

# Electronic Mail Message

**Date:** 8/24/00 10:30:00 AM  
**From:** Jerry Phillips ( PHILLIPSJ )  
**To:** Edward Fromm ( FROMME )  
**Cc:** Sammie Beam ( BEAMS )  
**Cc:** Peter Honig ( HONIGP )  
**Subject:** BENEVAS - OPDRA Consult 21-286

Edward:

This E-mail is in response to your 8/2/00 consult to OPDRA for a proprietary name review for Benevas (Olmesartan Medoxomil Tablets; NDA 21-286; Sankyo). A written response will follow, but I thought I would give you the jump on informing the applicant. OPDRA recognizes that the LNC reviewed this name on 4/28/99 and that it was found acceptable.

result in medication errors.

The PTO also states that Benevas was registered for trademark by Sankyo on 7/22/99 and 2/28/2000.

suggestion is that you inform Sankyo that OPDRA finds the proprietary name Benevas actionable

submit another name to the Agency for review.

If you would like to further discuss this, please contact me at 827-3246. Thanks.

Jerry

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
FDA/CDER/HFD-110  
5600 Fishers Lane  
Rockville, MD 20857

Woodmont II  
1451 Rockville Pike  
Rockville, MD 20852

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**Transmitted to FAX Number:** 212-308-2491  
**Attention:** Dr.. MaryJane Rafii  
**Company Name:** Sankyo U.S.A. Corporation  
**Phone:** 212-753-8207  
**Subject:** Trade Name  
**Date:** 4/29/99  
**Pages including this sheet:** 2  
**From:** Zelda McDonald  
**Phone:** 301-594-5333  
**Fax:** 301-594-5494

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

CDER LABELING AND NOMENCLATURE COMMITTEE

AND

CONSULT # 1170	HFD# 110	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION: Daruta G. Cunningham		Benevas	

A. Look-alike/Sound-alike

Potential for confusion:

Benadryl	XXX	Low	Medium	High
Bendazac (USAN)	XXX	Low	Medium	High
Benamid	XXX	Low	Medium	High
Denavir	XXX	Low	Medium	High
Demadex	XXX	Low	Medium	High

B. Misleading Aspects:

C. Other Concerns:

--	--

D. Established Name

Satisfactory  
 Unsatisfactory/Reason:

Recommended Established Name

E. Proprietary Name Recommendations:

ACCEPTABLE       UNACCEPTABLE

F. Signature of Chair/Dat

/s/ \_\_\_\_\_ 4/28/99

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 3, 2001

FROM: <sup>15</sup>Edward ~~Fro~~mm, Regulatory Health Project Manager  
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 21-286  
Benicar (olmesartan medoxomil) Tablets  
DSI Audits

At the September 20, 2000 filing meeting, the Division determined that DSI audits were not needed for this application. Dr. Stockbridge noted that the "sartans" were a well-studied class of drugs and that no trial or center contributed a critical amount of data by themselves to the application. Therefore it was unlikely that deficiencies at a center or small number of centers would affect the result of the trial. He subsequently sent an e-mail to Dr. Temple outlining the reasons why the Division would not be asking for DSI audits of this application.

DSI decided on their own volition to conduct audits of several study sites of the application. No major violations were reported. Copies of the audit reports will be included in the action package for this application.

**APPEARS THIS WAY  
ON ORIGINAL**

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



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**Transmitted to FAX Number:** (732) 906-5690

**Attention:** Mr. Albert Yehaskel

**Company Name:** Sankyo Pharma

**Phone:** (732) 590-5009

**Subject:** Minutes of Telecon w/FDA, March 7, 2002  
NDA 21-286, Benicar (olmesartan medoxomil) Tablets

**Date:** March 25, 2002

**Pages including this sheet:** 3

**From:** Edward Fromm  
**Phone:** 301-594-5313  
**Fax:** 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

## **Minutes of a Telephone Conference Call between Sankyo and the FDA**

**Date:** March 7, 2002  
**Application:** NDA 21-286  
Benicar (olmesartan medoxomil) Tablets  
**Sponsor:** Sankyo Pharma Inc.  
**Subject:** Discussion of Labeling Issues

### **FDA Participants**

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research  
Douglas C. Throckmorton, M.D., HFD-110, Acting Division Director  
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader  
Akinwale Williams, M.D., HFD-110, Medical Officer  
Shari Targum, M.D., HFD-110, Medical Officer  
James Hung, Ph.D., HFD-110, Statistician/Team Leader  
Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology and Biopharmaceutics, Team Leader  
J.V. Advani, Ph.D., HFD-810, Chemist  
Edward Fromm, HFD-110, Project Manager

### **Sankyo**

John Alexander, M.D., President  
James Molt, Ph.D., Vice President, Regulatory Affairs  
Albert Yehaskel, M.S., MBA, Senior Director, Regulatory Affairs  
Bruce Dornseif, Ph.D., Senior Director, Biostatistics  
Harvey Masonson, M.D., Senior Director, Clinical Research  
John Gargiulo, Vice President, Marketing and Commercial Operations

### **Background**

Benicar (olmesartan medoxomil) is an angiotension II antagonist proposed for the treatment of hypertension. On October 24, 2001, Sankyo was issued an approvable letter with marked-up draft labeling enclosed. One of the conditions of the approvable letter, however, was that concerns about an excess of renal tumors in animals associated with the drug be re-addressed before the full CAC (Carcinogenicity Assessment Committee). The CAC met on January 31, 2002 and concluded that olmesartan was not a human carcinogen.

Following the meeting, the Division revised the **Carcinogenesis, Mutagenesis, and Impairment of Fertility** subsection of the labeling and these changes were forwarded to the sponsor. Sankyo indicated that these revisions were acceptable and asked for a telecon to discuss the other sections of the labeling.

## Telecon

Shortly before the telecon began, a revision of the **Dosage and Administration** section was faxed to the Sankyo for review. They indicated that the revision was acceptable. Dr. Throckmorton noted that in reviewing the labeling of the approved sartans, a lower dose was available for special populations, even though this dose was not always specified for these populations. He suggested that a 5 mg dose be available for patients who fit this category (e.g., patients that are renally or hepatically impaired). Sankyo said that a 5 mg dose was acceptable. They will check on possible unresolved chemistry or biopharmaceutics issues related to the marketing of the 5 mg dose.

Dr. Temple noted that the sponsor should revise, under **Clinical Trials**, the bar graph entitled "Dose-Response for BENICAR, Sitting Blood Pressure, Change from Baseline" and change it into a line graph because the bar graph was confusing. Dose-response data from a meta-analysis of the trials should be generated to show placebo-subtracted lines (one each for systolic and diastolic blood pressures). Sankyo said they would revise the graph and asked if least square means could be used for statistical analysis of the data. Dr. Temple said this was acceptable.

The Agency and Sankyo also discussed changes to the **Clinical Pharmacology, Special Populations, Pharmacodynamics, Geriatric Use, Adverse Reactions, and How Supplied** sections of the labeling.

Minutes Preparation:

  
Edward Fromm

Concurrence, Chair:

  
Robert Temple, M.D.

drafted: ef/3-12-02/3-21-02

Rd: JVAdvani-3-18-02  
PMarroum-3-18-02  
JHung-3-18-02  
STargum-3-19-02  
AWilliams-3-19-02  
NStockbridge-3-19-02  
DThrockmorton-3-19-02

# MESSAGE CONFIRMATION

03/25/02 10:37  
ID=FDA CDER DCRDP

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## DIVISION OF CARDIO-RENAL DRUG PRODUCTS FOOD AND DRUG ADMINISTRATION



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**Transmitted to FAX Number:** (732) 906-5690

**Attention:** Mr. Albert Yehaskel

**Company Name:** Sankyo Pharma

**Phone:** (732) 590-5009

**Subject:** Minutes of Telecon w/FDA, March 7, 2002  
NDA 21-286, Benicar (olmesartan medoxomil) Tablets

**Date:** March 25, 2002

**Pages including this sheet:** 3

## Minutes of a Telephone Conference Call between Sankyo and the FDA

Date: May 23, 2001  
Application: NDA 21-286  
Benicar (olmesartan medoxomil) Tablets  
Applicant: Sankyo Pharma Inc.  
Subject: Approvability Issues

### FDA participants

Douglas Throckmorton, M.D., HFD-110, Deputy Division Director  
Norman Stockbridge, M.D., Ph.D., Medical Team Leader  
Shari Targum, M.D., HFD-110, Medical Officer  
Akinwole Williams, M.D., HFD-110, Medical Officer  
Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader  
Gowra Jagadeesh, Ph.D., HFD-110, Pharmacologist  
Natalia Morgenstern, HFD-110, Chief, Project Management Staff  
Edward Fromm, HFD-110, Project Manager

### Sankyo

Kanichi Nakamura, Ph.D., Chairman, Sankyo Pharma Inc.  
Thomas Robinson, M.D., V.P., Development  
Harvey Masonson, M.D., Senior Director, Clinical Research  
Donald Hinman, Ph.D., Director, Clinical Research  
Antonia Wang, Ph.D., Director, Biostatistics  
Hisashi Nakagaki, R.Ph., Assistant Director, Liaison  
John Short, R.Ph., Senior Director, Regulatory Affairs  
Mirei Tanaka, R.Ph., Assistant Manager, Regulatory Affairs  
— Consultant

### **Background**

The full CAC (Carcinogenicity Assessment Committee) met on May 4, 2001 to discuss genotoxicity and carcinogenicity issues associated with olmesartan medoxomil. A majority of the committee felt that olmesartan medoxomil was positive for carcinogenicity in the 2-year rat study.

