

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL 201 503 7500
FAX 201 503 6325

July 19, 1993

Solomon Sobel, MD
Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-04
Center for Drug Evaluation
and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 19-667
SANDOSTATIN® (octreotide
acetate) Injection

SUPPLEMENTAL NEW DRUG
APPLICATION

CHEMISTRY/BIOEQUIVALENCE
DRAFT LABELING

Dear Dr. Sobel:

In accordance with 21 CFR §314.70 (b)(2)(i), Sandoz Pharmaceuticals Corporation herewith submits a supplemental new drug application for Sandostatin® (octreotide acetate) Injection which provides for a new formulation for both the ampuls and the multi-dose vials.

Currently both dosage forms contain an aqueous solution with an acetate buffer system. However, there have been reports of pain at the site of injection. We propose to replace the current formulation with a buffered lactic acid solution, which is a weaker buffer than the acetic acid system. This allows the body to re-establish the pH at the injection site more rapidly than the current buffer solution.

In support of the proposed change bioavailability of the two formulations was studied. Please refer to the enclosed study report (Report No. DM-1-1/17/92). The lactate formulation was found to be bioequivalent to the acetate formulation in AUC and C_{max} . There was a difference in time to peak, t_{max} , of 9 minutes, but this is not of consequence since Sandostatin is indicated for chronic use.

Regarding the analytical testing and specifications of the drug product, the only change is found in the pH specifications, due to the change in buffer solutions. All other tests and specifications remain unchanged.

Four copies of draft labeling are included with this submission. The DESCRIPTION section of the package insert contains the information pertaining to the lactate buffer, and the container labels have a boxed statement alerting pharmacists and patients to the new formulation.

Solomon Sobel, MD

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A table of contents and an introduction is provided in each volume for your convenience. If you have any questions or comments, please contact me at (201) 503-6984.

Sincerely,



Norma P. Loeffler
Manager, Regulatory
Manufacturing and
Controls

/ccr

Enclosed: Pharmacokinetics/Biopharmaceutics copy contains: Draft Labeling (vol. 4) and Bioequivalence Study (vol. 1) only

Clinical copy contains: Draft Labeling (vol. 4) and Bioequivalence study (vol.1) only

Pharmacology copy contains: Draft Labeling (vol. 4) only

Chemistry copy contains: Draft Labeling (vol. 4), Bioequivalence Study (vol. 1) and Chemistry (vols. 2 and 3).

Archival copy contains: Draft Labeling (vol. 4), Bioequivalence study (vol. 1), and Chemistry (vols. 2 and 3).

blcc: G. Bennett, R. Clark, R. Coombs, M. Finkel, E. Jukniewicz, G. Kantorow,
L.Nally, V. Naringrekar, H. Ries, N. Rothwell, E. Ryan, M. Schlager,
A. Sodano, C. Steren, J. Taylor, H. Vickory (w/att), C. Walsh
Basle: D. Bates, H. Hauth, H. Ludwig, B. Widmer (w/att)

303-247
SANDOZ

PRODUCT DEVELOPMENT
DEPARTMENT

 **SANDOZ PHARMACEUTICALS, LTD.**
AKASAKA P.O. BOX 40 TOKYO JAPAN

31 March, 1988

BIOEQUIVALENCE STUDY OF THE TWO PARENTERAL PREPARATIONS OF SMS 201-995

Naokata Shimizu, M.D.
Principal Investigator: Naokata Shimizu

March 31, 1988

0036

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Sponsor : Sandoz Yakuhin K.K.
Address : 12-4-Minami-Aoyama 5-chome, Minato-ku,
Tokyo

Medical Institution : Medical Foundation Aoba-kai Hitotsubashi
Hospital
Address : 2-25 Gakuen-Nishimachi 1-chome,
Kodairashi, Tokyo

Study Period : September 1987 - October 1987

Principal Investigator : Prof. Naokata Shimizu
3rd Dept. of Medicine, Teikyo University,
School of Medicine

Attending Physician : Dr. Masao Tatsuno
Director Medical Foundation Aoba-kai
Hitotsubashi Hospital

I. Background of the Study

SMS 201-995 ampoules containing octreotide acetate as an active ingredient and its registration application file in the indication for gastrointestinal hormone secreting tumors is being investigated by the New Drug Investigational Committee. Its clinical efficacy and safety is being studied also in the indication for acromegaly and pituitary gigantism.

SMS 201-995 is applied by subcutaneous injection. During the clinical study of the drug, it was found that SMS 201-995 causes local pain at the injection site because of acetic acid which is added as an excipient. In order to eliminate the local pain, a new preparation (hereafter called "test preparation") was developed, using lactic acid in place of acetic acid. A bioequivalence study was performed comparing the test preparation and the preparation using acetic acid as the excipient (hereafter called the "control preparation").

In addition, effects of this drug on local pain were compared with the control.

II. Procedures

1. Contract

Sandoz Yakuhin K.K. (SYKK) requested K.K. Nippon Yakuri to perform this study at Aoba-kai Hitotsubashi Hospital. The three parties concluded a contract. The study was performed according to the protocol which was approved by the IRB of K.K. Nippon Yakuri.

2. Procedures of the Study

- 2.1. SYKK asked Prof. N. Shimizu to act as the principal investigator in this study; he accepted the request (June 1987).
- 2.2. SYKK committed this study to K.K. Nippon Yakuri (June 1987)
- 2.3. The three parties, SYKK, K.K. Nippon Yakuri and Aoba-kai Hitotsubashi Hospital concluded a contract on this study (July 1987).
- 2.4. K.K. Nippon Yakuri held a IRB-meeting in which this study was approved (July 1987).
- 2.5. Explanatory meeting and health check were held for the volunteers (Sept. 1987).
- 2.6. Subjects were selected according to the results of the health check (Sept. 1987).
- 2.7. The study was started at the first administration of the test drugs (Sept. 1987).
- 2.8. The second administration of the test drugs was given and the study was completed (Oct. 1987).

3. Investigation Review Board (IRB)

IRB members held a meeting as follows to review the propriety of this study. Details of the discussion were recorded in minutes.

Date: July 18, 1987
Place: Keio Plaza Hotel (2-1 Nishi-Shinjuku 2-chome,
Shinjuku-ku, Tokyo)

Attendants:

Advisor: T. Yanagida, Guest Prof. Tokyo Jikeikai Medical
College

Advisor: T. Tanaka, A.P., Tokyo Jeikeikai Medical College

Chairman: M. Saito, Director, Misato Clinic

Vice Chairman: K. Nakamura, Dept. of Clinical Medicine,
Tsukuba University, School of Medicine

Members: T. Fujii, Prof., Teikyo University, School of
Medicine

M. Tatsuno, Director, Hitotsubashi Hospital,
Investigator

T. Kobayashi, Pharmacist, Nishimachi Hospital

Y. Hattori, Chief of the Laboratory,
Hitotsubashi Hospital

S. Nakada, Attorney

K. Ogawa, SYKK

H. Morikawa, SYKK

Y. Nagasawa, SYKK

K. Kashihara, SYKK

T. Toyonaga, SYKK

Process of Review

3.1. SYKK explained the outline of the development of the test preparation, properties of the test preparation, results of the clinical studies in Phase I, protocol for bioequivalence study and the booklet for subjects.

- 3.2. Questions and answers were exchanged based on the following materials:
- a) Outline of SMS 201-995
 - b) Results of the Phase I study on SMS 201-995
 - c) Protocol for a bioequivalence study
 - d) Booklet on this bioequivalence study for the subjects.
- 3.3. Performance of the study was approved.

III. Objective

Objective of this study was to investigate the biological equivalence of two preparations of SMS 201-995 (octretide acetate), i.e. the one containing acetic acid and the other one containing lactic acid.

IV. Subjects

1. Selection of Subjects

Sixteen subjects, who fulfilled the following conditions, were selected as listed in Table 1 from healthy male volunteers.

- 1.1. Age 20 - 25 years.
- 1.2. No hepatic, renal, cardiac or gastrointestinal diseases.
- 1.3. No history of drug allergy.
- 1.4. No use of any drugs for a considerable period.
- 1.5. Those weighing less than 15% in percentage of overweight.

