CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-286

Statistical Review(s)

Statistical Review and Evaluation

Review of Carcinogenicity Studies

(ADDENDUM)

NDA#:	**21-286**
APPLICANT:	**Sankyo Pharma Inc.**
NAME OF DRUG:	**Benicar (olmesartan medoxiomil) Tablets**
INDICATION:	**Hypertension**
STUDIES REVIEWED: (Electronic NDA)	**TR 146-570 two-year carcinogenicity study in rats, APR 147-010 26-week study in p53(+/-) transgenic mice, TRC 146-030 26-week study in Hras2 transgenic mice.**

PHARMACOLOGY REVIEWER: Gowra Jagadeesh, Ph.D. (HFD-110)

STATISTICAL REVIEWER: Roswitha Kelly, M.S. (HFD-710)

1. Introduction

This Addendum is written at the request of Dr. Charles Resnick to document the evaluation of additional renal cell adenoma findings submitted by the sponsor in a 09/24/01 facsimile. In the original Statistical Review and Evaluation (03/06/01), the trend test for the combined renal cell (R-C) adenomas and carcinomas among the male rats did not reach statistical significance. The incidences were 0, 2, 4, 2 for the control, 200, 600, and 2000 mg/kg/day groups. After preparing additional sections from the preserved kidneys, four additional animals of the treated groups were found to have R-C adenomas. The combined incidences of R-C adenomas and carcinomas in the male rats are now 0, 3, 5, 4 for the control, low, medium, and high dose groups, respectively. This addendum discusses the sponsor's analysis of these findings as well as this reviewer's approach.

2. Sponsor's Results

In the 09/24/01 facsimile, the sponsor analyzed the original, new, and combined findings for R-C adenomas and carcinomas by pair-wise comparisons of control with each treated group, as well as by trend tests. The sponsor chose a two-sided Fisher's Exact test for the pair-wise comparisons and a two-sided Cochran-Armitage test for the trend. All tests were performed on unadjusted incidence rates with α=0.05. The adjustment for intercurrent mortality was deemed 'not appropriate' because no statistically significant differences had been observed between the mortality rates of the control and treated groups (pair-wise comparisons at α=0.05). No adjustment for multiplicity was adopted because α=0.05 (two-sided) will lead to conservative conclusions. Based on these conditions, the sponsor observed no statistically significant differences between controls and each treated group of the single and multiple sections for R-C adenomas and carcinomas (separately and combined). Similarly, the tests for linear trend for a dose-related increase in incidence of tumors did not reach statistical significance at α=0.05.

3. Reviewer's Results

The sponsor's use of two-sided p-values from trend and pair-wise comparison testing is inappropriate. In carcinogenicity evaluation, only increases in tumors among treated animals over controls are of interest, and therefore, only one-sided p-values are appropriate. In addition, using α=0.05 is only conservative for trend tests, not for the pair-wise comparisons (May 2001 Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals).

The sponsor's comment that adjustment for mortality 'was not deemed appropriate' is incorrect. Adjustment for intercurrent mortality improves the sensitivity of the results and is always appropriate. However, since the differences in mortality between groups were minor, the p-values of the adjusted and the unadjusted analyses are usually close.

The sponsor prepared additional sections from the kidneys consistently across all groups of animals. Therefore, the 'animal' (versus 'sections') is still the proper denominator for any testing of tumor incidences.

The table below shows the p-values (one-sided) associated with the trend and pair-wise comparisons of the combined R-C adenomas and carcinomas for the single and multiple sections (combined). The results for the unadjusted incidences are identical to the one-sided p-values provided by the sponsor. As noted above, the sponsor based their conclusions on the two-sided p-values.

P-values for Tests of the Combined Incidences (0, 3, 5, 4) of R-C Adenoma and Carcinoma of the Kidney in Control, Low, Medium, and High Dose Male Rats

Statistic	P-value (exact)	Alpha-level for Rare Tumor	Alpha-level for Common Tumors
Trend (mortality adjusted)	0.1235	0.025	0.005
C vs. Low (mortality adjusted)	0.1348	0.05	0.01
C vs. Med (mortality adjusted)	0.0254 *	0.05	0.01
C vs. High (mortality adjusted)	0.0722	0.05	0.01
C vs. Treated (mort. adjusted)	0.0282 *	0.05	0.01
Trend (unadjusted)	0.1259	0.025	0.005
C vs. Low (unadjusted)	0.1212	0.05	0.01
C vs. Med (unadjusted)	0.0281 *	0.05	0.01
C vs. High (unadjusted)	0.0587	0.05	0.01
C vs. Treated (unadjusted)	0.0011**	0.05	0.01

* stat. significant at 0.05
** stat. significant at 0.01

Usually, the determination of whether a tumor is considered rare or common is based on the observed incidence among the concurrent controls. Though the sponsor did not observe any of these tumors among the concurrent controls when the multiple sections were performed, Dr. Resnick communicated to this reviewer that the historical information submitted by the sponsor indicates that the background incidence from multiple section evaluations is not less than one percent, but greater than 4 percent. Therefore, the tumors based on single and multiple sections are considered common and none of the above comparisons reach statistical significance, with the exception of the unadjusted comparison of controls with the combined treated. The sponsor did not perform this latter comparison. Though the sponsor favored unadjusted analysis, this reviewer considers the mortality adjusted analyses more appropriate and, therefore, concludes that none of the analyses of the findings from the combined single and multiple sections of the kidneys of the male rats reached statistical significance.