Dr. Temple was informed, on May 17, 2001, of the results of the CAC meeting and other pharm/tox issues regarding the drug. After a briefing by Dr. DeGeorge and the Division pharmacologists, he believed, that overall, the potential risks of using the drug seemed to outweigh the potential benefits.

### **Telecon**

Dr. Throckmorton (for Dr. Lipicky who was unable to attend) opened the telecon by noting that the Division wanted to provide comments to the firm regarding the recently completed medical review as well as Dr. Temple's view of the genotoxic and carcinogenic issues associated with the drug.

Medical

Dr. Throckmorton said the drug appears to be efficacious and that this efficacy could be reasonably described in the labeling. The safety profile of the drug, however, is less clear. It appears that the drug causes liver enzyme elevations (e.g., AST, ALT) although the Division is uncertain about the severity of these increases. Further review of the liver data is planned, but at the present time, the elevations alone do not appear to warrant a not-approvable action.

CAC Results

Dr. Throckmorton said that Dr. Temple was briefed by Center and Division pharmacologists regarding the CAC meeting results. The Center is particularly concerned about increased renal tumor incidence in male rats in the 2-year carcinogenicity study as well as the increased incidence of hyperplasia in the kidneys of male and female rats in that study. Additionally, it appears that the genotoxic profile of the drug is more adverse than that of the previously approved sartans. Dr. Throckmorton said that Dr. Temple believed that, based on the genotoxicity and carcinogenicity evidence presented to him to date, a not-approvable action for the application was warranted.

Sankyo asked if the Division had any suggestions about changing Dr. Temple's opinion of the drug. Dr. Resnick said that one issue that the Agency was grappling with was how to distinguish hyperplasia in the rat kidneys from adenomas. An independent re-reading of the rat kidney slides might help in this regard, if the firm was agreeable to this. The firm said they had no objection to supplying the slides. Dr. Resnick said the address and contact information of the reviewing pathologist would be supplied to the firm after the telecon.

Dr. Throckmorton suggested a face to face meeting with Dr. Temple and the Division to discuss the genotoxicity/carcinogenicity and other issues associated with the drug. Mr. Fromm said that May 30<sup>th</sup>, 2001 was open for a meeting if this date was agreeable to the company. Sankyo said that date was acceptable and appreciated the opportunity to meet with the Agency to discuss the drug.

Minutes Preparation:

  
Edward Fromm

Concurrence, Chair:

  
Douglas Throckmorton, M.D.

6.8.01

## Minutes of a Telephone Conference Call between Sankyo and the FDA

Date: March 7, 2001  
Application: NDA 21-286  
Olmesartan Tablets  
Sponsor: Sankyo Pharma Inc.  
Subject: 20 and 40 mg dosage strengths

### FDA participants

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products  
Edward Fromm, HFD-110, Project Manager

### Sankyo

Kanichi Nakamura, Ph.D., Chairman of the Board, Sankyo Pharma Inc.  
Tom Robinson, M.D., Vice President, Clinical Development  
James Molt, Ph.D., Vice President, Regulatory and Drug Safety  
Harvey Masonson, M.D., Senior Director, Clinical Research  
Antonia Wang, Ph.D., Director, Biostatistics  
John Gariulo, Vice President, Marketing  
Albert S. Yehaskel, M.S., M.B.A., Associate Director, Regulatory Affairs  
Consultant

### **Background**

Sankyo submitted NDA 21-286 on July 25, 2000 for olmesartan Tablets for the treatment of hypertension. The Division requested a teleconference with the firm to clarify what dosage forms of olmesartan would be available for marketing, subject to approval of the drug.

### **Telecon**

Dr. Lipicky opened the telecon by noting that there appears to have been some confusion arising from a December, 2000 teleconference in which the Division stated that firm should consider eliminating either the 20 or 40 mg strength proposed for marketing. He said the Division was in error in making that suggestion and apologized for the confusion. Dr. Lipicky said it would be helpful if the 5, 20, and 40 mg dosage forms were available for prescribing. The firm said that they planned on marketing the 20 and 40 mg strengths of the tablets but thought that the 5 mg strength would not be used by many patients. Dr. Lipicky said the 5 mg dosage should be available for special populations. The firm said that they had CMC data to support the 5 mg strength and confirmed that 5 mg tablet will be included in the dosage strengths available for marketing. Dr. Lipicky encouraged the firm to send that data to the Division for review, if they had not done so already.

Sankyo asked if 5 mg would be the starting dose (as listed in **DOSAGE AND ADMINISTRATION**). Dr. Lipicky said the Division was still reviewing the efficacy data so it was too early to determine the dose-response effect of olmesartan or what would be included in the **DOSAGE AND ADMINISTRATION** section of the labeling. Dr. Lipicky ended the telecon by noting that there was now no need for the meeting scheduled with the Division on March 13, 2001 and therefore it was cancelled.

Dr. Lipicky ended the telecon by noting that there was now no need for the meeting scheduled with the Division on March 13, 2001 and therefore it was cancelled.

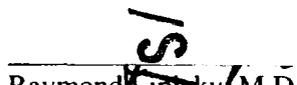
**Summary**

- The meeting for March 13, 2001 with the Division was cancelled.
- Dr. Lipicky said the firm could make available for marketing strengths of olmesartan in 5, 20 and 40 mg.
- Sankyo confirmed that they would make available for marketing strengths of olmesartan in 5, 20, and 40 mg. Dr. Lipicky said this was acceptable.
- CMC data to support the 5 mg strength should be sent in to the Division if it had not been sent in already.

Minutes Preparation:

  
Edward Fromm

Concurrence, Chair:

  
Raymond Lipicky, M.D.

drafted: ef/3-12-01

**Minutes of a Telephone Conference Call between Sankyo and the FDA**

Date: December 8, 2000  
Application: NDA 21-286  
Benevas (olmesartan) Tablets  
Sponsor: Sankyo Pharma Inc.  
Subject: Stability questions regarding the 5 mg strength of olmesartan

FDA participants

Kasturi Srinivasachar, Ph.D., Team Leader, Chemistry, Division of New Drug Chemistry I (HFD-810)  
Florian Zielinski, Ph.D., HFD-810, Chemist  
Edward Fromm, HFD-110, Consumer Safety Officer

Sankyo

Albert Yehaskel, MS, MBA (Associate Director, Regulatory Affairs, Sankyo Pharma Inc.)

**Background**

On December 7, 2000, the Division asked Sankyo to consider adding a 5 mg strength for special populations (i.e., renal impaired, geriatric patients). Sankyo requested a teleconference to discuss what stability information would be needed for the 5 mg strength of olmesartan prior to approval.

**Telecon**

Sankyo began the meeting by noting that it had 3-month stability information for 4 pilot scale batches of olmesartan in the 5 mg strength in both bottles and blisters. The firm asked the Division if this data, from a CMC point of view, would be sufficient to support a 5 mg strength of olmesartan for approval. Dr. Srinivasachar said the 3-month data should be sufficient to support approval of the 5 mg strength but said that the company would need to send in all 4 pilot studies data to the Division for review.