Calculation of overweight based on the following formula:

$$\% = \left[1 - \frac{(\text{height}-100\text{cm}) \times 0.9}{\text{weight}} \right] \times 100$$

- 1.6. Negative to subcutaneous test of SMS 201-995. No display of redness after s.c. injection of 0.01 µg SMS 201-995 into the upper arm.
- 1.7. Confirmation of good health by the following examinations (preliminary health check).

Items of preliminary health check:

- i) Anamnesis
- ii) Physical examination: blood pressure, pulse, auscultation, percussion, body temperature, height, weight and ECG.
- iii) Hematological examination: WBC, RBC, hemoglobin, hematocrit, platelets, leucocyte segmentation.
- iv) Blood chemistry examination: total protein, albumin, BUN, creatinine, uric acid, total cholesterol, triglyceride, Na, K, Cl, Ca, alk. phosphatase, GOT, GPT, LDH, -GTP, total bilirubin, blood glucose
- v) Urine examination: pH, protein, glucose, urobilinogen, ketone body, sedimentation
- vi) Others: HBs antigen-antibody reaction, STS

2. Consent of Subjects

According to the Declaration of Helsinki and the Tokyo Amendment (1975), the following items were explained to the subjects by the attending physician before obtaining written consent of the subjects for the participation in the study.

Explanation meeting for the subjects

Date: Sep. 16, 1987.

Place: Head office of K.K. Nippon Yakuri

Items explained: Following items were explained according to the booklet for the subjects:

- a) Test drugs
- b) The objective and method of the study and expected effects
- c) Compensation for unexpected accident
- d) The principle that any subject is free to leave the study
- e) Occurrence of expected side effects such as local pain at the injection site, gastric distress, diarrhea and vomiting.

Reference material: Explanation Booklet for Subjects in Bio-equivalence Study of SMS 201-995.

V. Test Drugs

Two preparations of SMS 201-995, 100 µg/ml each, were used in the study; the one containing lactic acid (test preparation) and the other one containing acetic acid (control preparation), as shown in Table 2.

Code name: SMS 201-995

Generic name: octreotide acetate

Structural formula:



Molecular formula : $C_{43}H_{66}N_{10}O_{10}S_2$ (2CH₃COOH)

Molecular weight : 1019.26(1139.36)

Galenic form : ampoule

Test preparation: : batch no. Y 1160587, composition no. KNGL 71275.17

Control preparation : batch no. Y 0110287, composition no. KNGL 71275.01

Quality : No problem was found in quality tests performed in Sandoz Ltd., Switzerland and SYKK, Japan.

VI. Method

The timing of administration, blood sampling and examinations is shown in Fig. 1.

1. Dose

One hundred µg (1 ml) of either the test preparation or the control preparation was used.

2. Basis for Determination of the Dose

The preceding Phase I study indicated that 100 µg was preferable to 50 µg for bioequivalence determination, since the former dosage results in higher SMS 201-995 plasma concentrations, which are more suitable for measurements. Furthermore, any clinically significant side effects were not observed in the Phase I study and in clinical studies in GI hormone

secretion tumors at 100 µg. Thus 100 µg was selected as the dose to be applied in this study.

3. Administration

As shown in Table 3, 16 subjects were randomized into two groups of 8 subjects. As the first dosage 100 µg (1 ml) of the test preparation was injected subcutaneously in the forearm of subjects from group I and 100 µg (1 ml) of the control preparation was injected subcutaneously in the forearm of subjects from group II. In the second dosage, preparations were switched by single blind cross-over method. Preparations were injected at 9 a.m. An interval of 1 week elapsed between the first and the second dosage.

Food and beverages were not allowed during 10 hours prior to the injections and 4 hours after the injection.

4. Observation and Measurement Items

The following examinations and observations were made:

4.1. Plasma drug level

- i) Blood sampling: 13 times, starting immediately before the administration and at 5, 10, 20, 30 and 45 min., 1, 1.5, 2, 3, 4, 6 and 8 hours after the administration.
- ii) Sampling volume: 5 ml of blood was withdrawn from a forearm vein in each sampling. The total blood volume for the assay of plasma SMS 201-995 was 5 ml x 13 times x 2 = 130 ml.
- iii) Treatment of the blood sample: Blood was withdrawn by Venoject vacuum sampling cylinder (VT-050H, Termo). The heparinized blood sample was immediately centrifuged (3,200 r.p.m./15 min., 4° C) and plasma was pipetted into 3 plasma tubes. The thus obtained plasma samples were frozen and stored at -20° C until analysis.
- iv) Method for the assay of plasma concentration of SMS 201-995: Plasma SMS 201-995 was determined by a RIA method developed by Sandoz Ltd., Switzerland¹⁾. This method is a conventional RIA using rabbit antiserum immunized with SMS 201-995 and ¹²⁵I-SMS 201-995 and human plasma coated active carbon for B/F separation. This method is specific to intact SMS 201-995. The RIA kit was supplied by Sandoz Ltd. Switzerland.

- v) Assay of SMS 201-995 in plasma and statistical analysis: Plasma levels of SMS 201-995 were assayed by the RIA method at the laboratory of Analytical R+D, SYKK. Plasma peak levels (C_{max}) were measured and the areas under the curve (AUC) of plasma SMS 201-995 were calculated to confirm bioequivalence of the two preparations.

4.2. Examination of subjective symptoms by interview, auscultation and percussion

Interview, auscultation and percussion were made immediately before the administration, and 2 hours and 24 hours after the administration. Subjective symptoms were orally inquired using subjective symptoms inquiry form (Table 4). In addition, local pain at the injection site was assessed according to the following 4 criteria, and the results were entered in the form (Table 5).

- 0: No pain
- 1: Mild (mild pain)
- 2: Moderate (tolerable but considerable pain)
- 3: Severe (intolerable pain)

4.3. Physical examination

Blood pressure, pulse and body temperature were examined immediately before and 24 hours after the administration.

4.4. Laboratory examinations

Following items were examined immediately before the first administration and 24 hours after the second administration.

- i) Hematology: WBC, RBC, hemoglobin, hematocrit, platelet count and leucocyte differential count.
- ii) Blood chemistry: Total protein, albumin, BUN, creatinine, uric acid, total cholesterol, triglyceride, Na, Cl, Ca, alk. phosphatase, GOT, GPT, LDH, -GTP, total bilirubin, glucose.
- iii) Urine: pH, protein, glucose, urobilinogen, ketone body, sedimentation.
- iv) Volume of blood sample: Twelve milliliter of blood was taken immediately before the first administration and 24 hours after the second administration, respectively.

5. Emergency Measures and Follow-up of the Subjects

In order to be ready for an accident, emergency measures were prepared. In case of any abnormality in physical or laboratory examination, it was determined to follow the condition of the subject until normalization. The relationship with the administration of the drug would have been investigated.

6. Changes in the Study

Minor changes in the study were left to the responsibility of the attending physician, as long as the objective of the study was still observed, or the conditions imposed on the subjects were not severer.

7. Discontinuation of the Study

It was stipulated that the subjects should be excluded from the study, or the study itself should be discontinued and adequate measures should be taken in any of the following cases:

- a) The attending physician considered that the safety of a subject is at risk.
- b) A subject or his family requested withdrawal from the study.
- c) The principal investigator and the attending doctor decided, upon discussion, the discontinuation of the study. In case it is impossible to contact the principal investigator, the decision is left to the attending physician alone.

8. Supervision of the Subjects

- 8.1. Subjects were hospitalized and supervised by the attending physician from 18.30 on the day before the administration up to 24 hours after the administration, both in the first and the second administrations.
- 8.2. Subjects were instructed to take care of their health for one week prior to the study.
- 8.3. Use of other drugs was prohibited from one week prior to the study to the completion of the study.
- 8.4. Food and beverages were served only as directed, and alcoholic drinks and beverages containing caffeine were prohibited. Smoking was not allowed from 10:00 in the previous night until 8 hours after the administration, and on the following day until the end of the examination.