4. Summary

The sponsor prepared additional sections from the preserved kidneys of the male rats to investigate possible increases in R-C adenomas and carcinomas among the male rats. Additional four treated animals were found to have R-C adenomas. The new incidences for the combined tumors were 0, 3, 5, 4, for control, low, medium, and high dose male rats, respectively. Using unadjusted analyses, the sponsor concluded that none reached statistical significance with two-sided alpha-levels of 0.05.

This reviewer agreed with the statistical methods chosen by the sponsor, namely Fisher's Exact test for pair-wise comparison and the Cochran-Armitage test for trend. However, this reviewer did not agree with the statement that adjustment for mortality is not 'appropriate' because differences in mortality between controls and treated groups were not statistically significant. Adjustment for intercurrent mortality is always appropriate and gives more sensitive results. More importantly, the use of two-sided p-values in tumor analyses is wrong. Therefore, this reviewer performed the adjusted and unadjusted analysis with the same methods, but with one-sided p-values. Since there were no tumors among the concurrent controls, the tumors could be considered rare, in which case the comparisons between controls and medium-dose animals, and between controls and all treated would reach statistical significance. However, historical data for incidence rates from multiple sections support that these tumors are common among these animals, and therefore, no findings reach statistical significance, with the exception of the unadjusted comparison of controls and all treated animals. However, as mentioned above, adjusted results are more appropriate and, therefore, this reviewer concludes that no pair-wise or trend tests for the R-C adenomas and carcinomas reached statistical significance (α=0.01).

/S/

Roswitha Kelly, MS
Mathematical Statistician

/S/

Concur:

George Chi, Ph.D.
Director, Division of Biometrics 1

Cc: Orig. NDA 21-286
HFD-110/ Division Files
HFD-110/Dr. Jagadeesh
HFD-110/Dr. Resnick
HFD-110/ Mr. Fromm (PM)
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Hung
HFD-710/Ms. Kelly
This addendum consists of 4 pages of text. 10/01//01, addend_Benicar.doc

Statistical Review and Evaluation

Review of Carcinogenicity Studies

NDA#:	**21-286**
APPLICANT:	**Sankyo Pharma Inc.**
NAME OF DRUG:	**Benicar (olmesartan medoxiomil) Tablets**
INDICATION:	**Hypertension**
STUDIES REVIEWED: (Electronic NDA)	**TR 146-570 two-year carcinogenicity study in rats,** **APR 147-010 26-week study in p53(+/-) transgenic mice,** **TRC 146-030 26-week study in Hras2 transgenic mice.**

PHARMACOLOGY REVIEWER: Gowra Jagadeesh, Ph.D. (HFD-110)

STATISTICAL REVIEWER: Roswitha Kelly, M.S. (HFD-710)

Note on Levels of Statistical Significance:

Trends in tumor incidence rates are tested for statistical significance at α=0.025 and 0.005 for rare and common tumors, respectively. These levels of significance ensure despite the multiplicity of testing an overall false positive rate of about 10 percent in the two-year two-species two-gender bioassay. In this submission, however, only one regular two-year study was conducted. The two alternate 26-week studies in transgenic mice do not contribute substantially to the multiplicity problem, as only few tumor types will be observed. Therefore, both trends and pair-wise comparisons for the single two-year study are being tested at α=0.05 and 0.01 for rare and common tumors, respectively. In the alternate bioassays, such as the 26-week studies in transgenic mice, all comparisons are tested at α=0.05 for statistical significance.

1. Rat Study TR 146-570

1.1 Introduction

This two-year carcinogenicity study was conducted in F344/DuCrj rats treated with Benicar mixed in the diet at dose levels of 0, 200, 600, and 2000 mg/kg/day. There were 50 animals per treatment group per gender.

1.2 Sponsor's Results

The sponsor reported no significant difference in mortality between the control and treated groups. Macroscopic examination of the rats revealed no neoplastic lesions suggestive of tumor induction attributable to the compound. Microscopic examination of the high dose and control animals showed tumors consistent with those reported as spontaneous lesions in F344 rats. No neoplastic lesions increased significantly in incidence in the high dose groups. In addition, the gastrointestinal tract, liver, kidney, adrenal gland, and uterus were target organs and examined in all animals. No tumors increased significantly in any of these organs. The sponsor concluded that Benicar has no carcinogenic potential in rats.

1.3 Reviewer's Results

This reviewer confirmed that Benicar did not affect the intercurrent mortality of either gender (Tables 1 and 3, Figures 1 and 2). Between 38 (controls) and 42 (mid dose) male rates and between 37 (controls) and 43 (high dose) female rats survived till terminal sacrifice at week 104. The Cox trend statistics for comparing proportions alive were non-significant ($p > 0.05$) (Tables 2 and 4).