Minutes Preparation: Edward Fromm

Concurrence, Chair: Kasturi Srinivasachar, Ph.D.

cc: NDA 21-286

drafted: 12/28/00

Rd: FZielinski-12/28/00

## **Minutes of a Telephone Conference Call between Sankyo and the FDA**

Date: December 7, 2000

Application: NDA 21-286  
Benevas (olmesartan medoxomil) Tablets

Applicant: Sankyo Pharma Inc.

Subject: Guidance on proposed dosages for olmesartan for hypertension

### FDA Participants

Douglas Throckmorton, M.D., HFD-110, Deputy Division Director  
Norman Stoekbridge, M.D., Ph.D., HFD-110, Team Leader, Medical  
Patrick Marroum, Ph.D., HFD-860, Team Leader, Clinical Pharmacology and Biopharmaceutics  
Zelda McDonald, HFD-110, Regulatory Health Project Manager  
Quynh Nguyen, Pharm.D., HFD-110, Regulatory Health Project Manager

### Sankyo

John C. Alexander, M.D., Executive Vice President  
Consultant

Harvey Masonson, M.D., Senior Director, Clinical Research

Antonia Wang, Ph.D., Director, Biostatistics

John Gargiulo, Vice President, Marketing

Albert Yehaskel, Associate Director, Regulatory Affairs

### **Background**

Olmesartan is an angiotensin II receptor antagonist proposed to treat hypertension. The sponsor is seeking to market the agent in two doses, at 20 mg and 40 mg. The teleconference was scheduled to discuss the reasons for marketing the agent at both doses and also whether a lower dose should be available for titration and special populations.

### **Teleconference**

#### Clinical difference between the 20 and 40 mg doses

Dr. Throckmorton began the teleconference by asking the sponsor what the difference in antihypertensive effect was between the 20 and 40 mg doses. The sponsor replied that at a daily dose of 20 mg, there was an additional decrease in diastolic blood pressure of 1 mmHg and at a daily dose of 40 mg, there was an additional decrease in systolic blood pressure of > 2 mmHg. When questioned whether this difference was considered to be significant, the sponsor said yes.

Because there seemed to be no appreciable difference in the 20 and 40 mg doses, the Division proposed that one dose be selected for marketing and a lower dose be selected for titration.

The sponsor disagreed that there was no difference in efficacy between the 20 and 40 mg doses and made reference to three studies that they believed demonstrated efficacy between the doses. In one U.S. study, the sponsor noted that there was a clear plateau in the dose-response curve above the 20 mg dose. In another study, there was a decrease of 4 to 5 mmHg in systolic blood pressure in a group of 85 to 90 patients. In a European study, in which there were 115 patients per group, there was a decrease in systolic blood pressure of > 2 mmHg when the dose was raised from 20 to 40 mg.

The sponsor stated that in the past, the Division had approved doses with similar efficacy, citing losartan, \_\_\_\_\_ as examples. The Division replied that the labels for those drugs would be reviewed by the Division to determine why that argument was previously made. The Division did note that the Cozaar (losartan) label states that the 150 mg dose did not produce a greater effect than the 50 and 100 mg doses, and that the 150 mg dose was not recommended. The Division suggested that the sponsor may wish to state that "there is no greater effect over 40 mg" in the label for olmesartan.

The Division asked whether the sponsor had analyzed for a difference between the two dose groups, noting that if both the 20 and 40 mg doses looked similar with respect to efficacy, then the sponsor would need a good argument for the 40 mg dose. The sponsor replied that they believed systolic blood pressure values were becoming more clinically relevant and that even small differences in systolic blood pressure were medically important.

The sponsor also noted that no side effects were observed at the 40 mg dose. The Division then asked why the sponsor did not market only the 40 mg dose. The sponsor replied that based on the dose-response curve, they thought some patients would receive additional benefit with the 40 mg dose. The sponsor added that there was a medically significant difference in marketing the 40 mg dose. In the case of \_\_\_\_\_ the sponsor noted that there appeared to be less efficacy with the larger doses. The sponsor also referred to the \_\_\_\_\_ label, which stated that raising the dose from 160 mg to 320 mg produced no change in systolic blood pressure and a decrease of only 1 mmHg in diastolic blood pressure. Based on these reasons, the sponsor believed that some individual patients would benefit at the higher dose and other patients would benefit from titration. However, the Division communicated that the Agency tends to attach more importance to mean, rather than responder, data.

In response to the Division's suggestion that the sponsor include an \_\_\_\_\_ mg dose in addition to the 20 and 40 mg doses already proposed, the sponsor said that an \_\_\_\_\_ mg dose was determined not to be useful. Additionally, the \_\_\_\_\_ mg dose was observed to cause dizziness. The Division encouraged the sponsor to compile this information, including that they had found the \_\_\_\_\_ mg dose not to be useful, in making their argument.

#### Titration dose

The Division indicated the need for a dose down from the maximal plateau of the dose-response curve to be used in patients who needed to be titrated. The Division asked if the sponsor had other formulations to be used in patients who needed a lower dose. The sponsor responded that they had a 5 mg and \_\_\_\_\_ mg formulation for commercial use and that the stability data for these doses were also available. The sponsor said that they were not ruling out a dose lower than 20 mg and that they could use a lower dose if needed. The sponsor added that they were proposing the 20 and 40 mg doses so as not to impose an extra economic burden, since it would be more financially challenging to double the 20 mg dose than to take one 40 mg dose. The sponsor also

said that the 20 and 40 mg doses would provide some benefit in terms of patient convenience when used for titration.

**Conclusion**

The Division reiterated that in order to market both the 20 and 40 mg doses, the sponsor needs to provide a good argument that there is a clear difference in efficacy between the doses. The Division indicated the need for a lower dose (e.g., 5 mg) that would be useful in patients who would need to be titrated. Additionally, the Division would review the labels for other angiotensin II receptor antagonists to determine why doses with similar efficacy were allowed previously.

The sponsor noted that it would take the Division's comments under advisement. The sponsor would like to meet with the Division again early next year to further discuss these issues.

Minutes Preparation:

  
\_\_\_\_\_  
Quynh Nguyen, Pharm.D. 1-2-01

Concurrence, Chair:

  
\_\_\_\_\_  
Douglas Throckmorton, M.D. 1-2-01

qn/12-15-00/12-26-00

rd: DThrockmorton/12-18-00  
NStockbridge/12-18-00  
PMarroum/12-18-00  
ZMcDonald/12-15-00  
EFromm/12-15-00

cc: NDA 21-286  
HFD-110  
HFD-110/QNguyen  
HFD-110/SMatthews

OCT 6 2000

**Minutes of a NDA Filing Meeting**

Date: September 20, 2000

Application: NDA 21-286  
Benevas (olmesartan medoxomil)  
5, — 20, and 40 mg Tablets

Applicant: Sankyo Pharma Inc.

Primary Goal Date: May 25, 2001

Secondary Goal Date: July 25, 2001

**Participants:**

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products  
Steven Fredd, M.D., HFD-110, Deputy Division Director  
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director  
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader  
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader  
Steven Mark Rodin, M.D., HFD-110, Medical Officer  
Akinwole Williams, M.D., HFD-110, Medical Officer  
James Hung, Ph.D., HFD-110, Statistician/Team Leader  
Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader  
Gowra Jagadeesh, Ph.D., HFD-110, Pharmacologist  
Kasturi Srinivasachar, Ph.D., Team Leader, Chemistry, Division of New Drug Chemistry I (HFD-810)  
Florian Zielinski, Ph.D., HFD-810, Chemist  
Sayed Al-Habet, Ph.D., HFD-860, Biopharmaceuticist  
Khin Maung U, M.D., HFD-45, DSI, Medical Officer  
Michael Skelly, Ph.D., HFD-48, DSI, Pharmacologist  
Edward Fromm, HFD-110, Consumer Safety Officer

**Background**

Sankyo has submitted this NDA for olmesartan medoxomil, an angiotensin II receptor blocker, for the treatment of hypertension. Studies for olmesartan medoxomil (formerly known as CS-866) were conducted under IND. —

An End-of-Phase 2 meeting was held on May 14, 1997 to discuss the design of phase 3 trials that would support filing of the NDA.

A Pre-NDA meeting was held on October 27, 1998.

**Meeting****Pharmacology**

Reviewer: Gowra Jagadeesh, Ph.D.

Dr. Jagadeesh had no objections to filing the NDA. Dr. Resnick said that because of the possible

clastogenic effects of the drug the review might take longer than normal. He noted that the carcinogenicity data submitted by the sponsor would have to be reviewed by the CAC (Carcinogenicity Assessment Committee).