VII. Results

1. Quantitative Determination

Fig. 2 shows an example of a calibration curve for octreotide acetate in the range from 2500 pg/ml to 19.53 pg/ml using plasma aliquots of 0.25 ml. Binding ratio against the blank zero (B0) was within the range of 20 - 98%. Detection limit was ca. 20 pg/ml.

2. Plasma Levels of SMS 201-995

Time-profiles of the mean plasma levels of SMS 201-995 in healthy male volunteers after subcutaneous injection of 100 µg (1 ml) of the test preparation and the control preparation are shown in Fig. 3. Table 6 shows plasma concentration, C_{max} and AUC for SMS 201-995, and C_{max} (mean \pm SE) and AUC (mean \pm SE) of the test preparation (4.80 \pm 0.22 ng/ml, 746.44 \pm 19.30 ng · min/ml, respectively), and of the control preparation (5.21 \pm 0.31 ng/ml and 745.52 \pm 29.07 ng · min/ml, respectively). Differences in the bioavailability of the two preparations were 7.9% in C_{max} and 0.1% in AUC. C_{max} and AUC were statistically analyzed according to the Guideline on the Method of Bioequivalence Study²⁾.

This study was designed by Latin Square Method and the results of variance analysis of C_{max} and AUC are shown in Tables 7 and 8. Statistically significant differences in C_{max} and AUC were observed between subjects and subjects/group, however no significant difference was observed between the two preparations and the two time periods.

Table 9 presents the results of computation of the minimum detectable difference and the confidence limit of the difference in bioavailability. Minimum detectable difference was 18.2% for C_{max} and 9.6% for AUC. Confidence limits for the difference in bioavailability of the two preparations were within \pm 20%, approximately. Minimum necessary number of subjects ($\alpha = 0.05$, $1 - \beta = 0.8$, $\delta = 0.2$) were calculated as 5 subjects for C_{max} and 2 subjects for AUC.

3. Subjective symptoms

Types and severity of side effects occurring after administration of each preparation are tabulated in Table 10.

3.1. Severity of local pain at the injection site

- i) Control preparation: Local pain was reported by 9 out of 16 cases. Pain was mild in these cases and disappeared without any treatment in 10 - 40 min. after the injection.
- ii) Test preparation: Pain was experienced only in 1 case out of 16. The pain was mild and disappeared in 10 min. after the injection without any treatment. This subject complained also of mild pain after the injection of the control preparation.
- iii) Statistical analysis: Incidence of pain in both groups was tested by McNemar test, which demonstrated that the test preparation showed significantly less incidence of pain at the probability of 5%.

3.2. Other subjective symptoms

- i) Control preparation: Subjective symptoms were found in 5 out of 16 cases (31.3%). These were 2 incidences of nausea and 1 incidence of gastric distress, dry mouth, dizziness and heavy-headedness. These symptoms were mild and disappeared within 1.5 hours after the administration without any treatment, except for the case who complained of heavy-headedness. This heavy-headedness in Case No. 4 occurred 4 hours after the treatment, and disappeared without any treatment 9 hours after the administration.
- ii) Test preparation: Subjective symptoms were found in 2 out of 16 cases (12.5%). Types, incidence and severity of these symptoms were: a single incidence of flushing (moderate), headache (mild) and gastric distress (mild), respectively. In one subject (Case No. 8) who complained of headache and flushing, the former appeared within 30 min. after the administration and disappeared without any treatment 10 min. later, followed by moderate face flushing which lasted 15 min. Milder flushing persisted until 2 hours after the administration but disappeared without any treatment. One subject (Case No. 11) who complained of gastric distress had noticed the same symptom prior to the administration, and the symptom disappeared without any treatment within one hour after the administration.

4. Physical Examinations

measurements of blood pressure, pulse and body temperature immediately before and 24 hours after the administration are shown in Table 11. Any clinically significant changes were not observed before and after the administration.

5. Laboratory Examinations

Laboratory data before the first and after the second administration are shown in Table 12. Significant abnormalities in laboratory data were not observed.

VIII. Discussion

1. Plasma Levels of SMS 201-995

Differences in bioavailability of SMS 201-995 of the test preparation group against the control preparation group were 7.9% in C_{max} and 0.1% in AUC. Both were within 20%.

The results of analysis of variance showed that there were no significant differences between the two preparations and also between the two time periods in both C_{max} and AUC. But significant differences were observed at the source of "Between subjects" and "Subjects / Group" in C_{max} and AUC. According to the comments in the Guidelines for the Method of Bioequivalence Study, the ratio of variance of "Between subjects" and "Subjects / Group" may be significant in some cases.

On the other hand, the values of minimum detectable differences have satisfied the requirements of the Guidelines (less than 20%), and the confidence intervals in bioavailability of the two preparations were within $\pm 20\%$ approximately.

Minimum necessary numbers of subjects were calculated as 5 subjects based on the actual AUC values of this study, and both were within the actual subject number of 8.

These statistical data, i.e. minimum detectable difference, confidence interval in difference in bioavailability of the two preparations and the minimum required number of subjects, supported the results of this analysis of variance.

2. Subjective Symptoms, Physical Examinations and Laboratory Examinations

Mild pain at the injection site was observed in 9 out of 16 cases (56.3%) in the control preparation group, while it was observed in a single case out of 16 cases in the test preparation group. Thus, the incidence of local pain was significantly decreased in the test preparation group; this result suggests that the incidence of local pain will be reduced in the clinical application of this preparation.

As for subjective symptoms other than local pain, such symptoms as nausea, gastric distress and heavy-headedness were observed in 5 out of 16 cases (31.3%) in the control preparation group, in contrast to 2 out of 16 cases (12.5%) in the test preparation group. This would allow the conclusion that the tolerability of the test preparation is superior to the tolerability of the control preparation.

No abnormality was observed in vital signs such as blood pressure, pulse and body temperature after the administration of either preparation. The present administration of 100 µg octreotide acetate was assumed as having no effect on vital signs.

No abnormalities in laboratory data were observed.