For the specified target organs (gastrointestinal tract, liver, kidney, adrenal gland, and uterus) all animals were microscopically examined and therefore, a trend test in tumor incidence rates is appropriate (Table 5 and 6). For the remaining tissues, pair-wise comparisons between controls and high dose were appropriate (Tables 7 and 8). This reviewer used exact permutation tests (trend or pair-wise) for all comparisons with $\alpha=0.05$ for rare and $\alpha=0.01$ for common tumors as explained in the above note. For the male rats, leukemia in the forestomach, jejunum, ileum, colon, rectum (by trend tests), and leukemia in the submandibular lymph node (pair-wise test) were observed as rare tumors and reached statistical significance at $\alpha=0.05$. The high dose incidences were two animals in each case with the exception for leukemia in the submandibular lymph node, where four high dose animals had these findings. For the female rats, only endometrial sarcoma in the uterus may be considered statistically significant ($p=0.0511$, cf. Table 6). Again, there were only two high dose animals with this finding.

Dr. Jagadeesh requested the combining of certain tumors for certain tissues. None of these combinations reached statistical significance.

Table A: Selected Tumor and Tissue Combinations in Rats

SEX	TISSUE	TUMOR	P (TREND)	P (PAIR-WISE)
Male	All Organs*	Leukemia-LG		0.507
	Thyroid	C-cell Adenoma + Carcinoma	---	0.839
	Thyroid	F-cell Adenoma + Carcinoma	---	0.169
	Kidney	Adenoma + Carcinoma	0.311	
	Liver	Adenoma + Carcinoma	0.870	
Female	All Organs*	Leukemia-LG		0.949
	Thyroid	C-cell Adenoma + Carcinoma	---	0.925
	Thyroid	F-cell Adenoma + Carcinoma	---	0.285
	Kidney	None	---	
	Liver	Adenoma + Carcinoma	0.293	
	Uterus	Adenoma + Carcinoma	0.173	

- Includes target and non-target organs

1.4 Validity of Female Rat Study

As the statistically significant tumor finding among the female rats was right at the α-level, the validity of this study was assessed. The fundamental questions are (1) were enough animals exposed for a sufficient length of time to allow for late developing tumors, and (2) were the dose levels high enough to pose a reasonable tumor challenge in the animals. Criteria to answer these questions have been proposed by Haseman[1,2], Chu, Cueto, and Ward[3], and Bart, Chu, and Tarone[4]. The proportions of animals surviving at 52 weeks, 80-90 weeks, and at two years are of interest in determining the adequacy of the length of exposure. Detectable weight loss of up to 10% in dosed versus control animals and slightly increased mortality compared to controls indicate that the dose is close to the MTD. With these criteria in mind, it is clear that a sufficient number of animals (43) survived a sufficient length of time (103 weeks) to allow for late developing tumors in the high dose group. Survival of the high dose females was somewhat better than the controls' (86% versus 74%), but according to the sponsor's Figure 5, average body weights of the high dose group were between 4 and 8 percent less than the controls' for the first year, indicating that the high dose was close to the MTD.

1 Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984

2 Issues in Carcinogenicity: Dose Selection, Fundamental and Applied Toxicology, Vol 5, pp 66-78, 1985

3 Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981

4 Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute, 62, pp 957-974, 1979

2. P53(+/-) Mouse Study

2.1 Introduction

This 26-week study was conducted in p53(+/-) transgenic mice receiving Benicar by gavage at dose levels of 0 (vehicle control), 100, 300, 1000 mg/kg/day. Additionally, a positive control group received p-cresidine, a bladder carcinogen, in corn oil at 400 mg/kg/day. There were 15 animals per treatment group per gender.

2.2 Sponsor's Results

The sponsor reported that one male positive control animals died before terminal sacrifice. Among the females, there were 1, 1, 2, 1, premature deaths among the vehicle control, low, medium, and high dose groups, respectively. The female positive control animals did not experience any early deaths.

The sponsor did not perform any statistical analysis on tumor findings because the incidence difference between groups was less than 2.

2.3 Reviewer's Results

The number of animals dying before termination of the study was as reported by the sponsor.

Table B: Mortality of P53(+/-) Mice

MALES					
Time Interval	Vehicle Ctrl	Positive Ctrl	100 mg	300mg	1000mg
0-25	0	1	0	0	0
Termination	15	14	15	15	15
FEMALES					
0-25	1	0	1	2	1
Termination	14	15	14	13	14

Testing for trend in survival is only meaningful if there were any deaths while on treatment. This is true for all groups only when comparing the treated females to the vehicle control. As is apparent from the data, the results were non-significant (Cox p = 0.98, Kruskal-Wallis p = 0.99).

Only lung, liver, kidney and gross lesions were examined for all animals and would, therefore, be tested with a trend test. All other findings should be tested by a vehicle control-high dose comparison. Also, as there were very few deaths prior to terminal sacrifice, this reviewer did not adjust for intercurrent mortality.

Among the males, there was a single occurrence of malignant granulocytic leukemia in a mid-dose animal and a single occurrence of malignant transitional cell carcinoma in the urinary bladder in a positive control animal.

