

Address: 28 Yeongeon-dong, Jongno-gu, Seoul 110-744, Korea

TEL: +82-2-2072-1679 FAX: +82-2-3675-8334

Responsible person: Sung-Hee Han

<US>

Esoterix-LABCORP

Address: 13900 Park Center RD, Herndon, VA 20171, USA

LABCORP Clinical Trials

Address: 69 First Ave., Raritan, NJ 08869, USA

TEL: +1-908-526-2400 (ext. 2505) FAX: +1-908-707-9049

Responsible person:Angela Murphy

[Duties]

- To measure samples for hematology, blood biochemistry and urinalysis.

5.5 Gene polymorphism test facility

<Japan, Korea and US>:

Division of Medicinal Safety Science, National Institute of Health Sciences

Address: 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501

TEL: 03-3700-1141 FAX: 03-3700-9788

Responsible person: Masahiro Tohkin, Director

<China>

Shin Nippon Biomedical Shanghai Laboratories,Ltd. Jiaxing Pharmacokinetics and Bioanalysis Center

Address: No2, Lig Gong Tang Road. Jiaxing, Zhe Jiang Province, China

TEL: +86-573-8258-6381 FAX: +86-573-8258-6058

Responsible person: Qian Wen

[Duties]

- To perform the gene polymorphism examination and keep the specimens for 3 years at -20 ℃ or less.
- Data analysis of gene polymorphism are performed at Division of Medicinal Safety Science of National Institute of Health Sciences

5.6 Laboratory center for measurement of drug concentrations

Bayer HealthCare AG / Bayer Schering Pharma AG,

Address: Wuppertal, Elberfeld, 0468, Germany

TEL: +49 202 36 5223 FAX: +49 202 36 4224

Responsible person: Dr. Uwe Thuß

[Duties]

- To measure plasma and urine drug concentrations.

5.7 Summary of the safety data

<Japan and China>

CMIC, Co., Ltd., CRO company, Clinical Research Dept. CRO East Japan Head Office
Address: Gotanda First Bldg. 2-8-1 Nishigotanda, Shinagawa-ku, Tokyo 141-0031
TEL: +81-3-5719-6325 FAX: +81-3-5496-9805
Responsible person: Kunimitsu Yamazaki

<Korea>

CMIC Korea Co. Ltd
Adrress:#702 Hanseong Bldg. 47-2 Seosomun-dong, Jung-gu, Seoul 100-110, Korea
TEL: +82-2-3708-3600 FAX: +82-2-3789-6900
Responsible person: Yong-Jun Kwon

<US>

SNBL Clinical Pharmacology Center
Adrress:800 W. Baltimore St., 6th FL, Baltimore, MD 21201, USA
TEL: +1-410-706-8707 FAX:+1-410-706-8964
Responsible person: Tomoka Inoue Davidsen

[Duties]

- To check the safety data, and making tables and figures.

5.8 Statistical analysis

<Pharmacokinetics and polymorphism>

Division of Medicinal Safety Science, National Institute of Health Sciences
Address: 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501
TEL: 03-3700-1141 FAX: 03-3700-9788
Responsible person: Masahiro Tohkin, Director

[Duties]

- To draw up the statistical analysis plan, implement the PK analysis and other tabulation analyses, prepare reports (draft).

5.9 Audit

CMIC, Co., Ltd., CRO company, Quality Management
Address: Kongo Bldg. 7-10-4 Nishigotanda, Shinagawa-ku, Tokyo 141-0031
TEL: +81-3-5745-7045 FAX: +81-3-5745-7095
Responsible person: Noriaki Suzuki

[Duties]

- To perform the audit of the study sites.

STUDY: Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Announcement by the Japanese, Chinese and Korean Ministers of Health, Labor and Welfare, Clinical Pharmacokinetic Study of Moxifloxacin in Healthy Adult Male Subjects

EXECUTIVE INVESTIGATOR: Professor Shinichi Kawai, MD, PhD, Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine

LISTING OF REVISIONS OF PROTOCOL: Version 1.0 DATED, December 28, 2009

Protocol section	Page (Ver.1.0)		Ver. 1.0 (December 28, 2009)	Ver. 2.0 (January 13, 2010)	Comment
	i		Ver.1.0: Issued on December 28,2009	Ver.2.0: Issued on January 13,2010	
	i	Title of Dr. Kawai	Shinichi Kawai Professor of Internal medicine Division of Rheumatology School of medicine Toho University	Professor Shinichi Kawai, MD, PhD Division of Rheumatology Department of Internal Medicine (Omori) Toho University School of Medicine	Title changed
	i	Bottom (Line 1-2)	principal investigators, investigators and personnel directly involved in the study (e.g. collaborators….	principal investigators, investigators and others (e.g. collaborators….	Revised
	i		–	Study number ID: UMIN000002968	Created
	ii	Exclusion criteria 8) ~	1.5 times higher and other liver function tests	1.5 times higher or other liver function tests	Error
	iv	Study schedule	12-lead electrocardiography Day3 ( )	12-lead electrocardiography Day3 (O)	Error
4.2	5	Exclusion criteria 8)	1.5 times higher and other liver function tests	1.5 times higher or other liver function tests	Error
8.2.2	14	5) Back-up samples : line 6	Shin Nippon Biomedical Shanghai Laboratories, Ltd.	Biomedical Research (GZ), Ltd.	Firm name changed
8.2.3	15	Line 5	Shin Nippon Biomedical Shanghai Laboratories, Ltd.	Biomedical Research (GZ), Ltd.	Firm name changed
8.2.3	15	Table 8-4 China	Shin Nippon Biomedical Shanghai Laboratories, Ltd.	Biomedical Research (GZ), Ltd.	Firm name changed
8.2.4	16	(1) 3) Test method (Line 4)	The principal investigator or investigator should ….	The principal investigator or investigator and others should …	Revised
8.2.4	16	(2) 3) Test method	The principal investigator should …	The principal investigator or investigator and others should …	Revised
8.2.4	18	⑩ Amount of blood sampling in the entire study (China)	Infectious disease test 5ml (5ml x 1) Laboratory test 15ml (5ml x 3) Total 106ml	Infectious disease test 3ml (3ml x 1) Laboratory test 21ml (7ml x 3) Total 110ml	Sampling amount changed
11.3.1	25	At enrollment (Line 6)	Prior to the screening, the primcipal investigator should …	Prior to the screening, the primcipal investigator or investigators and others should …	Revised

Protocol Attachment			Ver. 1.0 (December 28, 2009)	Ver. 2.0 (January 13, 2010)	Comment
Top			Ver.1.0: Issued on December 28,2009	Ver.2.0: Issued on January 13,2010	
Top / 18.1		Title of Dr.Kawai	Shinichi Kawai Professor of Internal medicine Division of Rheumatology School of medicine Toho University	Professor Shinichi Kawai, MD, PhD Division of Rheumatology Department of Internal Medicine (Omori) Toho University School of Medicine	Title changed
18.2		Study site and principle investigators (China)	TEL: +86-10-6655-1122(Ext 2043,3456)	TEL: +86-10-6611-0802	Telephone number changed
18.3		Ethic (Institutional) Review Committee <China>	Shin Nippon Biomedical Shanghai Laboratories, Ltd.	Biomedical Research(GZ), Ltd.	Firm name changed
18.5.1		Study drug storage manager (China)	Tan Zhizhen TEL: +86-10-6513-9211	Zhao Dongfang TEL: +86-10-6611-0802	Person in charge and telephone number changed
18.5.4		Clinical laboratory center (China)	Responsible person: Feng Zhenru TEL: +86-10-6655-1122(ext. 2043,3456)	Xu Guobin TEL: +86-10-83572426	Person in charge and telephone number changed
18.5.5		Gene polymorphism test facility <China>	Shin Nippon Biomedical Shanghai Laboratories, Ltd. Responsible person: Wen Qian	Biomedical Research(GZ), Ltd. Responsible person: Zheng Guodong	Firm name and person in charge changed
* Some word "Ethic" were mistyped as "Ethnic". Those words are corrected.					