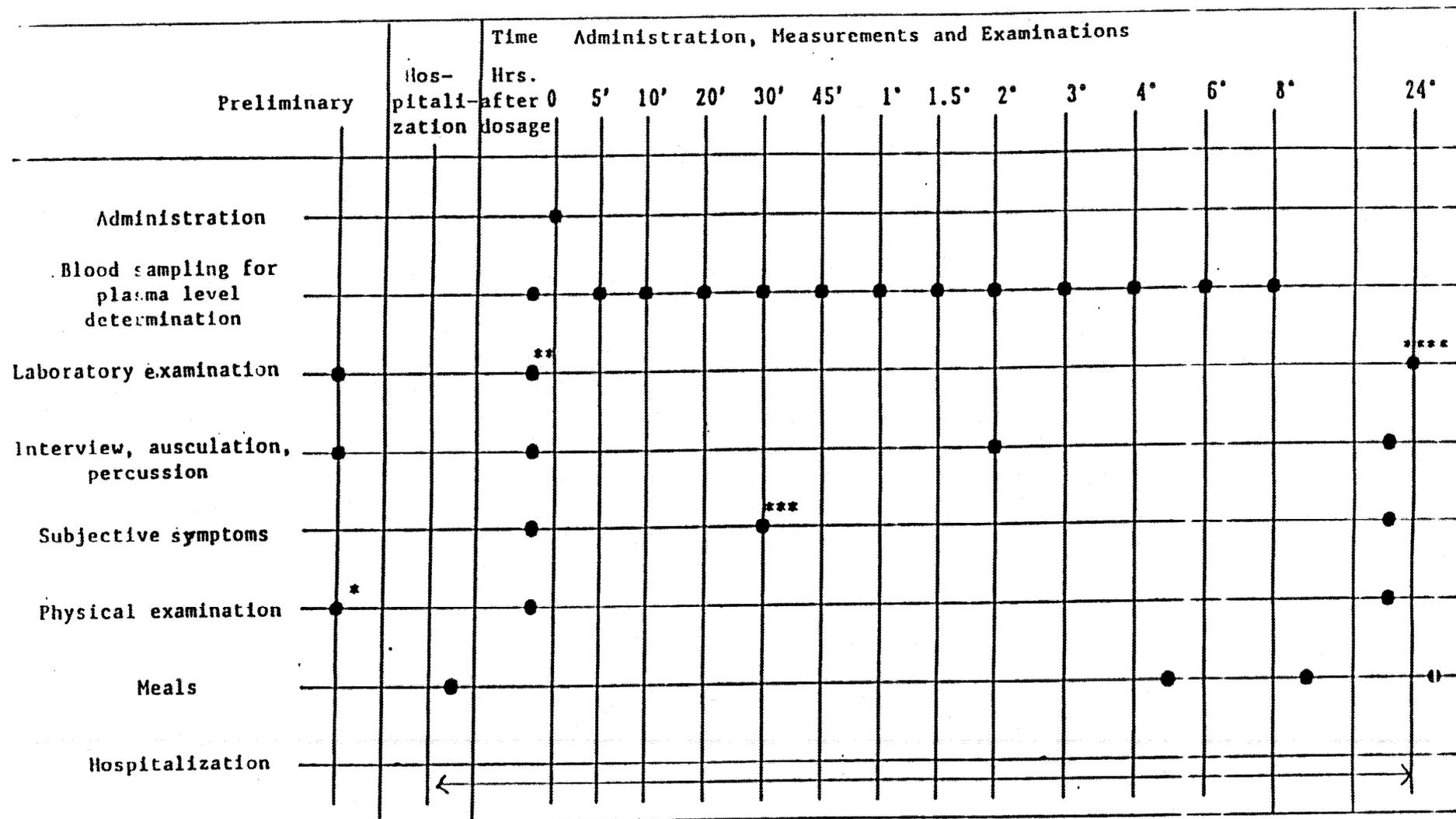
IX. Conclusion

The test preparation is a new modified preparation in which the excipient acetic acid has been replaced by lactic acid. Results of the present study demonstrate that after the injection of the test preparation the pain at the injection site is markedly reduced. It was also proved that the bioavailabilities of the test preparation and the control preparation are equivalent.

References

- 1) J. Rosenthaler: Radioimmunoassay of Sandostatin, 13.03.1986,
Document no. 0303-015 of Sandoz Ltd., Switzerland

- 2) A. Ejima et al.: Iyakuhin Kenkyu, 13(5), 1106-1119 (1982)
ditto. Iyakuhin Kenkyu, 13(6), 1267-1271 (1982)
ditto. Iyakuhin Kenkyu, 15(1), 123-133 (1984)



* Height, body weight and ECG were recorded in the preliminary examination alone.