Dr. Resnick said he expects the pharmacology review to be completed by April 30, 2001.

#### Chemistry

Reviewer: Florian Zielinski, Ph.D.

Dr. Zielinski had no objections to filing the NDA. He expects his review to be completed by February 28, 2001.

Facility inspections were requested already.

#### Biopharmaceutics

Reviewer: Sayed Al-Habet, Ph.D.

Dr. Al-Habet had no objections to filing the NDA. Dr. Al-Habet expects his review to be completed by December 25, 2000.

#### Statistical

Reviewer: Jim Hung, Ph.D.

Dr. Hung had no objections to filing the NDA. The review is expected to be completed by February 28, 2001.

#### Medical

Medical Officers: Steve Rodin, M.D.  
Shari Targum, M.D.  
Akinwole Williams, M.D.

There are twelve controlled trials that support efficacy for this NDA. Drs. Rodin, Targum and Williams will write one integrated review of safety and efficacy. They expect to complete their review by January 15, 2001.

#### Secondary Medical Review

Reviewer: Norman Stockbridge, M.D., Ph.D.

Dr. Stockbridge expects his review to be completed by January 31, 2001.

#### DSI

Dr. Stockbridge said that foreign or domestic inspections are not needed for this product. He will draft a memo to DSI through Dr. Temple stating why the Division believes inspections are not needed.

**Conclusion**

The application will be filed. Dr. Lipicky noted that if the apparent clastogenic effect of olmesartan is supported by carcinogenicity data then the drug might have to be presented before a future Cardiovascular and Renal Advisory Committee.

Minutes Preparation:

  
Edward Fromm

Concurrence Chair:

  
Raymond Lipicky, M.D.

dr: ef/9-21-00/9-28-00

- Rd: FZielinski-9/22/00  
KSrinivasachar-9/22/00  
GJagadeesh-9/25/00  
CResnick-9/25/00  
JHung-9/25/00  
PMarroum-9/25/00  
SAI-Habet-9/25/00  
SRodin-9/26/00  
STargum-9/26/00  
AWilliams-9/26/00  
AKarkowsky-9/26/00  
NStockbridge-9/27/00  
DThrockmorton-9/28/00  
SFredd-9/28/00  
MSkelly-9/21/00

- cc: NDA 21-286  
HFD-110  
HFD-110/Morgenstern  
HFD-110/EFromm/SMatthews

SEP 21 2000

**CSO Filing Review**

Application: NDA 21-286  
 Benevas (olmesartan medoxomil)  
 5, 20, and 40 mg Tablets

Applicant: Sankyo Pharma Inc.

Application Date: July 25, 2000

Receipt Date: July 25, 2000

Primary Goal Date: May 25, 2001

Secondary Goal Date: July 25, 2001

**Background**

Sankyo has submitted this NDA for olmesartan medoxomil, an angiotensin II receptor blocker, for the treatment of hypertension. Studies for olmesartan medoxomil (formerly known as CS-866) were conducted under IND.

At a meeting with the Division on February 16, 2000, the sponsor was informed that CS-866 was positive for clastogenicity in some of the in-vitro tests. Dr. Lipicky noted that this finding was a major concern to the Division but said that it would be viewed in the context of other animal and human data submitted with the NDA.

Meetings

End-of Phase 2: May 14, 1997  
 Pre-NDA-October 27, 1998

Reviewers:

Chemistry:	Florian Zielinski, Ph.D.
Biopharm:	Sayed Al Habet, Ph.D.
Pharmacology:	Gowra Jagadeesh, Ph.D.
Statistics:	Jim Hung, Ph.D.
Medical:	Steven Rodin, M.D.
	Shari Targum, M.D.
	Akinwole Williams, M.D.
Sec. Medical:	Norman Stockbridge, M.D., Ph.D.

**Review**

This NDA was submitted electronically with volume 1.1 in paper form.

The index to the NDA is adequate. The NDA appears to be well organized but based on the reviewer's comments to date, is incomplete with respect to data that are supposed to be included in a particular section but are not present. These omissions are probably not enough for "refuse to file" but certainly will make the review process more tedious than normal.

There are twelve controlled trials that support efficacy for this NDA with 4 being placebo-controlled studies (866-204, 866-306, SE-866/09, SE-866/10) that Dr. U considers pivotal.

The sponsor has requested a waiver for conducting pediatric studies pursuant to the Pediatric Rule.

The sponsor has submitted a Debarment Certification and Financial Interests and Arrangements of Clinical Investigators Certification.

OPDRA has found the tradename Benevas unacceptable due to potential confusion

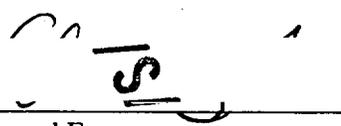
The company was informed of OPDRA's decision and will internally review the matter before deciding on how to proceed.

### **Summary of Deficiencies**

There are spot omissions throughout the submission. The sponsor has been notified of these and is working to correct the deficiencies.

### **Recommendation**

Provided that the reviewers have not identified reasons for refusing to file, I recommend that the application be filed.

  
\_\_\_\_\_  
Edward Fromm  
Consumer Safety Officer

cc: NDA 21-286  
HFD-110  
HFD-110/Fromm

## **Minutes of a Meeting between Sankyo and the FDA**

Date: October 3, 2001

Application: NDA 21-286  
Benicar (olmesartan medoxomil) Tablets

Applicant: Sankyo Pharma Inc.

Subject: Genotoxicity and Carcinogenicity Issues

### FDA participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research  
Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products  
Joseph DeGeorge, Ph.D., HFD-024, Associate Director for Pharmacology and Toxicology, ORM  
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director  
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader  
Akinwale Williams, M.D., HFD-110, Medical Officer  
Shari Targum, M.D., HFD-110, Medical Officer  
Charles Resnick, Ph.D. HFD-110, Supervisory Pharmacologist  
Gowra Jagadeesh, Ph.D., HFD-110, Pharmacologist  
John Koerner, Ph.D., HFD-110, Pharmacologist  
Anthony Proakis, Ph.D., HFD-110, Pharmacologist  
Natalia Morgenstern, HFD-110, Chief, Project Management Staff  
Quynh Nguyen, Pharm.D., HFD-110, Project Manager  
Edward Fromm, HFD-110, Project Manager

### Sankyo

John C. Alexander, M.D., President  
Donald Hinman, Ph.D., Director, Clinical Research  
James Molt, Ph.D., Vice President, Regulatory Affairs  
Sunao Manabe, DVM, Ph.D., Vice Director, Medicinal Research Safety Labs  
Hisashi Nakagaki, Manager of Clinical Research  
Hiroyuki Koike, Ph.D., Deputy General Manager, Research Institute  
Bruce Dornseif, Ph.D., Senior Director, Statistics  
Kan-ichi Nakamura, Ph.D., General Manager

### Consultants

### **Background**

The full CAC (Carcinogenicity Assessment Committee) met on May 4, 2001 to discuss genotoxicity and carcinogenicity issues associated with olmesartan medoxomil. A majority of the committee felt that olmesartan medoxomil had tested positive for carcinogenicity in the 2-year rat study.

On May 30, 2001, the Agency discussed the CAC's concerns with the firm and suggested that the firm conduct additional studies (e.g., MutaMouse and Comet Assays, Step-Sectioning of rat kidneys) that might support their

contention that olmesartan was not mutagenic or carcinogenic. Sankyo performed all of the studies and submitted the study reports to the Division on August 30, 2001.

The firm requested a meeting to discuss the test results and whether the toxicology issues associated with the drug were still an impediment to approval (the goal date for the application is October 25, 2001).

## Meeting

### Regulatory Considerations

Dr. Temple opened the meeting by noting that the Agency was not ready at the present time to dismiss the findings that suggest the drug's potential for mutagenicity and carcinogenicity. Because of uncertainties concerning the relationship of chronic progressive nephropathy observed in rats to renal tumor findings and whether the latter findings are real or due to chance, the Agency would like the new test and relevant original results presented before the CAC. Input from the CAC is critical to knowing whether Benicar should be approved, and because this meeting could not take place before the October 25, 2001 goal date, the Agency would probably issue a not-approvable letter. Of course, the firm could choose to withdraw the application.

Sankyo asked if the Agency could

Dr. Temple replied that we would consider the firm's request but noted that the Agency was ultimately concerned about the carcinogenic potential of the drug, as it could be used in a large number of patients for long periods of time. Moreover, there are six other approved angiotensin II blockers currently available for use.