STUDY: Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Announcement by the Japanese, Chinese and Korean Ministers of Health, Labor and Welfare, Clinical Pharmacokinetic Study of Moxifloxacin in Healthy Adult Male Subjects

EXECUTIVE INVESTIGATOR: Professor Shinichi Kawai, MD, PhD, Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine

LISTING OF REVISIONS OF PROTOCOL: Version 2.0 DATED, January 13, 2010

Protocol Section		Ver. 2.0 (January 13, 2010)	Ver.3.0 (January 18, 2010)	Comment
5.2	Explanation of Moxifloxacin (between indications and active ingredient)	**Moxifoloxacin** is a new quinolone….	**Moxifloxacin** is a new quinolone….	Error
5.3	Control/Storage of the Study drug	the study drug storage personnel should take a count of the remaining study drug and discard them under the direction of the principal investigator .	The study drug storage personnel should discard or dispose the study drug after destruction under the direction of the principal investigator following the standard procedure at the study site.	As per discussion with SNBL
10.1	Handling of data in analyses	2) Time allowance of laboratory tests 3 hours from administration: less than 20 minutes 24 hours from administration: less than 30 minutes 48 hours from administration: less than 1 hour	2) Time allowance of laboratory tests 48 hours from administration: less than 1 hour	Error
Protocol Attachment		**Ver. 2.0 (January 13, 2010)**	**Ver.3.0 (January 18, 2010)**	**Comment**
Top		Ver. 2.0: Issued on January 13, 2010	Ver. 3.0: Issued on January 18, 2010	
5.3	Monitoring (US)	To be decided	Scientific Consulting, LLC Adrress:6871 Daly Road, Dexter, MI 48130, USA TEL: +1-317-910-2351 Fax: +1-317-245-2325 Responsible person: Emily Huston	Decided

Protocol Amendment as of February 4, 2010

Study title : Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Announcement by the Japanese, Chinese and Korean Ministers of Health, Labor and Welfare, Clinical Pharmacokinetic Study of Moxifloxacin in Healthy Adult Male Subjects

Sponsor : Shinichi Kawai, MD, PhD, Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine

Protocol to be revised : Ver.3.0, Dated January 18, 2010

Revision: Revision was done for the protocol to be provided to the site in China (Version : 3.1C)

No.	Section	item	page	Before revision (Ver.3.0)	Revision (Ver. 3.1c)	Reason of revision
1	8.2.1 (1) 5)	Back-up samples	13	After that, the back-up samples should be sent to the National Institute of Health Sciences.	After that, the back-up samples should be sent to the National Institute of Health Sciences (Japan, Korea, and U.S.), sent to Biomedical Research (GZ), Ltd. Jiaxing Pharmacokinetics and Bioanalysis Center (China).	Storage place for back-up samples of plasma and urine was changed in Chinese
2	8.2.1 (2) 5)	Back-up samples	14-15	ditto	ditto	ditto

Protocol Amendment as of February 15, 2010

Study title : Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Announcement by the Japanese, Chinese and Korean Ministers of Health, Labor and Welfare, Clinical Pharmacokinetic Study of Moxifloxacin in Healthy Adult Male Subjects

Sponsor : Shinichi Kawai, MD, PhD, Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine

Protocol to be revised : Ver.3.0, Dated on January 18, 2010

New version: Ver.3.1K, Dated on Februay 15, 2010

No.	Section	item	page	Before revision (Ver.3.0)	Revision (Ver. 3.1K)	Reason of revision
1	8.2.1 (1) 5) 8.2.1 (2) 5)	Back-up samples	13-15	After that, the back-up samples should be sent to the National Institute of Health Sciences.	After that, the back-up samples should be sent to the National Institute of Health Sciences (Japan, Korea, and U.S.), sent to Biomedical Research (GZ), Ltd. Jiaxing Pharmacokinetics and Bioanalysis Center (China).	Storage place for back-up samples of plasma and urine was changed in Chinese
2	8.2.1 (1) 4) 8.2.1 (2) 4) 8.2.2 4)	Labeling and transport method of a storage container for plasma specimens:	13-15	the study site code (Japan:00001, Korea:00002, China: 00003 and....)	the study site code (Japan:00001, China:00002, Korea: 00003 and....)	Mistakes in translation

Protocol Amendment as of February 26, 2010

Study title : Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Announcement by the Japanese, Chinese and Korean Ministers of Health, Labor and Welfare, Clinical Pharmacokinetic Study of Moxifloxacin in Healthy Adult Male Subjects

Sponsor : Shinichi Kawai, MD, PhD, Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine

Protocol to be revised : Ver.3.1K, Dated on Februay 15, 2010

New version: Ver.3.2K, Dated on Februay 26, 2010

No.	Section	item	page	Before revision (Ver.3.1)	Revision (Ver.3.2K)	Reason of revision
1	Page v footnote a)			Collected specimens(EDTA-2Na Added)	Collected specimens(EDTA-2Na or EDTA-2K Added)	EDTA-2K is acceptable
2	8.1.2.	Table 8-2 Gene polymorphism examination	10	Collected blood specimens(EDTA-2Na Added)	Collected blood specimens(EDTA-2Na or EDTA-2K Added)	ditto
3	8.1.2	Table 8-3 footnote a)	12	Collected specimens(EDTA-2Na Added)	Collected specimens(EDTA-2Na or EDTA-2K Added)	ditto
4	8.2.2	3) Processing method	15	Two of 7 mL of venous blood (EDTA-2Na Added)	Two of 7 mL of venous blood (EDTA-2Na or EDTA-2K Added)	ditto

Protocol Amendment as of March 1, 2010

Study title : Global Clinical Study on Ethnic Differences in Drug Metabolism Based on the Announcement by the Japanese, Chinese and Korean Ministers of Health, Labor and Welfare, Clinical Pharmacokinetic Study of Moxifloxacin in Healthy Adult Male Subjects

Sponsor : Shinichi Kawai, MD, PhD, Division of Rheumatology, Department of Internal Medicine (Omori), Toho University School of Medicine

Protocol to be revised : Ver.3.1C, Dated on Februay 4, 2010

New version: Ver.3.2C, Dated on March 1, 2010

No.	Section	item	page	Before revision (Ver.3.1C)	Revision (Ver. 3.2C)	Reason of revision
1	Page v footnote a)			Collected specimens(EDTA-2Na Added)	Collected specimens(EDTA-2Na or EDTA-2K Added)	EDTA-2K is acceptable
2	8.1.2.	Table 8-2 Gene polymorphism examination Table 8-3 footnote a)	10, 12	Collected blood specimens(EDTA-2Na Added)	Collected blood specimens(EDTA-2Na or EDTA-2K Added)	ditto
3	8.2.1	(1) 4 (2) 4)	13-14	Study site code: Korea 002, China 003	Study site code: China 002, Korea 003	Mistake in translation from Japanese into English
4	8.2.1	(2) 3)		another 4 mL of urine for back-up from each 2L Urine-Bottle, and fill them into a labeled 10 mL polypropylene tube,	another 4 mL of urine for back-up from each 2L Urine-Bottle, and fill them into a labeled 15 mL polypropylene tube,	10 ml tube was not available at the study site
5	8.2.2	4) Labeling and transport method of a storage container for specimens	14	Study site code: Korea 002, China 003	Study site code: China 002, Korea 003	Mistake in translation from Japanese into English
6	8.2.2	3) Processing method	15	Two of 7 mL of venous blood (EDTA-2Na Added)	Two of 6 mL of venous blood (EDTA-2Na or EDTA-2K Added)	EDTA-2K is acceptable. Amount of blood sampling has been changed since the 7 ml tube was not available at the study site.
7	8.2.4	10) Amount of blood sampling in the entire study <Details of the number and amount of blood sampling>	19	Polymorphism examination (China) 14ml (14mlx1), Total 110ml	Polymorphism examination (China) 12ml (12mlx1), Total 108 ml	Amount of blood sampling has been changed since the 7 ml tube was not available at the study site.

（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シンバスタチンの薬物動態学的臨床試験

（終了報告：2010年7月31日現在）

研究統括責任者 川合 眞一
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要 約

この試験の目的は既に市販されているシンバスタチンを用いて、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う。目標被験者数は日中韓および米国の4ヵ国で160例（各国40例）、シンバスタチン20mgを単回経口投与する。2010年7月31日現在、各国の試験進捗状況は以下のとおりである。

日本：北里大学臨床薬理研究所にて7月5-7日、7月7-9日と2群に分けて試験を実施し、試験薬の投与・検査・観察を終了した。スクリーニングを65例実施し、40例の被験者を組み入れたが、中止症例はいなかった。現在、症例報告書のSDVを実施し、8月上旬に回収予定で進めている。薬物動態評価のための血漿検体と遺伝子多型検査のための血液検体を各測定機関へ送付し、現在測定中である。

韓国：ソウル国立大学病院にて7月22日開催の倫理審査委員会にて審議され、7月23日付で承認を得た。8月中旬に試験を実施する予定である。

添付資料：臨床研究計画書、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シンバスタチンの薬物動態学的臨床試験、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、臨床研究登録ID:UMIN000003644：2.0版、作成日2010年6月18日

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シンバスタチンの薬物動態学的臨床試験

臨床研究計画書

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