** Immediately before the first dosage.

*** Severity of local pain was also inquired.

**** 24hours after the second dosage.

Fig.1 Study Schedule

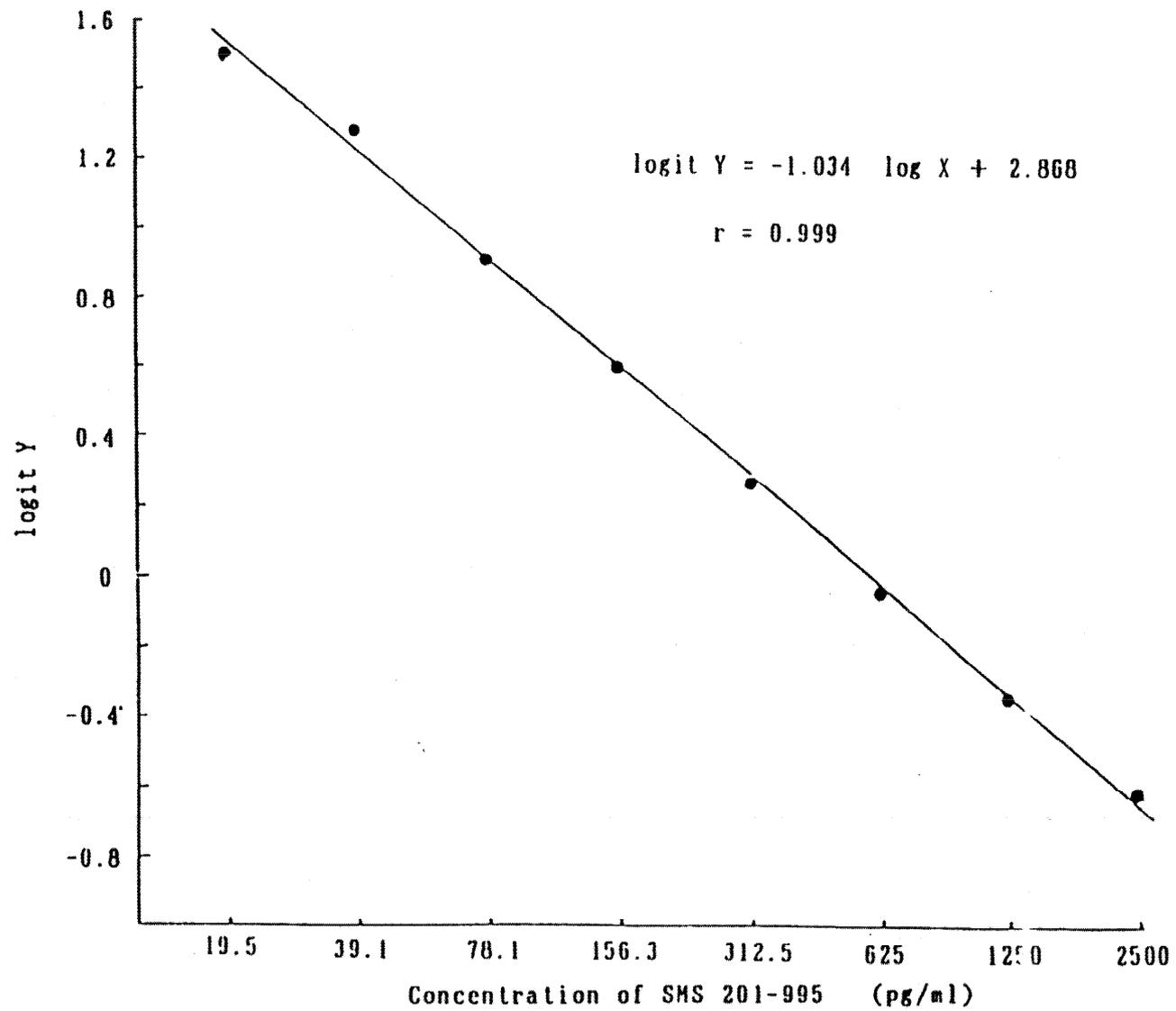


Fig. 2 An example of calibration curve

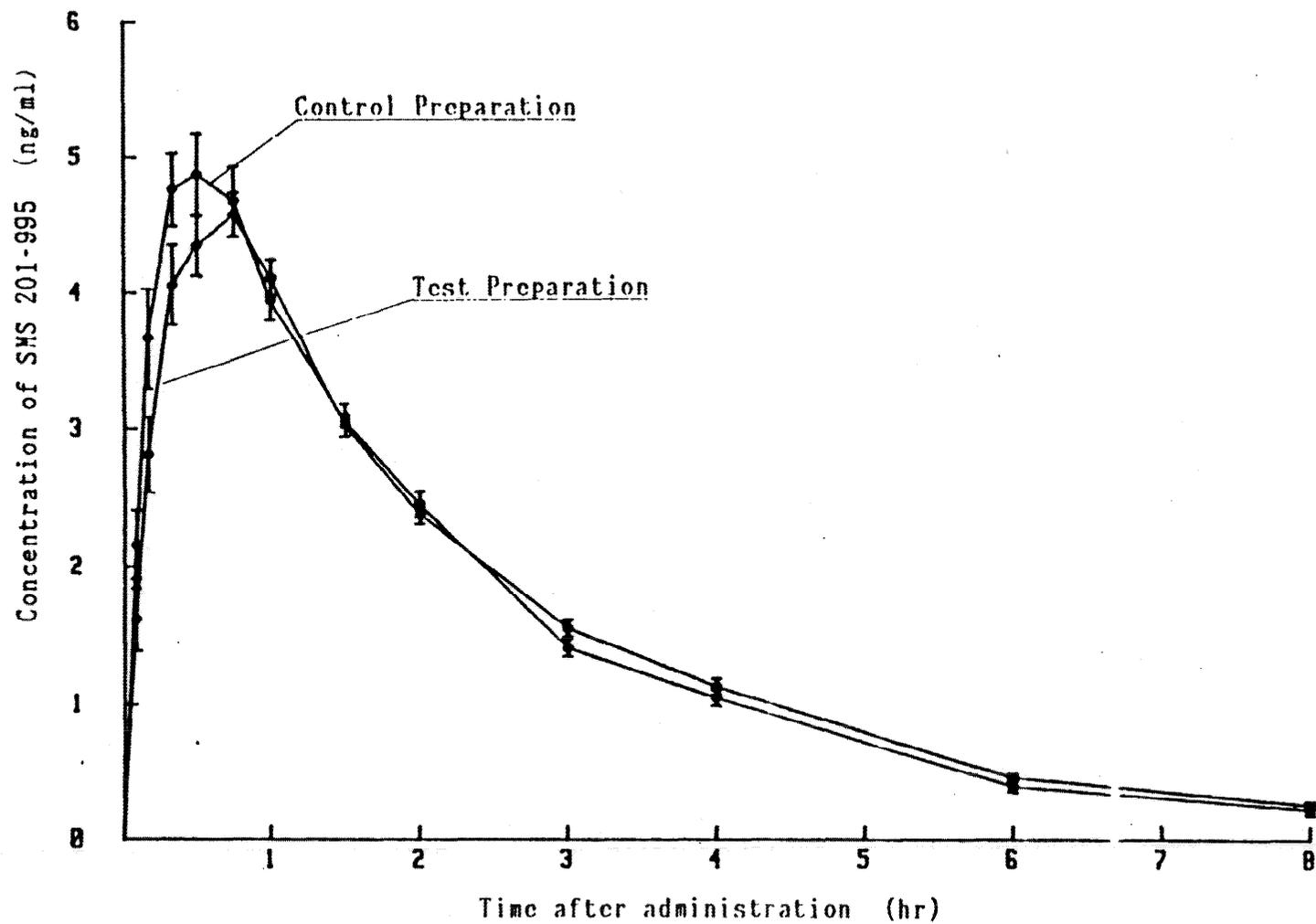


Fig. 3 Plasma concentrations of SMS 201-995 in healthy volunteers after subcutaneous injection of the test preparation (1 ml) and the control (1 ml) Mean \pm SE (n=16)

Table 1 Background of subjects

Item Group	Subject No.	Sex	Age (Year)	Height (cm)	Weight (kg)
I	1	male	23	171	72
	2	male	22	160	50
	3	male	23	169	60
	4	male	20	181	64
	5	male	22	176	61
	6	male	20	174	57
	7	male	24	180	68
	8	male	20	176	73
II	9	male	24	171	64
	10	male	22	175	70
	11	male	20	172	57
	12	male	21	170	60
	13	male	21	162	58
	14	male	20	170	59
	15	male	25	170	68
	16	male	24	170	60

Table 2 Test preparations

Test preparations		Batch No.	Content(%)
Test Preparation	SMS 201-995(100 μ g/ml) containing lactic acid as an excipient	Y116 0587	99.7
Control Preparation	SMS 201-995(100 μ g/ml) containing acetic acid as an excipient	Y011 0287	105.6

Table 3 Administration sequence, dose and number of subjects

Number of subjects		First administration	Second administration
Group I	8	Test preparation 100 μ g (1 ml) s.c.	Control preparation 100 μ g (1 ml) s.c.
Group II	8	Control preparation 100 μ g (1 ml) s.c.	Test preparation 100 μ g (1 ml) s.c.

Table 4 Investigation List of Subjective Effects (1)

Investigation Period
Yr. Mon. Day
Time

No. :
Name :

Investigation Period
Yr. Mon. Day
Time

No. :
Name :

Investigation Period
Yr. Mon. Day
Time

No. :
Name :

Investigation Period
Yr. Mon. Day
Time

No. :
Name :

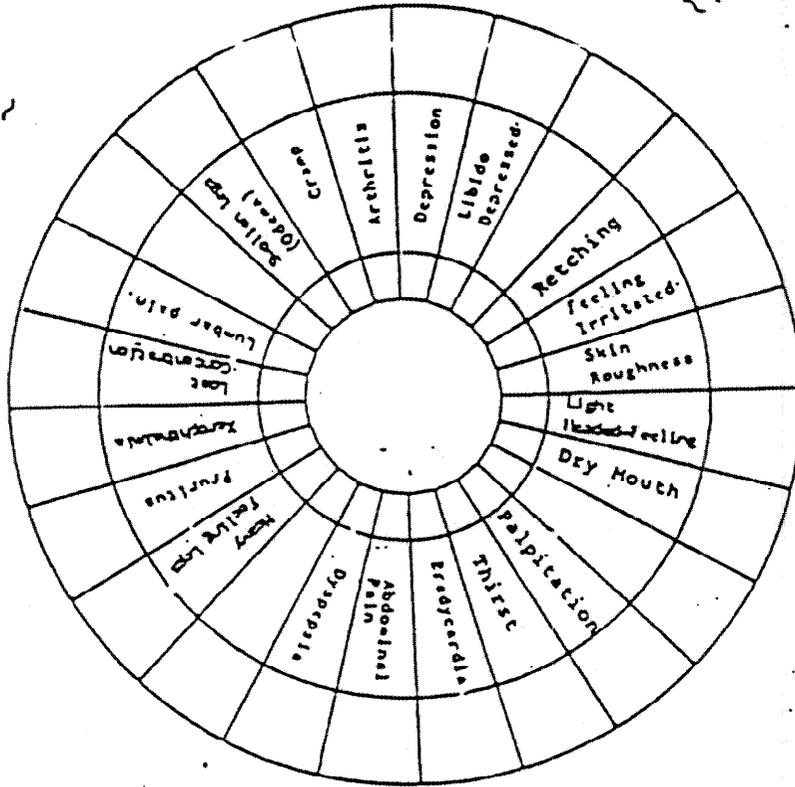
Headache
Nausea
Tinnitus
Malaise
Distress
Diaphoresis
Coldness of limbs
Anorexia
Polyuria
Pollakiuria
Shortness of breath
Fatigue

Table 4 Investigation List of Subjective Effects (2)

Investigation Period
 Investigation Period
 Yr. Mon. Day
 Time ~

No. :
 Name :

Investigation Period
 Yr. Mon. Day
 Time ~



No. :
 Name :

Investigation Period
 Yr. Mon. Day
 Time ~

Investigation Period
 Yr. Mon. Day
 Time ~

No. :
 Name :

Table 5

Questionnaire on the Local Pain after Injection of SMS 201-995

I. Circle the number representing the pain you felt after the first injection.

After the first injection

- 0 : No pain.
- 1 : Mild (mild pain)
- 2 : Moderate (considerable pain, yet tolerable)
- 3 : Severe (strong, intolerable pain)

Date: _____

II-(1). Circle the number representing the pain you felt after the second injection.

After the second injection

- 0 : No pain.
- 1 : Mild (mild pain)
- 2 : Moderate (considerable pain, yet tolerable)
- 3 : Severe (strong, intolerable pain)

II-(2). Which pain was stronger, comparing between the first and the second injection? (Don't enter, if you had no pain at all.)

- 1. After the first injection.
- 2. After the second injection.
- 3. Similar extent.