Sankyo asked if a committee other than the CAC could discuss the drug; this would not necessarily be an Advisory Committee per se, but some type of outside peer review group. Dr. DeGeorge replied that conflict of interest issues would probably prohibit using outside peer review groups but said he was open to inviting NTP (National Toxicology Program) experts to the CAC meeting.

### Sankyo's Arguments that Olmesartan is not Carcinogenic

The firm presented slides arguing that olmesartan medoxomil is not carcinogenic for the following reasons:

- The small number of adenomas and carcinomas seen were present only in male rats.
- Tumor findings in the original and step-sectioned rats were not statistically significant.
- There was an absence of evidence of preneoplastic activity in the renal tubules in rats.
- There was no evidence of drug-related cell injury in the rat kidneys. It was noted that this was a different representation of the data than was submitted in the NDA.
- An absence of dose-response was seen in the tumor groups.
- The historical control incidence of renal tubule carcinomas was close to 1% in the laboratory that conducted the study.
- One tumor classified as an adenoma may in fact be a pheochromocytoma.

Dr. DeGeorge noted that the size of carcinogenicity study may mean that conventional levels of statistical significance will not be obtained for low background tumors and that all the data must be considered. He also asked about the evidence of chronic progressive nephropathy in rats in the 2-year carcinogenicity study. The original study pathologist had seen an increased incidence in olmesartan-treated rats. However, noted that almost 100% of treated and control rats exhibited this nephropathy (by his grading method) and said that he believes his pathogenesis grading is more specific than that used even by the NTP. Dr. DeGeorge said the Agency was concerned about drug-induced nephrotoxicity and said that he believes it is inappropriate to characterize the

nephrotoxicity seen as not indicative of cell injury. [redacted] replied that, based on his grading system, he did not find any nephrotoxic changes in the rat kidneys that would indicate potential neoplastic development.

[redacted] noted that the hypertrophy seen in rat kidneys was generally found in the distal tubule and was believed to be due to Angiotensin II receptor blockade. Dr. DeGeorge asked if other chemicals or pharmaceuticals cause this type of change to the kidney. [redacted] replied that he was not aware of any other agent that caused these specific changes.

Dr. Williams asked why the firm believes that one tumor they defined as an oncocytic adenoma (oncocytoma) could not be an oncocytic change in an adenoma. [redacted] replied that the oncocytic adenoma was an eosinophilic type of adenoma that could be differentiated from an oncocytic tumor by its color when stained. He noted that the oncocytoma in the rat kidney does not specifically stain eosinophilic as in other organs.

Dr. Lipicky asked if adenomas and carcinomas could be thought of as being on the same continuum. The firm replied that was a correct inference.

#### Pathology Working Group (PWG)

Dr. DeGeorge suggested that it might be helpful before the CAC meeting to have a PWG (Pathology Working Group), which would be made up of experts in the field, to review carcinogenicity and nephrotoxicity issues discussed to date. Specifically, the group could review the following issues:

- Histopathology: Can the tumors be determined to be spontaneous in origin or drug-related? Is the nephrotoxicity spontaneous or drug-related? Are the tumors related to the nephropathy? Were all of the renal tumors considered primary renal tumors?

Sankyo agreed to a PWG to review the above and other issues and said it would be in contact with the Agency to discuss the formation of the Working Group.

- Genotoxicity issues: Comet Assay and MutaMouse Assay. Dr. DeGeorge noted that the firm had submitted Comet Study results that showed that the drug was negative for causing DNA damage; he noted however, that the Agency's Genotoxicity Committee had reviewed the results and had found evidence that the drug was positive for the Comet Assay based on its analysis. The sponsor should evaluate the findings based on a scientifically supportable analysis.

Sankyo asked what slides (original or step-sectioned) of the rat kidneys should be submitted to the PWG.

Dr. DeGeorge said that the original slides would suffice unless the step-sectioned slides would help the evaluation of tumor origin (primary or not) or spontaneous versus drug induced.

#### Summary of Main Action Items

- Dr. Temple will notify the firm in a timely manner as to whether the Agency will issue an approvable or not-approvable letter.
- The Agency will discuss with the firm the formation of a Pathology Working Group that would review the study results to try to resolve differences in the classification of certain carcinogenicity and nephrotoxicity data.
- The Agency would recommend two government pathologists to participate in the PWG.
- After an action letter is issued, the firm will present before the CAC its arguments as to why olmesartan is not a potential human carcinogen. If the CAC agrees that the drug is not a potential human carcinogen, then approval of the drug would be likely.

Minutes Preparation: Edward Fromm  
Concurrence, Chair: Robert Temple, M.D.

**Addendum to the Meeting**

After a short internal conference, Dr. Temple notified the firm that an approvable action will be taken by the October 25, 2001 goal date.

drafted/ef: 10-09-01/10-22-01/10-30-01/10-31-01

Rd: NNguyen-10-9-01  
STargum-10-10-01  
AWilliams-10-10-01  
JKoerner-10-10-01  
AProakis-10-10-01  
GJagadeesh-10-23-01  
CResnick-10-24-01  
NStockbridge-10-25-01  
DThrockmorton-10-25-01  
JDeGeorge-10-30-01/11-9-01  
NMorgenstern-10-31-01  
RTemple-11-1-01

## **Minutes of a Meeting between Sankyo and the FDA**

Date: May 30, 2001  
Application: NDA 21-286  
Benicar (olmesartan medoxomil) Tablets  
Applicant: Sankyo Pharma Inc.  
Subject: Genotoxicity and Carcinogenicity Issues

### FDA participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research  
Joseph DeGeorge, Ph.D., HFD-024, Associate Director for Pharmacology and Toxicology, ORM  
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director  
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader  
Akinwole Williams, M.D., HFD-110, Medical Officer  
Shari Targum, M.D., HFD-110, Medical Officer  
Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology and Biopharmaceutics, Team Leader  
Juan Carlos Pelayo, M.D., HFD-110, Medical Officer  
Charles Resnick, Ph.D. HFD-110, Supervisory Pharmacologist  
Gowra Jagadeesh, Ph.D., HFD-110, Pharmacologist  
James Hung, Ph.D., HFD-110, Statistician/Team Leader  
Howard Lee, M.D., HFD-110, Medical Fellow  
Natalia Morgenstern, HFD-110, Chief, Project Management Staff  
Edward Fromm, HFD-110, Project Manager

### Sankyo

John Alexander, M.D., Development  
Donald Hinman, Ph.D., Director, Clinical Research  
James Molt, Ph.D., Regulatory Affairs  
Albert Yehaskel, M.S., Regulatory Affairs

### **Background**

The full CAC (Carcinogenicity Assessment Committee) met on May 4, 2001 to discuss genotoxicity and carcinogenicity issues associated with olmesartan medoxomil. A majority of the committee felt that olmesartan medoxomil was positive for carcinogenicity in the 2-year rat study. They were also concerned with hyperplasia in the kidneys of rats in that study.

Sankyo was informed, in a May 23, 2001 telephone conversation, of the Agency's concern with the apparent genotoxic and carcinogenic effects of the drug and the likelihood of an unfavorable action letter based on those effects. The firm disagreed with the Agency's conclusions and believed that new data and insights will lessen the Agency's concern.

## Meeting

### Carcinogenicity in the 2-Year Rat Study

To address concerns the Agency has with the finding of adenomas and carcinomas in the kidneys of olmesartan medoxomil (OM) treated male rats, the firm presented the following arguments:

- The male rat kidney tumor incidence at the highest dose of OM in the 2-year study (2000mg/kg/day) is less than the incidence at the mid-dose (600 mg/kg/day). This suggests an absence of a dose-response.
- The incidence of renal tubular neoplasia with OM in the rat carcinogenicity study is similar to that seen with some other angiotensin receptor blockers (ARBs). Specifically, the firm noted that \_\_\_\_\_ and \_\_\_\_\_ treated rats also developed kidney tumors, yet those drugs are labeled as having no evidence of carcinogenicity. Dr. DeGeorge agreed that there were some tumors in those cases but pointed out that OM had a higher incidence of kidney tumors than any of the other ARB's studied to date. He also said that \_\_\_\_\_ was studied in a different strain of rat (not the Fisher rat) and that the Agency does not know what the historical control rate is for that study to put the finding in context.
- The incidence of renal tubular neoplasia in the OM treated rats was at the upper end but within the range of historical control data. The firm noted that the National Toxicology Program (NTP) historical control range for F344 male rats (the strain used in the OM rat study) was 0-4% (the adenoma plus carcinoma rate for males in the olmesartan rat study ranged from 4 to 8%).