Table C: Tumor Findings among Male P53(+/-) Mice

Sites/ Tumors	Vehicle Control	Positive Control	Low Dose	Medium Dose	High Dose	P-Value
Hemato neoplasia/m-leukemia gran	0/15	0/15	0/15	1/15	0/15	0.75 (trend)
Urinary Bladder/ m-transitnl. cell carcinoma	0/15	1/15	0/15	0/15	0/15	NA

Among the females there were the following findings, none of which reached statistical significance.

Table D: Tumor Findings among Female P53(+/-) Mice

Sites/ Tumors	Vehicle Control	Positive Control	Low Dose	Medium Dose	High Dose	P-Value
Hemato neoplasia/m-leukemia gran.	0/15	0/15	1/15	0/15	0/15	0.500 (trend)
Hemato neoplasia/m-lymphoma, lymph.	0/15	0/15	1/15	1/15	1/15	0.296 (trend)
Subcutaneous tis/ m-fibrosarcoma	1/15	0/15	1/15	0/15	1/15	0.540 (trend)
Thoracic cavity/ m-osteosarcoma	1/15	0/15	0/15	0/15	1/15	0.759 (pair-wise)

There were no statistically significant tumor findings among the Benicar treated animals of either gender. However, only one animal of the positive control group exhibited the expected urinary bladder tumor. This lack of response may imply that this study had insufficient sensitivity to show any tumorigenic potential of Benicar.

3. Hras2 Transgenic Mouse Study

3.1 Introduction

In this study 15 animals per gender were treated with corn oil by gavage (negative controls) or 1000 mg/kg/day (in diet) for 26 weeks. There was also a positive control group, which was treated with a single i.p. injection of 75 mg/kg N-methyl-N-nitrosourea, a known carcinogen.

3.2 Sponsor's Results

The sponsor reported that all positive control animals died prior to week 24. Among the remaining animals, only one negative control female died prior to the end of the study.

3.3 Reviewer's Results

Testing for trends in intercurrent mortality or adjusting tumor tests by it is not appropriate for these data. Among the male positive controls there were 28 tissue sites with malignant lymphoma as well as other tumor findings. None of the high dose animals had malignant lymphomas. The only tumor findings among the high dose were two adenomas of the lung and one squamous cell papilloma in the forestomach. None of these findings were statistically significant when compared to the (negative) controls. (Findings for the positive controls were reported below only when there were corresponding findings in either the negative controls or the high dose animals.)

Table E: Tumor Findings among Male Hras2 Mice

Tumor/Tissue	Control Incidence	High Dose Incidence	P-Value	Positive Control Incidence
Alveolar Bronchiolar Adenoma / Lung	0/15	2/15	0.241	1/15
Adenoma / Abdominal Cavity	1/15	0/15	1.000	0/15
Squamous Cell Papilloma / Forestomach	1/15	1/15	0.759	13/15
Squamous Cell Carcinoma / Forestomach	1/15	0/15	1.000	2/15

Among the female positive controls there were 22 tissue sites with malignant lymphoma as well as other tumor findings. Again, the incidences of the positive controls are reported below only when there were corresponding findings among the negative control or high dose animals. None of the high dose animals experience malignant lymphoma. The only tumor finding among the high dose females were two alveolar bronchiolar adenomas of the lung, which were not statistically significant when compared to the controls. In addition to the two A/B adenomas of the lung, the (negative) control animals experiences several other tumors in single occurrences:

Table F: Tumor Findings among Female Hras2 Mice

Tumor/Tissue	Control Incidence	High Dose Incidence	P-Value	Positive Control Incidence
Alveolar Bronchiolar Adenomas / Lung	2/15	2/15	0.527	3/15
Adenoma / Harderian Gland	1/15	0/15	1.000	3/15
Hemangiosarcoma / Spleen	1/15	0/15	1.000	0/15
Squamous Cell Papilloma / Forestomach	1/15	0/15	1.000	13/15
Squamous Cell Papilloma / Skin	1/15	0/15	1.000	7/15
Malignant Lymphoma / Whole Body (many sites)	1/15*	0/15	1.000	13/15

*This animal died prematurely

It is noted that the three groups of animals received their treatment by different administrations. If any treatment effects are dependent on route of administration, they cannot be separated in this study. Otherwise, the numerous findings in the positive control animals seem to support the sensitivity of the study. The tumor findings in the negative controls and high dose animals were few and their differences did not reach statistical significance.

4. Summary

4.1 The Rat Study

In this study, 50 animals per gender per group received the compound in the diet at dose levels of 0, 200, 600, and 2000 mg/kg/day for two years. Both genders experienced excellent survival till week 103. Among the male rats there were several statistically significant trends in tumor incidences as well as a pair-wise comparison when testing with α=0.05 for rare tumors. There was a single significant tumor findings among the female rats, right at the level of significance. When evaluating the validity of the female study, suppression of average body weights of the high dose compared to the controls would indicate that the high dose was close to the MTD.