Date: _____

Name: _____

Table 6 Plasma concentration, C_{max} and AUC of SMS 201-995

Drugs	Time (min) Subject No.	Concentration of SMS 201-995 (ng/ml)														C _{max} (ng/ml)	AUC (ng·min/ml)
		0	5	10	20	30	45	60	90	120	180	240	360	480			
Test Preparation	1	ND	1.25	2.27	3.50	3.76	3.61	3.84	2.45	2.02	1.31	1.07	0.49	0.26	3.84	659.53	
	2	ND	1.76	3.16	3.87	4.71	4.25	4.52	3.13	2.21	1.54	0.93	0.38	0.18	4.71	721.38	
	3	ND	0.67	2.27	3.08	3.38	4.04	3.41	2.77	2.46	1.67	1.06	0.53	0.35	4.04	704.75	
	4	ND	1.50	2.30	3.72	4.28	4.60	4.55	3.16	2.30	1.72	0.89	0.31	0.12	4.60	712.83	
	5	ND	0.41	1.03	2.04	2.86	3.71	3.87	2.50	2.92	1.66	1.41	0.46	0.24	3.87	711.15	
	6	ND	1.00	2.45	4.01	3.96	4.77	4.21	3.32	2.58	1.86	1.25	0.35	0.08	4.77	765.85	
	7	ND	1.65	2.83	4.28	4.40	4.36	3.78	2.76	2.20	1.25	0.98	0.38	0.04	4.40	670.73	
	8	ND	1.45	2.70	4.00	4.22	3.96	3.53	3.14	2.83	1.80	1.12	0.76	0.48	4.22	809.43	
	9	ND	1.52	2.36	2.81	4.11	4.51	4.08	2.89	1.99	1.11	0.98	0.34	0.36	4.51	657.68	
	10	ND	1.78	3.85	4.58	4.72	5.19	4.81	3.42	2.65	1.94	1.38	0.68	0.22	5.19	885.90	
	11	ND	1.33	1.59	4.01	4.17	5.12	4.33	3.56	2.51	1.55	1.07	0.48	0.33	5.12	771.48	
	12	ND	1.76	3.36	4.63	4.77	4.83	4.56	3.32	2.34	1.29	1.00	0.44	0.18	4.83	750.88	
	13	ND	3.62	5.57	7.22	6.00	6.30	5.22	3.35	2.72	1.86	1.17	0.47	0.21	7.22	927.03	
	14	ND	3.73	4.03	5.71	6.19	4.72	4.06	2.92	2.11	1.21	0.93	0.36	0.31	6.19	746.15	
	15	ND	0.65	1.69	3.34	3.25	4.54	3.40	2.83	2.28	1.52	0.97	0.44	0.33	4.54	673.15	
	16	ND	1.69	3.52	4.08	4.69	4.58	3.59	2.82	1.98	1.47	1.86	0.35	0.32	4.69	774.25	
		Mean	ND	1.61	2.81	4.06	4.34	4.57	4.11	3.02	2.38	1.55	1.13	0.45	4.80	746.44	
	S.E.	--	0.23	0.28	0.30	0.22	0.16	0.13	0.08	0.07	0.06	0.06	0.03	0.22	19.30		
Control Preparation	1	ND	1.81	3.52	3.81	3.84	3.80	3.80	2.68	2.11	1.22	0.77	0.24	ND	3.84	610.70	
	2	ND	2.97	4.81	5.57	5.64	5.72	4.62	2.96	2.28	1.13	0.74	0.25	0.09	5.72	728.08	
	3	ND	1.74	3.67	4.63	3.78	3.63	4.13	2.73	2.37	1.65	1.15	0.48	0.37	4.63	748.00	
	4	ND	2.49	3.93	5.27	5.61	5.95	4.47	3.43	1.96	1.41	0.97	0.50	0.35	5.95	798.58	
	5	ND	0.97	1.75	4.13	3.98	4.40	4.06	2.78	2.56	1.51	1.24	0.22	0.17	4.40	703.78	
	6	ND	2.67	3.42	6.24	4.78	5.79	4.37	3.02	2.99	1.58	1.02	0.19	0.13	6.24	788.68	
	7	ND	1.92	3.24	4.39	4.30	4.53	3.86	3.23	2.46	1.52	1.18	0.42	0.22	4.53	754.95	
	8	ND	1.38	2.61	4.26	5.11	4.40	3.38	3.52	2.81	1.50	1.39	0.64	0.32	5.11	818.15	
	9	ND	1.00	1.45	3.55	3.46	2.93	3.13	2.86	1.81	0.97	1.23	0.30	0.03	3.55	582.95	
	10	ND	2.69	4.66	4.65	6.43	5.44	4.07	3.58	2.80	1.58	1.39	0.62	0.49	6.43	905.55	
	11	ND	1.08	2.59	3.95	4.11	4.12	3.74	2.92	2.37	1.37	0.81	0.22	0.07	4.12	641.60	
	12	ND	3.32	4.78	5.96	5.94	5.15	4.55	3.44	2.63	1.57	0.92	0.48	0.44	5.96	848.48	
	13	ND	3.89	5.97	6.04	7.20	6.10	4.61	4.13	3.27	1.87	1.25	0.68	0.35	7.20	1008.20	
	14	ND	2.00	4.27	6.10	6.31	5.60	4.37	2.86	2.13	0.99	0.68	0.51	0.24	6.31	742.08	
	15	ND	0.74	1.44	2.29	2.55	2.91	2.60	2.72	2.34	1.50	1.21	0.30	0.20	2.91	605.23	
	16	ND	3.89	6.45	5.22	4.81	4.16	3.30	2.07	2.31	1.14	0.81	0.15	0.02	6.45	643.35	
		Mean	ND	2.16	3.66	4.75	4.87	4.66	3.94	3.06	2.45	1.41	1.05	0.39	5.21	745.52	
	S.E.	--	0.25	0.37	0.27	0.31	0.26	0.15	0.12	0.10	0.06	0.06	0.04	0.31	29.07		

ND: Not detected (<0.02ng/ml)

Table 7 Analysis of variance for Cmax

Constitution of data by Latin Square

No.	Time period		Total
	I	II	
1	3.55	4.51	8.06
2	6.43	5.19	11.62
3	4.12	5.12	9.24
4	5.96	4.83	10.79
5	7.20	7.22	14.42
6	6.31	6.19	12.50
7	2.91	4.54	7.45
8	6.45	4.69	11.14
Subtotal	42.93	42.29	85.22
1	3.84	3.84	7.68
2	4.71	5.72	10.43
3	4.04	4.63	8.67
4	4.60	5.95	10.55
5	3.87	4.40	8.27
6	4.77	6.24	11.01
7	4.40	4.53	8.93
8	4.22	5.11	9.33
Subtotal	34.45	40.42	74.87
Total	77.38	82.71	160.09

ANOVA table

Source of variance	Df	Ss	Ms	Fcal	Ftab
Between subject	15	27.21	1.81	4.11*	> 2.43
Group or subject	1	3.35	3.35	1.97	< 3.10
Subject/Group	14	23.86	1.70	3.86*	> 2.48
Time period	1	0.89	0.89	2.02	< 4.60
Drug	1	1.37	1.37	3.11	< 4.60
Residual	14	6.22	0.44		
Total	31	35.69			

*: Significant
 Df: Degree of freedom
 Ss: Sum of squares
 Ms: Mean squares

Table 8 Analysis of variance for AUC

Constitution of data by Latin Square

No.	Time period		Total
	I	II	
1	582.05	657.68	1240.63
2	905.55	885.90	1791.45
3	641.50	771.48	1413.08
4	848.48	750.88	1599.36
5	1008.20	927.83	1936.03
6	742.08	746.15	1488.23
7	605.23	673.15	1278.38
8	643.35	774.25	1417.60
Subtotal	5977.44	6187.32	12164.76
1	658.54	610.70	1270.23
2	721.38	728.08	1449.46
3	704.75	748.00	1452.75
4	712.83	798.58	1511.41
5	711.15	703.78	1414.93
6	765.85	788.68	1554.53
7	670.73	754.95	1425.68
8	809.43	818.15	1627.58
Subtotal	5755.65	5950.92	11706.57
Total	11733.09	12138.24	23871.33

ANOVA table

Source of variance	Df	Ss	Ms	Fcal	Ftab
Between subject	15	252248.18	16816.55	6.75*	> 2.43
Group or sequence	1	6560.56	6560.56	0.37	< 3.10
Subject/Group	14	245687.62	17549.12	7.05*	> 2.48
Time period	1	5129.58	5129.58	2.06	< 4.60
Drug	1	6.67	6.67	0.003	< 4.60
Residual	14	34857.03	2489.79		
Total	31	292241.46			

*: Significant
 Df: Degree of freedom
 Ss: Sum of squares
 Ms: Mean squares

Table 9 Minimum detectable difference, confidential interval in difference in bioavailability of the two preparations and minimum necessary number of subjects