### Hyperplasia vs. Hypertrophy in the F344 Rat Study

Sankyo presented the following arguments regarding the hyperplasia seen in female and male rats in the 2-year rat study:

- The non-neoplastic renal tubular changes seen with OM are better described as hypertrophy, not as hyperplasia. They now think that the original diagnosis of hyperplasia was wrong.

Dr. Williams suggested that the firm do a PCNA (Positive Cell Nuclear Antigen) histochemical evaluation on the kidney slides that may show quantitative differences between hyperplasia and hypertrophy. He noted the importance of counting nuclei in observed lesions so as to have objective standards when evaluating the results. The firm agreed to do the evaluation and send the results to the Division.

- Renal tubular hypertrophy or hyperplasia has been reported in rat chronic toxicology and carcinogenicity studies with ARB's that have already been approved.

### Relative Exposure in Rats vs. Humans

Sankyo presented data to show that the AUC (area under the concentration vs. time curve) for olmesartan in rats following 200 and 2000 mg/kg/day dosage regimens are 6.8 and 31.9 times, respectively, the AUC following a 40 mg dose in humans. Dr. Resnick questioned the value of these ratios in supporting a probable absence of carcinogenic potential in man because a No Effect Dose for neoplastic effects had not been documented in the rat carcinogenicity study. Dr. Temple added that OM appears to be genotoxic and therefore, the relative exposure ratios are less meaningful.

Additional Testing

Dr. Temple said the Agency was concerned with the genotoxicity of olmesartan as well as the increased incidence of renal tumors and hyperplasia seen in the 2-year rat carcinogenicity study. The firm needs to focus on convincing the Agency that these findings are not significant rather than showing other ARB's may behave in a similar manner. The Agency believes that further testing may be helpful in determining the extent of the genotoxic and carcinogenic properties of the drug and suggested the following:

- A re-reading of the rat carcinogenicity study kidney slides by a NTP pathologist. The idea is to confirm that the adenomas seen so far are in fact tumors and not hyperplasia and that none of the hyperplasias that were identified are adenomas. Additionally, the re-reading of the slides may be able to differentiate hypertrophy from hyperplasia.

Procedurally, the firm should separate the 8 kidney slides that show adenomas or carcinomas from the slides that show possible renal tubular hyperplasia. The slides should be separated by gender and numbered in a blinded manner. The slides should then be sent to the NTP pathologist who will evaluate them and will then review all of the kidney slides of the male rats and make a determination as to whether the changes in the renal cells are hypertrophy, hyperplasia, or tumors. If the reading of the male slides indicates an increase in tumors versus the original count, the pathologist may review the female rat kidney slides as well.

Dr. Temple said that after the firm sends the slides to the NTP pathologist, they should acknowledge this in a letter to the Division. The Agency will classify this letter (when received by July 25, 2001) as a major amendment, which will extend the 12-month review clock by 3 months. Consequently, the new goal date would be October 25, 2001.

- The firm should consider step sectioning the rat kidney tissues and reading them in a blinded manner.
- The PCNA test (as mentioned above) may help differentiate hypertrophy from hyperplasia.
- The firm should consider doing the "Comet Assay" which is a method to examine DNA damage. This test may provide additional information about the genotoxic potential of the drug.
- The firm should submit the results of the third Muta-Mouse study to the Division. The Muta-Mouse study looked for mutations in intestinal tissue from the mouse.

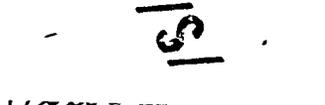
Sankyo agreed to do all of the tests suggested by the Agency. They indicated that they would send a letter to the Division by July 25, 2001 acknowledging that the rat kidney slides have been sent to the NTP pathologist.

**Conclusion**

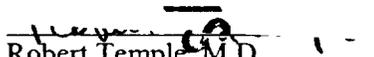
Dr. Temple said that the Agency was concerned about the increased incidence of kidney tumors and hyperplasia seen in the 2-year rat carcinogenicity study. Additionally, the drug appears to possess genotoxic properties.

The Agency suggested additional tests that may help it in its review of the apparent genotoxic and carcinogenic properties of the drug. Sankyo agreed to conduct the additional tests and send the results to the Division in a timely manner.

Minutes Preparation:

  
Edward Fromm

Concurrence, Chair:

  
Robert Temple M.D.

drafted/ef: 6-01-01/6-22-01/6-25-01

Rd: JCPelayo-6/4/01  
Targum-6/4/01  
FWilliams-6/4/01  
JHung-6/7/01  
NStockbridge-6/05/01  
JDeGeorge-6/19/01  
DThrockmorton-6/23/01  
ADeFelice for CResnick-6/25/01  
Temple-6/25/01  
Morgenstern-6/25/01

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Edward Fromm

6/27/01 09:00:33 AM

Dr. Temple signed the minutes on June 26, 2001

Minutes  
 October 27, 1998  
 IND — CS-866  
 Sankyo U.S.A. Corporation  
 Pre-NDA Meeting/Clinical

**Attending:**FDA:

Raymond Lipicky, M.D.	HFD-110	Division Director
Shaw Chen, M.D., Ph.D.	HFD-110	Group Leader/Medical
Maryann Gordon, M.D.	HFD-110	Medical Officer
James Hung, Ph.D.	HFD-710	Statistician
Gabriel Robbie, Ph.D.	HFD-860	Biopharmaceutist
Nancy Algranaḡi, Pharm.D.	HFD-860	Biopharm. Fellow
Kathleen Bongiovanni	HFD-110	Regulatory Health Project Manager

Sankyo U.S.A.:

Harvey N. Masonson, M.D.	Director, Clinical Research
David L. Woodward, Ph.D.	Vice President, Development
Antonia Wang, Ph.D.	Director, Biostatistics
Lee Schwocho, Ph.D.	Assistant Director, Clinical Research
John R. Short, R.Ph.	Senior Director, Regulatory Affairs
MaryJane Rafii, Ph.D.	Assistant Director, Regulatory Affairs

**Related Submissions:** serial number 069, dated August 20, 1998 (request for meeting)  
 serial number 072, dated September 21, 1998 (background package)  
 serial number 076, dated October 19, 1998 (revised background package)

**Background:** Sankyo U.S.A. is studying an angiotensin receptor antagonist, CS-866, for the treatment of hypertension. They asked for this Pre-NDA meeting to help them prepare for the submission of the NDA in mid-2000.

**Meeting:**DISCUSSION POINTS:Submission of Full or Abbreviated Reports or Synopses

Sankyo included a proposal in their revised background package for submitting full or abbreviated reports or synopses of reports of their clinical trials. They explained that they will have full reports of all trials, and they would prepare abbreviated reports or synopses for the NDA. Dr. Lipicky said that they should do whatever is easier for them. If they already have full reports, they should submit them. Sankyo does not want to submit unnecessary information that would slow the reviewers down. Dr. Lipicky said that it would not matter; the reviewers will decide what to review of the submitted reports. If the firm submits less than full reports, we may ask for full reports, depending on the data.

SAS Datasets

Sankyo agreed to submit SAS datasets of all blood pressure measurements, including all standing and sitting measurements (in addition to averages) from multiple-dose, placebo-controlled trials.

Dr. Lipicky asked the firm to include not only the visit number, but also the number of days before or after randomization that the measurements were taken; we would also like to know the time of day the dose was taken, if that information is available. He also asked for the date of the first and the last dose.

Sankyo asked whether we would want any electronic data on European active-controlled trials. Dr. Lipicky said that it may have some academic interest, so if it is easy they could submit it, but it is not necessary.

Dr. Lipicky advised the firm to submit electronic data from studies comparing \_\_\_\_\_ if they plan to use that information in their package insert or in advertising.

Sankyo said that they will provide two flags, one for intent-to-treat and one for per-protocol analyses, in the datasets for U.S. studies; they will check to see if they can do the same for European trials.

#### Appendices from European Trials

Sankyo asked whether they could delete the appendices from the full reports of European trials. Dr. Lipicky told them that was their choice.

#### ABPM Data

Dr. Lipicky told the firm that we will give them a copy of the preferred format for ambulatory blood pressure monitoring (ABPM) data. They could use that same format, modified if necessary, for cuff data. He noted that ABPM data would be used for research and is not required. They could submit ABPM data after the NDA is submitted, or not at all. We agreed that submission of separate files for each ABPM study is acceptable.