4.2 p53(+/-) Transgenic Mouse Study

In this 26-week study, 15 animals per gender per group received the drug via gavage at levels of 0, 100, 300, and 1000 mg/kg/day. A positive control group received the urinary bladder carcinogen, p-cresidine, at 400mg/kg/day. There was one early death among the males (positive control) and zero to two deaths in each the female groups. The distribution of deaths among the females was statistically non-significant. No tumor finding among the Benicar treated animals reached statistical significance when compared to the vehicle controls. It needs to be pointed out, that there was only a single occurrence of a urinary bladder tumor in the positive control animals, which raises concerns regarding the sensitivity of this study.

4.3 Hras2 Transgenic Mouse Study

In this 26-week study, 15 animals per gender received either 0 (corn oil via gavage) or 1000 mg/kg/day of Benicar in the diet. An additional 15 animals per gender received a single i.p. injection of 75 mg/kg/ N-methyl-N-nitrosourea, a know carcinogen. None of the positive control animals lived till week 26. Of the remaining animals, only one (negative control) female did not reach terminal sacrifice. Most positive control animals exhibited tumors, mostly malignant lymphomas. The Benicar treated animals exhibited alveolar bronchiolar adenomas of the lung (males and females, two each) and squamous cell papilloma in the forestomach (single male). The comparisons with the (negative) controls did not reach statistical significance. As most positive control animals exhibited tumors, the study appears to have been sufficiently sensitive. However, if treatment effects are dependent on route of administration, this study may not be valid.

Roswitha Kelly, MS
Mathematical Statistician

Concur:

George Chi, Ph.D.
Director, Division of Biometrics 1

Cc: Orig. NDA 21-286
HFD-110/ Division Files
HFD-110/Dr. Jagadeesh
HFD-110/Dr. Resnick
HFD-110/ Mr. Fromm (PM)
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Hung
HFD-710/Ms. Kelly
This review consists of 8 pages of text, 10 pages of tables, and 1 page of figures. 2/27/01. Benicar.doc

Table 1: Number of Animals Dying in Given Interval

Species: Rat, Sex: Male

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	N
Week					
0-52	.	.	.	1	1
53-78	2	1	.	.	3
79-91	4	4	3	5	16
92-103	6	4	5	4	19
104-104	38	41	42	40	161
Total	50	50	50	50	200

Table 2: Dose-Mortality Trend Tests

This test is run using Trend and HomogeneityAnalyses of Proportions and Life Table Data

Version 2.1 by Donald G. Thomas, National Cancer Institute

Species: Rat, Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.01	0.9168
	Depart from Trend	1.04	0.5955
	Homogeneity	1.05	0.7898
Kruskal-Wallis	Dose-Mortality Trend	0.00	0.9530
	Depart from Trend	0.99	0.6092
	Homogeneity	0.99	0.8025

Table 3: Number of Animals Dying in Given Interval

Species: Rat, Sex: Female

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	N
Week					
0-52	.	.	1	.	1
53-78	3	2	2	2	9
79-91	2	3	2	1	8
92-103	8	5	5	4	22
104-104	37	40	40	43	160
Total	50	50	50	50	200

Table 4: Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data

Version 2.1 by Donald G. Thomas, National Cancer Institute

Species: Rat, Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.77	0.1837
	Depart from Trend	0.41	0.8138
	Homogeneity	2.18	0.5360
Kruskal-Wallis	Dose-Mortality Trend	1.72	0.1902
	Depart from Trend	0.39	0.8232
	Homogeneity	2.10	0.5509

Table 5: Test for Dose-Tumor Positive Linear Trend in Target Organs

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Adrenal	0330	Histio-S	0618	.0%	0	0	1	0	IN	0.5000	0.5884
Adrenal	0330	Cortex-A	1843	.0%	0	1	2	1	IN	0.3271	0.3524
Adrenal	0330	Pheochro	1848	10%	5	8	8	10	IN	0.1248	0.1177
Adrenal	0330	M-pheoch	1849	.0%	0	1	1	0	IN	0.6369	0.7112
Adrenal	0330	Leuke-LG	1991	2%	1	2	0	2	IN	0.3010	0.2663
Renal lymph node	0460	Metastas	0602	.0%	0	0	1	0	IN	0.4737	0.5115
Renal lymph node	0460	Histio-S	0618	.0%	0	1	0	0	IN	0.8000	0.7763
Renal lymph node	0460	Leuke-LG	1991	6%	3	0	1	5	IN	0.0222	0.0147
Mesenteric lymph node	0470	Histio-S	0618	.0%	0	1	0	0	IN	0.7333	0.7685
Mesenteric lymph node	0470	Leuke-LG	1991	2%	1	1	1	5	IN	0.0162	0.0101
Lympho-Hematopoietic syst	0480	Leuke-LG	1991	24%	12	3	5	12	IN	0.0523	0.0466
Kidney	1110	R-C-aden	1662	.0%	0	2	3	1	IN	0.5168	0.5229
Kidney	1110	R-C-carc	1663	.0%	0	0	1	1	IN	0.1726	0.1185
Kidney	1110	Trasit-P	1666	.0%	0	1	0	0	IN	0.7640	0.7424
Kidney	1110	Leuke-LG	1991	2%	1	0	0	2	IN	0.1447	0.0690
Liver	2150	Histio-S	0618	.0%	0	1	1	0	IN	0.6667	0.7501
Liver	2150	Heman-En	0621	2%	1	0	0	1	IN	0.4067	0.2658
Liver	2150	Hemangio	0681	2%	1	0	0	0	IN	1.0000	0.8182
Liver	2150	H-C-Aden	1447	4%	2	1	1	1	IN	0.6833	0.6634
Liver	2150	H-C-Carc	1448	4%	2	0	0	0	IN	1.0000	0.9012
Liver	2150	Leuke-LG	1991	22%	11	3	5	6	IN	0.5923	0.5885
Forestomach	2181	Squam-pa	0613	2%	1	0	0	0	IN	1.0000	0.8182
Forestomach	2181	Leuke-LG	1991	.0%	0	0	0	2	IN	0.0351	0.0037
Glandular stomach	2182	Leuke-LG	1991	4%	2	0	0	2	IN	0.2325	0.1815
Duodenum	2191	Leuke-LG	1991	.0%	0	0	0	1	IN	0.2222	0.0376
Jejunum	2192	Adenoma	0632	.0%	0	0	1	1	IN	0.1910	0.1381
Jejunum	2192	Leuke-LG	1991	.0%	0	0	0	2	IN	0.0441	0.0059
Ileum	2193	Leuke-LG	1991	.0%	0	0	0	2	IN	0.0500	0.0075
Cecum	2201	Leuke-LG	1991	.0%	0	1	0	2	IN	0.0743	0.0382