Parameter	C _{max}	AUC
Minimum detectable difference ($\alpha=0.05$, $1-\beta=0.8$, $n=8$)	18.2	9.6
Confidential interval (λ)	$-5.2 \leq \delta \leq 20.9$	$-8.8 \leq \delta \leq 7.0$
Minimum necessary number of subjects	5	2

Table 10 Subjective Symptoms

subjects No.	First administration			Second administration		
	drug	pain at the site of injection ⁼²	Subjective Symptoms ⁼²	drug	pain at the site of injection ⁼²	Subjective Symptoms ⁼²
1	=3 Test prep.	--=5	-	=4 Control prep.	(1) 15'	-
2		-	-		(1) 20'	-
3		-	-		-	-
4		-	-		(1) 30'	Dull Headache (1)
5		-	-		-	-
6		-	-		(1) 10'	-
7		-	-		-	-
8		-	Facial Hot Flashes (2). Headache (1)		-	-
9	=4 Control prep.	(1) 30'	-	=3 Test prep.	-	-
10		(1) 30'	-		-	-
11		-	Stomach Discomfort (1)		-	Stomach Discomfort (1)
12		(1) 40'	Nausea (1)		-	-
13		(1) 10'	Thirst (1)		-	-
14		(1) 15'	Nausea · Wooziness (1)		(1) 10'	-
15		-	-		-	-
16		-	-		-	-
SUM	Test prep n=16	Subjec. Symptoms	Facial Hot Flashes 1 Headache 1 Stomach Discomfort 1	1 2 1	2 Cases 12.5%	pain 1 Case 6.3%
	Control n=16	Subjec. Symptoms	Stomach Discomfort 1 Nausea 1 Thirst 1 Wooziness 1 Dull Headache 1	1 2 1 1 1	5 Cases 31.3%	pain 9 Cases 56.3%

* 1 This means continuous time (min)
 * 2 (2): moderate (1): mild
 * 3 Batch No. Y116 0587
 * 4 Batch No. Y011 0287
 * 5 "-- means no pain at the site of injection

Table 11 Results of Physical Examination

No					No						
		(mmHg)		(°C)			(mmHg)		(°C)		
1	first	B	133/77	62	36.7	9	first	B	129/81	74	35.9
		A	125/70	54	36.5			A	124/79	77	35.7
	second	B	130/70	58	36.2		second	B	130/78	76	35.9
		A	121/68	58	36.4			A	114/74	64	35.6
2	first	B	113/62	62	36.2	10	first	B	113/63	68	35.9
		A	102/62	59	36.3			A	113/63	68	35.9
	second	B	102/60	58	36.0		second	B	105/63	78	36.0
		A	104/56	56	35.9			A	120/62	68	36.0
3	first	B	105/68	64	35.5	11	first	B	125/71	84	36.1
		A	109/64	63	36.0			A	119/69	85	36.4
	second	B	116/63	76	35.7		second	B	122/67	90	36.1
		A	113/67	65	35.9			A	111/65	75	36.2
4	first	B	102/60	68	35.6	12	first	B	128/79	79	35.9
		A	101/56	54	35.8			A	126/76	75	36.2
	second	B	91/52	67	35.9		second	B	125/81	82	35.8
		A	97/51	54	35.9			A	121/73	75	35.9
5	first	B	125/70	67	36.0	13	first	B	125/72	73	36.1
		A	130/74	58	36.0			A	107/64	57	35.9
	second	B	122/69	64	36.2		second	B	125/70	66	35.9
		A	109/69	60	35.9			A	119/68	58	35.9
6	first	B	99/54	64	35.6	14	first	B	109/65	76	35.8
		A	99/53	59	35.6			A	119/68	67	35.8
	second	B	97/59	62	35.3		second	B	108/60	77	35.8
		A	98/58	66	35.5			A	108/65	66	35.8
7	first	B	95/61	68	36.4	15	first	B	128/76	60	35.4
		A	104/61	63	36.2			A	123/58	62	35.4
	second	B	98/57	73	36.0		second	B	119/70	68	35.3
		A	110/63	66	36.2			A	118/67	56	35.3
8	first	B	131/75	71	35.8	16	first	B	116/68	87	36.3
		A	131/63	61	36.1			A	107/60	75	36.2
	second	B	131/74	75	36.0		second	B	107/67	80	35.1
		A	120/68	75	36.1			A	107/62	79	36.0

No Data Missing, pagination correction made.

Table 12 Laboratory Data (1)

Examination Item	Baseline value	Unit	No 1		No 2		No 3		No 4		No 5		No 6		No 7		No 8		
			I	II															
WBC	4500~8000	/mm ³	7,800	7,000	6,900	6,100	5,000	4,300	5,900	6,100	6,300	5,900	4,900	5,500	7,100	4,700	7,600	6,700	
RBC	410~530	$\times 10^4/\text{mm}^3$	454	438	450	453	483	478	511	503	547	541	471	467	517	490	545	519	
Hemoglobin	14~18	g/dl	14.5	14.2	14.4	14.4	15.2	15.1	15.1	14.7	16.5	16.4	14.2	14.0	16.0	15.6	16.3	15.7	
Hematocrit	40~48	%	43	42	45	45	48	48	48	46	52	52	45	44	48	47	50	49	
Platelet	12~40	$\times 10^4/\text{mm}^3$	18	18	25	24	18	19	21	21	18	19	19	20	24	22	22	22	
Leu. Differ. (%)	Rhabdocytic	0~19	%	0	1	1	0	0	2	1	0	0	2	1	5	3	1	1	0
	Karyoblastic	27~72	%	45	62	54	49	45	53	40	53	59	53	39	55	50	43	44	61
	Lymphocytes	20~60	%	44	29	35	34	48	37	53	34	31	35	52	34	38	36	44	33
	Eosinophils	0~10	%	3	8	1	8	1	6	2	5	3	5	3	2	8	10	5	4
	Basophils	0~3	%	2	0	3	3	3	1	1	1	1	1	1	1	0	2	1	0
	monocytes	0~12	%	6	0	6	6	3	1	3	7	4	4	4	3	1	8	5	2
Total protein	6.5~8.0	g/dl	7.2	7.1	6.6	6.8	6.6	7.0	7.0	7.0	7.2	6.8	7.3	7.0	7.0	7.0	7.7	7.6	
Albumin	3.7~5.2	g/dl	4.9	4.8	4.5	4.6	4.5	4.8	4.5	4.5	4.8	4.6	4.9	4.7	4.8	4.4	5.1	4.7	
BUN	8~20	mg/dl	10	10	12	14	8	10	11	14	10	12	18	14	15	12	1	12	
Creatinine	0.8~1.7	mg/dl	0.8	0.8	0.8	1.0	0.7	1.0	0.8	0.9	0.8	1.0	0.8	0.9	0.8	0.9	0.8	0.8	
Uric acid	3.5~7.9	mg/dl	6.7	5.9	4.9	4.7	5.1	5.4	6.0	6.0	4.9	5.2	3.1	3.1	4.6	4.2	5.5	5.5	
Total cholesterol	130~230	mg/dl	167	169	173	170	115	123	116	107	160	146	156	141	144	139	205	204	
Triglyceride	70~170	mg/dl	95	71	112	118	104	63	64	55	89	81	51	45	78	86	157	136	
Electrolytes	Na	135~147	mEq/l	143	143	141	141	139	140	139	140	139	140	141	140	140	139	139	
	K	3.6~5.2	mEq/l	4.1	4.3	4.6	5.1	4.4	4.4	4.5	4.6	4.2	4.6	4.0	4.7	4.5	4.4	4.6	
	Ca	98~108	mEq/l	102	102	103	102	100	101	100	100	99	99	101	102	101	101	99	
	Ca	4.5~5.5	mEq/l	4.9	4.8	4.9	5.0	5.0	4.9	4.9	4.8	5.1	4.9	5.0	4.8	4.8	4.7	5.1	
Al-p	2.6~10	U	4.9	4.7	6.4	6.4	6.4	6.6	8.5	9.0	5.5	5.6	5.5	5.5	7.8	7.9	9.0	8.9	
GOT	8~40	U	16	16	14	14	12	13	15	15	15	15	12	11	15	16	19	17	
GPT	5~35	U	19	22	10	10	10	11	11	10	17	15	10	10	15	15	16	14	
LDH	50~400	U	241	251	303	299	223	236	268	265	228	211	248	244	271	266	307	310	
γ -GTP	0~50	mU/ml	16	14	14	13	9	8	15	12	54	52	8	7	14	13	15	15	
Total bilirubin	0.2~1.0	mg/dl	0.5	0.5	0.5	0.5	0.4	0.4	0.5	0.5	0.5	0.5	0.4	0.4	0.5	0.5	0.5	0.5	
Glucose	70~110	mg/dl	84	94	86	92	88	93	89	93	91	92	82	88	91	89	89	93	