#### Safety Data

Dr. Lipicky asked the firm to submit all datasets used to prepare the analyses of safety in the NDA. Sankyo said that they will prepare three integrated summaries of safety; one for single-dose trials in healthy subjects, one for multiple-dose trials in healthy subjects, and one for multiple-dose studies in patients. They agreed to send in the data from the third group, including studies with either a placebo or active control.

Dr. Lipicky asked the firm to provide information on the blood pressure-lowering effect of CS-866 in healthy volunteers, if possible. Sankyo agreed to prepare a summary table of the blood pressure changes in healthy volunteers from all studies. Dr. Lipicky said they could omit this if it is too much work.

We asked the firm to submit all adverse reactions and laboratory values, including normal ranges for the laboratory tests, demographic information, and information on the first and last dose. Sankyo asked whether laboratory values should be in international units or U.S. units. Dr. Lipicky asked them to use the same values throughout, so we could compare data and prepare summaries.

### Counting Rules

Sankyo asked whether we would prefer them to apply U.S. counting rules for treatment-emergent adverse events to all the data, even though the non-IND European studies used European rules in their trial reports. They presented an overhead (attached) that shows the difference between the two systems. Dr. Lipicky told them they could choose how to present these data.

### ANCOVA Model

Dr. Hung said that the proposed ANCOVA model for the subgroup analysis for the integrated summary of efficacy is acceptable. He said that we will do our own analyses, regardless of what the firm provides.

### Electronic Submission

Sankyo asked whether the archival compact disc needs to contain crosslinking and hyperlinking. Dr. Lipicky said that they should provide those links if they have the resources and expertise to do so. Otherwise, they may omit them from this submission.

We suggested that Sankyo discuss computer tools and training with Drs. Gordon, Hung, and Stockbridge.

### CONCLUSIONS

- Sankyo may submit reports in the format outlined in the proposal in the pre-meeting package, or they may submit all full reports.
- Sankyo agreed to submit SAS datasets of all blood pressure measurements, including all standing and sitting measurements (in addition to averages) from multiple-dose, placebo-controlled trials. We asked the firm to include not only the visit number, but also the number of days before or after randomization that the measurements were taken; we would also like to know the time of day the dose was taken, if that information is available, and the date of the first and the last dose.
- Sankyo asked whether they could delete the appendices from the full reports of European trials. Dr. Lipicky told them that was their choice.
- We will give Sankyo a copy of the preferred format for ambulatory blood pressure monitoring (ABPM) data [Note: copy FAXed to the firm on November 1, 1998.]. ABPM data is not required.
- Sankyo agreed to send in safety data from multiple-dose studies in patients, including studies with either a placebo or active control.
- We asked Sankyo to submit all adverse reactions and laboratory values, including normal ranges for the laboratory tests, demographic information, and information on the first and last

dose. We asked them to use the same values, either international units or U.S. units, throughout, so we could compare data and prepare summaries.

- Sankyo may choose whether to apply U.S. counting rules or European rules for treatment-emergent adverse events in European studies.
- The proposed ANCOVA model for the subgroup analysis for the integrated summary of efficacy is acceptable.
- Dr. Lipicky said that Sankyo should provide crosslinking and hyperlinking in the archival compact disc if they have the resources and expertise to do so. Otherwise, they may omit them from this submission.
- We suggested that Sankyo discuss computer tools and training with Drs. Gordon, Hung, and Stockbridge.

Signature, minutes preparer: \_\_\_\_\_

  
Kathleen F. Bongiovanni

11-4-98

Concurrence Chair: \_\_\_\_\_

  
Raymond Lipicky, M.D.

cc: IND ✓  
HFD-110  
HFD-110/KBongiovanni  
HFD-110/SBenton

kb/11/2/98; 11/4/98.

R/D: SChen/11/2/98; MGordon/11/2/98; JHung/11/3/98; GRobbie/11/3/98; NAlgranati/11/3/98.

Div file  
JUL 1 1997

Minutes  
May 14, 1997  
IND  CS-866  
Sankyo U.S.A. Corporation  
End-of-Phase II Meeting/Clinical

**Attending:**

FDA:

Robert Temple, M.D.	HFD-101	Office Director
Raymond Lipicky, M.D.	HFD-110	Division Director
Shaw Chen, M.D., Ph.D.	HFD-110	Group Leader/Medical
Maryann Gordon, M.D.	HFD-110	Medical Officer
Walid Nuri, Ph.D.	HFD-710	Statistician
Ahmed El-Tahtawy, Ph.D.	HFD-860	Biopharmaceutist
Kathleen Borgiovanni	HFD-110	Regulatory Health Project Manager

Observers:

Khin Maung U, M.D.	HFD-110	Medical Officer
Isaac Hammond, M.D., Ph.D.	HFD-110	Medical Officer
Ramana Uppoor, Ph.D.	HFD-860	Biopharmaceutist

Sankyo U.S.A.:

Harvey N. Masonson, M.D.	Director, Clinical Research
David L. Woodward, Ph.D.	Vice President, Clinical Development
Donald Hinman, Ph.D.	Director, Clinical Research
John R. Short, R.Ph.	Senior Director, Regulatory Affairs
MaryJane Rafii, Ph.D.	Manager, Regulatory Affairs

**Related Submissions:** serial number 028, dated March 24, 1997 (request for meeting)  
serial number 032, dated April 29, 1997 (background package)

**Background:** Sankyo U.S.A. is studying an angiotensin receptor antagonist, CS-866, for the treatment of hypertension.

Sankyo has completed three Phase 1 trials and one Phase 2 trial. The Phase 2 trial (Protocol 886-204) was an 8-week, randomized, double-blind, placebo-controlled, dose-ranging study using ABPM in hypertensive patients. 334 patients were randomized to 7 parallel-treatment groups: placebo, CS-866 5, 20, and 80 mg QD, and 2.5, 10, and 40 mg BID. The background package includes a summary of the results of this trial.

The firm is proposing two Phase 3 trials:

- Protocol 866-305: a randomized, parallel-group, placebo-controlled study in 420 hypertensive patients. For the first 12 weeks, patients would receive placebo or CS-866 2.5, 5, 10, 20, or 40 mg. From month 4 through 12, patients would continue on the previous treatment, but could have open-label addition of hydrochlorothiazide (HCTZ) and/or amlodipine for uncontrolled blood pressure.
- Protocol 866-306: a randomized, placebo-controlled study in 400 hypertensive patients. Patients would begin on placebo or 5 mg CS-866. After 6

weeks, doses would be titrated in patients with uncontrolled blood pressure to 5, 10, or 20 mg. From month 4 through 12, there will be an open-label extension, with all patients initially receiving 20 mg CS-866. The dose of CS-866 can be titrated to 40 mg, and HCTZ (12.5 and 25 mg) or amlodipine (5 and 10 mg) can be added.

They asked to come in to discuss the design of the Phase 3 studies.

**Meeting:**

**DISCUSSION POINTS:**

**Factorial Trial:**

Dr. Lipicky told the firm that we are convinced that CS-866 lowers blood pressure from the results of their Phase 2 trial. He suggested that, rather than the two proposed studies, they do a factorial trial to further explore the dose range of the drug and to get information on the use of the drug in combination with another drug, such as hydrochlorothiazide or a calcium channel blocker. The two proposed studies would use a total of more than 800 patients; with a smaller number of patients in a factorial trial, they would get a great deal of usable information.

Dr. Temple referred the firm to the draft guidance document "Providing Evidence of Effectiveness for Human Drug and Biological Products," available on the FDA Home Page on the Internet ([www.fda.gov](http://www.fda.gov)).

**Doses for Factorial Trial:**

There was a discussion of the doses that might be used in a factorial trial. Dr. Temple suggested CS-866: 0, 2, 5, 20, and 80 mg; HCTZ: 0, 6.25, 12.5, and 25 mg, although 25 mg HCTZ may not be necessary.

Sankyo asked whether they could study 40 rather than  $\infty$  mg of CS-866. Dr. Lipicky said that one would only know the correct doses to choose after the results are known. Some people are convinced that 20 mg is the top of the CS-866 dose-response curve; the only way to prove them wrong would be to try a very large dose, such as 300 mg of CS-866. The firm noted that they have not seen any adverse effects with higher doses of CS-866 in humans or animals, but they believe that they have shown the highest effective doses. Dr. Temple said that from the data, he thought that the highest effect of CS-866 would be seen at doses between 20 and  $\infty$  mg.