Colon	2202	Leuke-LG	1991	0%	0	0	0	2	IN	0.0392	0.0047
Rectum	2203	Leuke-LG	1991	0%	0	0	0	2	IN	0.0392	0.0047

Table 6: Test for Dose-Tumor Positive Linear Trend in Target Organs

Source: Female Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Adrenal	0330	Cortex-A	1843	8%	4	2	1	4	IN	0.3279	0.3239
Adrenal	0330	Cortex-C	1844	0%	0	1	0	1	IN	0.1932	0.1070
Adrenal	0330	Pheochro	1848	2%	1	3	2	3	IN	0.2832	0.2791
Adrenal	0330	M-pheoch	1849	0%	0	0	0	1	IN	0.2688	0.0561
Adrenal	0330	Leuke-LG	1991	4%	2	4	3	1	IN	0.7123	0.7200
Renal lymph node	0460	Metastas	0602	0%	0	0	1	0	IN	0.5432	0.6833
Renal lymph node	0460	Leuke-LG	1991	6%	3	3	2	0	IN	0.8948	0.8921
Mesenteric lymph node	0470	Metastas	0602	0%	0	0	1	0	IN	0.5366	0.6784
Mesenteric lymph node	0470	Leuke-LG	1991	2%	1	2	2	1	IN	0.3541	0.3813
Lympho-Hematopoietic syst	0480	Leuke-LG	1991	22%	11	6	10	5	IN	0.7768	0.7720
Kidney	1110	Leuke-LG	1991	0%	0	1	0	1	IN	0.1991	0.1328
Abdominal cavity	1230	Metastas	0602	0%	0	0	1	0	IN	0.5187	0.5690
Liver	2150	Metastas	0602	0%	0	0	1	0	IN	0.5187	0.5690
Liver	2150	Histio-S	0618	2%	1	0	0	0	IN	1.0000	0.8236
Liver	2150	Mesothel	0649	0%	0	1	0	0	IN	0.7687	0.7509
Liver	2150	H-C-Aden	1447	4%	2	0	0	2	IN	0.2927	0.2524
Liver	2150	Leuke-LG	1991	12%	6	6	10	4	IN	0.5530	0.5468
Glandular stomach	2182	Aden-pol	1730	0%	0	0	0	1	IN	0.2688	0.0561
Glandular stomach	2182	Leuke-LG	1991	0%	0	0	0	1	IN	0.1818	0.0219
Jejunum	2192	Leiomyom	0644	0%	0	0	0	1	IN	0.1905	0.0243
Cecum	2201	Leuke-LG	1991	0%	0	0	0	1	IN	0.2000	0.0279
Colon	2202	Adenoma	0632	0%	0	1	0	0	IN	0.7658	0.7484
Colon	2202	Leuke-LG	1991	0%	0	0	0	1	IN	0.2000	0.0279
Uterus	2910	EndometA	1874	2%	1	0	1	2	IN	0.1922	0.1473
Uterus	2910	EndometC	1875	2%	1	2	0	2	IN	0.3741	0.3424
Uterus	2910	EndometS	1876	0%	0	0	1	2	IN	0.0511	0.0243
Uterus	2910	Uter_Pol	2062	8%	4	12	3	10	IN	0.2267	0.2204

Table 7: P-Values for Pair-Wise Comparisons of Tumor Incidences

(Target and Non-Target Organs)