I : before the first dosage
 II : after the second dosage

Table 12 Laboratory Data (2)

Examination Item	Baseline value	Unit	No 9		No 10		No 11		No 12		No 13		No 14		No 15		No 16	
			I	II														
WBC	4500-8000	/mm ³	6,300	5,400	5,800	5,000	6,700	4,100	4,900	4,900	5,700	5,100	5,600	5,600	4,500	5,500	6,300	5,600
RBC	410-530	10 ⁶ /mm ³	485	468	491	477	549	528	468	459	498	488	483	479	465	435	445	431
Hemoglobin	14-18	g/dl	15.5	15.0	15.6	15.5	15.7	14.7	14.0	14.1	15.2	15.3	14.5	14.4	14.4	13.7	14.6	14.3
Hematocrit	40-48	%	45	43	48	47	51	47	45	46	47	47	45	45	44	47	43	42
Platelet	12-40	10 ⁶ /mm ³	20	20	23	25	23	19	21	22	17	16	25	22	19	19	21	21
Leu. Differ. (%)	Rhabdocytic	0-19	%	0	0	0	0	2	2	0	1	1	0	0	1	1	1	0
	Karyoblastic	27-72	%	50	58	45	43	48	62	52	60	50	65	32	53	50	59	54
	Lymphocytes	20-60	%	37	29	43	43	43	29	34	28	41	27	52	28	32	30	36
	Eosinophils	0-10	%	3	4	8	5	1	1	8	2	5	3	9	10	6	3	2
	Basophils	0-3	%	2	1	0	2	1	1	3	0	0	1	1	0	1	0	2
	monocytes	0-12	%	8	8	4	7	5	5	3	9	3	4	6	8	10	7	3
Total protein	6.5-8.0	g/dl	7.2	6.5	7.1	7.0	7.8	7.1	7.0	6.8	7.2	7.2	7.0	6.8	7.6	6.6	7.1	
Albumin	3.7-5.2	g/dl	4.6	4.4	4.8	4.7	5.3	4.8	4.6	4.5	4.7	4.7	4.6	4.6	5.2	4.5	4.7	
BUN	8-20	mg/dl	11	11	13	12	11	12	11	11	14	16	8	9	13	12	17	
Creatinine	0.8-1.7	mg/dl	0.8	0.8	0.8	1.1	0.9	1.1	0.7	0.2	0.9	0.9	0.8	1.0	0.8	0.8	0.7	
Uric acid	3.5-7.9	mg/dl	5.9	6.3	4.6	4.8	4.3	3.9	6.6	6.3	6.8	5.7	6.8	5.5	5.4	5.2	6.2	
Total cholesterol	130-230	mg/dl	208	169	152	145	166	149	158	150	129	122	157	156	161	137	153	
Triglyceride	70-170	mg/dl	127	118	104	114	80	39	48	60	67	76	62	47	153	118	88	
Electrolytes	Na	135-147	mEq/l	140	141	140	142	139	141	140	140	143	142	140	141	140	140	
	K	3.6-5.2	mEq/l	4.0	4.0	4.2	4.0	4.5	5.3	3.9	4.3	3.8	4.4	4.1	4.0	4.4	4.5	
	Cl	98-108	mEq/l	100	102	102	101	99	101	100	100	103	103	102	101	101	101	
	Ca	4.5-5.5	mEq/l	4.8	4.6	4.8	4.6	5.1	5.0	4.9	4.7	4.9	5.0	4.9	4.4	4.9	4.8	
Al-p	2.6-10	U	5.9	6.2	3.8	4.1	8.8	8.4	8.2	8.3	5.4	6.0	6.0	5.6	5.8	6.2		
GOT	1-40	U	12	15	10	11	17	14	13	12	14	14	12	10	14	14		
GPT	5-35	U	19	18	11	10	11	10	13	12	11	10	10	10	22	20		
LDH	50-400	U	276	235	270	254	230	219	240	249	310	282	234	219	286	264		
γ-GTP	0-50	u/l	11	9	7	7	11	7	19	16	12	10	21	18	27	18		
Total bilirubin	0.2-1.0	mg/dl	0.4	0.5	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.4	0.4	0.4	0.6	0.5		
Glucose	70-110	mg/dl	85	96	86	94	81	78	83	89	91	92	89	94	102	103		

I : before the first dosage
 II : after the second dosage

Table 12 Laboratory Data (3)

Examination Items	Baseline Value	Unit	No. 1		No. 2		No. 3		No. 4		No. 5		No. 6		No. 7		No. 8	
			I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II
pH			6.0	6.0	5.5	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	5.5	5.5	6.0	6.0
Urobilinogen			±	±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
Icton Body			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Glucose			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Protein			±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urinary Examination Sediments	RBC			0-1/SF*				0-1/SF*		0-1/SF*		0-1/SF*		0-1/SF*				0-1/SF*
	WBC		1-2/1	1-2/1	1-2/1	0-1/1	1-2/1	1-2/1	1-2/1	0-1/SF*	1-2/1	1-2/SF*	0-1/1	0-1/1	0-1/SF*	0-1/SF*	2-1/1	1-2/SF*
	Epithelium		0-1/1	0-1/SF*		0-1/SF*	0-1/SF*	0-1/1	1-2/SF*	3/V**	0-1/1	1-2/SF*	0-1/1	1-2/SF*	0-1/SF*	0-1/SF*	0-1/SF*	
	Cylinder					0-1/SF*		0-1/SF*										
	Bacteria																	
	Mutin		+	+	+	+		+	+		+	+	+	+		+		+
	Amorphous phosphate							+	+					+				+
	CaC ₂ O ₄				+				+			+	+	+	+			

I: before the first dosage
 II: after the second dosage

SF*: several fields
 V**: whole fields

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Table 12 Laboratory Data (4)

Examination Items	Baseline Value	Unit	No 9		No 10		No 11		No 12		No 13		No 14		No 15		No 16	
			I	II	I	II	I	II										
pH			6.0	6.0	6.0	6.0	7.0	6.0	6.0	5.5	6.0	6.0	6.5	6.0	6.0	5.5	6.0	6.5
Urobilinogen			±	±	±	±	±	±	±	±	+	±	±	±	±	±	±	±
Keton body			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Glucose			-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Protein			-	-	-	-	-	-	-	-	±	-	±	-	-	-	-	-
Sediments	RBC		0-1/SF*	2/V**	0-1/SF*	0-1/SF*	0-1/SF*	2-3/SF*	0-1/SF*									
	WBC		0-1/1	1-2/SF*	1-2/1	1-2/SF*	1-2/1	0-1/1	1-2/1	1-2/1	0-1/1	1-2/1	0-1/1	0-1/1	1-2/1	1-2/1	0-1/1	0-1/1
	Epithelium		1-2/SF*	0-1/SF*	0-1/SF*	0-1/SF*	0-1/1	1-2/SF*	0-1/SF*	0-1/1	0-1/SF*	0-1/SF*	0-1/SF*	0-1/SF*	1-2/SF*	0-1/1	1-2/S*	2/V**
	Cylinder																	
	Bacteria					+												
	Mutin			+	+		+	+	+	+		+	+	+	+	+	+	+
	Amorphous phosphate					+		+	+		+	+	+					+
	CaC ₂ O ₄									+	+	+						

I: before the first dosage
 II: after the second dosage

SF*: several fields
 V**: whole fields

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