Dr. Temple said that they should choose any reasonable doses. We are comfortable interpolating, but not extrapolating, data. For the smallest dose, he said we would accept anything from 0 to 5 mg. Since there is low toxicity with this drug, one would not have to start with the absolutely lowest dose that had any effect. Dr. Temple encouraged the firm to provide data that shows that they have reached the top of the dose-response curve. He noted that data from a trial in non-responders would show if there is any value in increasing doses in these patients.

Analyses of Factorial Data:

Sankyo asked whether the factorial trial could be analyzed to pull out individual treatment arms. Drs. Temple and Lipicky assured them that it could; although there would be fewer patients exposed to a dose of CS-866 alone, there would be the additional data on that dose in combination with various doses of HCTZ. Dr. Temple noted that they did not have to enroll the same number of patients in each cell of the trial; the cell with the lowest dose of diuretic alone might have a smaller number of patients than the rest, and the cell with doses of CS-866 alone could be larger. Dr. Lipicky said that one would usually define the margins of the trial and have fewer patients on the inside. No cell would have to survive on its own; the analyses would take all of the cells into account.

Number of Patients:

Dr. Temple noted that under the ICH guidelines they would need to have 1500 total patients exposed to the drug. Sankyo showed their estimates for drug exposure: 1048 patients from the U.S., 2234 patients from Europe, and 468 from Japan, for a total of 3750 patients exposed to CS-866 (see attached copy of overhead).

Sankyo said that they will have 150 non-U.S. patients with long-term exposure, and they plan to have 500 U.S. patients with long-term exposure. Dr. Temple encouraged the firm to re-randomize patients from short-term trials to either CS-866 or a positive control, to allow for a comparison of numbers of adverse events. This trial could be done in patients who responded to therapy, or in all patients, with non-responders being dropped after the top dose. He noted that long-term data from a continuation trial, without patients being re-randomized, would be less useful. If patients are allowed to continue on CS-866 with other antihypertensive medications added as needed, any adverse effects seen could be attributed to CS-866.

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Sankyo asked how many patients they would need with one-year exposure. Dr. Temple said that we would like to see 600 patients exposed for 6 months for drugs of this class (the ICH guideline asks for 300-600), and 100 patients treated for one year.

Duration of Trials:

Drs. Temple and Lipicky suggested that the firm shorten the duration of the treatment phase of their trials from 12 to 4-8 weeks.

Titration Trial:

There was a discussion of the design of Protocol 866-306. Dr. Temple noted that it would be useful to know if patients who do not respond to 5 mg of CS-866 would respond to higher doses. A study might include a placebo group initially to identify the non-responders, but once they are

identified a placebo-group is no longer necessary.

Positive-Controlled Trials:

Sankyo said that they will have trials comparing CS-866 to losartan, atenolol, and enalapril. Dr. Temple said that if these trials did not show that one drug was better than the other, we would use them only for their safety information. He asked the firm to send in only abbreviated study reports for positive-controlled trials.

NDA Submission Without 12-Month Safety Data:

Sankyo asked whether they could submit the NDA with 6-month safety data, and amend the NDA with 12-month safety data. They estimated that they could submit these data within the first 4 to 6 months. Drs. Temple and Lipicky agreed.

Peak/Trough:

CONCLUSIONS

- Although the proposed trials may be adequate to support an NDA, we encouraged the firm to perform a factorial trial, to learn more about the full dose range of the drug alone and in combination with another antihypertensive.
- Dr. Temple asked for 1500 patients exposed to the drug, with at least 600 exposed for 6 months and 100 exposed for one year.
- We asked the firm to shorten the treatment period of the trials from 12 to 4-8 weeks.
- We encouraged the firm to explore higher doses of their drug in patients who do not respond to lower doses.
- Dr. Temple asked the firm to submit safety data and abbreviated study reports for positive-controlled trials that do not show superiority.
- We agreed that the 12-month safety data could be submitted by 6 months after the NDA is submitted.

Signature, minutes preparer: \_\_\_\_\_

Kathleen F. Bongiovanni

7-1-97

Concurrence Chair: \_\_\_\_\_

Robert Temple, M.D.

7/4/97

Attachment: copies of overheads

cc:

~~IND~~

HFD-110

HFD-101/RTemple

HFD-111/KBongiovanni

HFD-111/SBenton

kb/5/21/97; 7/1/97.

R/D: WNuri/5/21/97; AEI-Tahtawy; SChen/6/17/97; MGordon/6/17/97;  
RTemple/6/30/97.



mg/kg/day dose (3 month study) in rats and dogs. Dr. Jagadeesh said that he is not comfortable with such a high dose in humans. Dr. Bunker pointed out, however, that the study being proposed in humans is a single dose study, while the animal studies referred to by Dr. Jagadeesh were chronic administration studies. The lowest toxic dose in single dose studies in animals was 1500 mg/kg. Dr. Jagadeesh recommended that these comparisons be added to the Investigator's Brochure.

Dr. Jagadeesh was also concerned about the results of the mutagenicity studies. The Ames test showed only a weak positive result, but the chromosomal aberration test in Chinese hamster cell lines showed about a 40% increase in chromosomal breaks. These results were seen with both the parent compound and in the metabolite. Dr. Jagadeesh recommended that the investigator's brochure and the patient informed consent be revised to include this information.

### Clinical

Dr. Bunker has completed his review and believes that their proposed study is safe. It is a single dose randomized, double blind, placebo-controlled phase I study in healthy volunteers. It is an ascending dose study so if they can identify any safety problems before administering the highest doses. Dr. Chen noted a written comment by Dr. Fenichel that they should not exclude women in this study. Dr. Gordon raised the issue of studying adequate numbers of blacks with drugs of this class, which appears to have marginal efficacy in the black population. Dr. Chen noted that there are no regulations to require such studies, but if they do not include adequate numbers of blacks in their trials (enough to at least show a trend in the right direction), they might get adverse labeling.

### **Addendum**

Dr. Jagadeesh prepared a set of recommendations to the firm, asking that they revise the investigator's brochure, the protocol, and the patient informed consent (see attachment 1). These recommendations were faxed to the sponsor. They did not object to making these changes, but they spoke with Dr. Resnick on May 31 and said that it would be difficult to change the investigator's brochure at this late date. He agreed that they could provide the investigators with a one page addendum until the time the investigator's brochure is reprinted (see attachment 2). This agreement was acceptable to Dr. Chen.

  
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David Roeder  
Regulatory Health Project Manager

### Attachments

dr/5-30-957-10-95

RD: DCunningham/6-1-95  
GJagadeesh/6-5-95  
CResnick/6-6-95  
GBunker/6-6-95  
SChen/6-6-95

cc:

IND

HFD-110

HFD-111/KBongiovanni

HFD-111/SBenton

IND #. \_\_\_\_\_

**RECOMMENDATIONS**

The proposed clinical study may proceed with the following changes in the investigator's brochure, the toxicology portion of the background synopsis included with the clinical protocol, and the patient informed consent.

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b). Protocol: The fourth paragraph on page 2 (page 89, vol. 1) should be revised to strengthen the statement on mutagenic activity. Thus, this para should now read:

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c) Informed Consent: The \_\_\_\_\_ should be reflected in the patient consent form.

should

/S/

G. Jagadeesh, Ph.D

Attachment 2

IND (CS-866)

As the request of Dave Roeder, I called Dr. Rafii of Sankyo to hear the firm's concerns regarding recommended changes to their investigator's brochure, the toxicology portion of the preamble to the clinical protocol, and the patient informed consent. These recommendations were faxed to them by Mr. Roeder. Although there was some confusion as to whether we were requesting or demanding these changes, the company does not object to making them. They were concerned, however, with a delay in the start of the investigation while waiting for reprinting of the investigator's brochure. I gave them tentative approval to provide investigators with a one page addendum to the current brochure. I further told them that full approval could be assumed if they did not hear otherwise from the division during the next 24 hours.

  
CA Resnick  
5/31/95

Dr. Mary Jane Rafii  
Regulatory Affairs  
Sankyo USA  
(212) 753-4432

Integrated Summary of Safety

The Integrated Summary of Safety submitted by the applicant is over 2000 pages long and is available for viewing through the Electronic Document Room (EDR).

APPEARS THIS WAY  
ON ORIGINAL