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Heart	0110	Leuke-LG	1991	2%	1	1	IN	0.7333	0.4747
Heart	0110	EndoC-Sc	2320	4%	2	1	IN	0.8891	0.7358
Aorta	0120	Leuke-LG	1991	0%	0	2	IN	0.1333	0.0331
Pituitary	0320	Adenoma	0632	52%	26	14	IN	0.9942	0.9892
Pituitary	0320	Leuke-LG	1991	0%	0	1	IN	0.4000	0.1104
Adrenal	0330	Cortex-A	1843	0%	0	1	IN	0.5128	0.1650
Adrenal	0330	Pheochro	1848	10%	5	10	IN	0.1381	0.0862
Adrenal	0330	Leuke-LG	1991	2%	1	2	IN	0.4296	0.2163
Thyroid	0340	F-cell-A	1819	2%	1	2	IN	0.4622	0.2513
Thyroid	0340	F-cell-C	1820	0%	0	2	IN	0.2597	0.0827
Thyroid	0340	C-cell-A	1821	28%	14	10	IN	0.8917	0.8389
Thyroid	0340	C-cell-C	1822	0%	0	1	IN	0.5128	0.1650
Thyroid	0340	Leuke-LG	1991	0%	0	1	IN	0.4000	0.1104
Spleen	0410	Heman-En	0621	0%	0	1	IN	0.4000	0.1104
Spleen	0410	M-Hem-En	0622	2%	1	0	IN	1.0000	0.8477
Spleen	0410	Leuke-LG	1991	24%	12	12	IN	0.5065	0.4007
Thymus	0420	Leuke-LG	1991	2%	1	3	IN	0.2593	0.1200
Bone marrow	0430	Hemangio	0681	2%	1	1	IN	0.7077	0.4506
Bone marrow	0430	Leuke-LG	1991	6%	3	6	IN	0.0794	0.0298
Lymph node	0440	Leuke-LG	1991	4%	2	5	IN	0.1402	0.0605
Submandibular lymph node	0450	Leuke-LG	1991	0%	0	4	IN	0.0370	0.0121
Renal lymph node	0460	Leuke-LG	1991	6%	3	5	IN	0.2679	0.1324
Mesenteric lymph node	0470	Leuke-LG	1991	2%	1	5	IN	0.0816	0.0326
Lympho-Hematopoietic syst	0480	Leuke-LG	1991	24%	12	12	IN	0.5065	0.4007
Skin	0520	Tricho-e	0611	2%	1	0	IN	1.0000	0.8477
Skin	0520	Keratoac	0612	8%	4	0	IN	1.0000	0.9829
Skin	0520	Leuke-LG	1991	0%	0	2	IN	0.1333	0.0331
Subcutis	0530	Fibroma	0615	6%	3	0	IN	1.0000	0.9280
Skeletal muscle	0650	Leuke-LG	1991	0%	0	1	IN	0.4000	0.1104
Cerebrum	0711	Leuke-LG	1991	2%	1	1	IN	0.8333	0.5673
Cerebrum	0711	M-Reticu	2436	4%	2	0	IN	1.0000	0.9280
Cerebellum	0712	Leuke-LG	1991	0%	0	1	IN	0.5556	0.1857

Spinal cord	0720	Leuke-LG	1991	0%	0	2	IN	0.2778	0.0882
Lung	0930	A/B Aden	1528	12%	6	4	IN	0.8650	0.7763
Lung	0930	A/B Carc	1529	2%	1	0	IN	1.0000	0.8477
Lung	0930	Leuke-LG	1991	16%	8	6	IN	0.7589	0.6331
Harderian gland	1030	Adenoma	0632	0%	0	1	IN	0.5556	0.1857
Zymbal gland	1050	Squam-Ca	0614	2%	1	0	IN	1.0000	0.8683
Kidney	1110	R-C-aden	1662	0%	0	1	IN	0.5556	0.1857
Kidney	1110	R-C-carc	1663	0%	0	1	IN	0.5128	0.1650
Kidney	1110	Leuke-LG	1991	2%	1	2	IN	0.4296	0.2163
Urinary bladder	1120	Metastas	0602	2%	1	0	IN	1.0000	0.7930
Urinary bladder	1120	Leiomyo-	0645	0%	0	1	IN	N/A	N/A
Urinary bladder	1120	Trasit-P	1666	2%	1	2	IN	0.7659	0.5147
Urinary bladder	1120	Leuke-LG	1991	0%	0	1	IN	0.4000	0.1104
Urinary bladder	1120	UN-Polyp	2281	2%	1	0	IN	1.0000	0.7930
Abdominal cavity	1230	Mesothel	0649	0%	0	1	IN	0.4000	0.1104
Abdominal cavity	1230	Leuke-LG	1991	0%	0	1	IN	0.4000	0.1104
Scrotal cavity	1260	Mesothel	0649	0%	0	2	IN	0.2051	0.0602
Cranial cavity	1270	Osteo-Sa	1972	2%	1	0	IN	1.0000	0.7930
Tongue	2120	Leuke-LG	1991	0%	0	1	IN	0.4000	0.1104
Liver	2150	Heman-En	0621	2%	1	1	IN	0.7077	0.4506
Liver	2150	Hemangio	0681	2%	1	0	IN	1.0000	0.8477
Liver	2150	H-C-Aden	1447	4%	2	1	IN	0.8891	0.7358
Liver	2150	H-C-Carc	1448	4%	2	0	IN	1.0000	0.9280
Liver	2150	Leuke-LG	1991	22%	11	6	IN	0.9415	0.8894
Forestomach	2181	Squam-pa	0613	2%	1	0	IN	1.0000	0.8477
Forestomach	2181	Leuke-LG	1991	0%	0	2	IN	0.1333	0.0331
Glandular stomach	2182	Leuke-LG	1991	4%	2	2	IN	0.6111	0.3929
Duodenum	2191	Leuke-LG	1991	0%	0	1	IN	0.4000	0.1104
Jejunum	2192	Adenoma	0632	0%	0	1	IN	0.5128	0.1650
Jejunum	2192	Leuke-LG	1991	0%	0	2	IN	0.1333	0.0331
Ileum	2193	Leuke-LG	1991	0%	0	2	IN	0.1667	0.0455
Cecum	2201	Leuke-LG	1991	0%	0	2	IN	0.1071	0.0243
Colon	2202	Leuke-LG	1991	0%	0	2	IN	0.1333	0.0331
Rectum	2203	Leuke-LG	1991	0%	0	2	IN	0.1333	0.0331
Pancreas	2230	Islet-ad	1773	8%	4	0	IN	1.0000	0.9829
Pancreas	2230	Leuke-LG	1991	0%	0	3	IN	0.0741	0.0226
Preputial gland	2830	Keratoac	0612	2%	1	0	IN	1.0000	0.8477

Preputial gland	2830	Adenoma	0632	6%	3	0	IN	1.0000	0.9641
Prostate	2840	Adenocar	0633	2%	1	0	IN	1.0000	0.7930
Prostate	2840	Leuke-LG	1991	.0%	0	1	IN	0.4000	0.1104
Seminal vesicle	2850	Leuke-LG	1991	.0%	0	2	IN	0.1333	0.0331
Testis	2870	Mesothel	0649	.0%	0	2	IN	0.2051	0.0602
Testis	2870	Leydig-A	1854	82%	41	40	IN	0.8408	0.7575
Testis	2870	Leuke-LG	1991	.0%	0	1	IN	0.4000	0.1104
Epididymis	2880	Mesothel	0649	.0%	0	2	IN	0.2051	0.0602
Epididymis	2880	Leuke-LG	1991	.0%	0	1	IN	0.4000	0.1104

Table 8: P-Values for Pair-Wise Comparisons of Tumor Incidences

(Target and Non-Target Organs)

Source: Female Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRLS	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Pituitary	0320	Adenoma	0632	48%	24	24	IN	0.6627	0.5858
Adrenal	0330	Cortex-A	1843	8%	4	4	IN	0.6703	0.5283
Adrenal	0330	Cortex-C	1844	.0%	0	1	IN	0.3333	0.0787
Adrenal	0330	Pheochro	1848	2%	1	3	IN	0.3667	0.1925
Adrenal	0330	M-pheoch	1849	.0%	0	1	IN	0.5375	0.1769
Adrenal	0330	Leuke-LG	1991	4%	2	1	IN	0.8038	0.5999
Thyroid	0340	F-cell-A	1819	.0%	0	1	IN	0.5375	0.1769
Thyroid	0340	F-cell-C	1820	.0%	0	1	IN	0.5375	0.1769
Thyroid	0340	C-cell-A	1821	26%	13	8	IN	0.9549	0.9237
Thyroid	0340	C-cell-C	1822	.0%	0	1	IN	0.5375	0.1769
Parathyroid	0350	Adenoma	0632	.0%	0	1	IN	0.5256	0.1712
Spleen	0410	Leuke-LG	1991	22%	11	5	IN	0.9486	0.9061
Thymus	0420	Leuke-LG	1991	.0%	0	1	IN	0.3333	0.0787
Thymus	0420	M-Thymom	2254	2%	1	0	IN	1.0000	0.7604
Bone marrow	0430	Leuke-LG	1991	2%	1	2	IN	0.2364	0.0879
Lymph node	0440	Leuke-LG	1991	.0%	0	1	IN	0.5375	0.1769
Submandibular lymph node	0450	Leuke-LG	1991	4%	2	2	IN	0.4061	0.2036
Renal lymph node	0460	Leuke-LG	1991	6%	3	0	IN	1.0000	0.8822
Mesenteric lymph node	0470	Leuke-LG	1991	2%	1	1	IN	0.5758	0.3001
Lympho-Hematopoietic syst	0480	Leuke-LG	1991	22%	11	5	IN	0.9486	0.9061
Skin	0520	Squam-pa	0613	.0%	0	1	IN	0.5375	0.1769
Skin	0520	Amelano-	0680	2%	1	0	IN	1.0000	0.8596
Subcutis	0530	Fibroma	0615	.0%	0	2	IN	0.2858	0.0934
Cerebrum	0711	Metastas	0602	2%	1	0	IN	1.0000	0.7604
Cerebrum	0711	Leuke-LG	1991	2%	1	0	IN	1.0000	0.7604
Cerebellum	0712	Leuke-LG	1991	.0%	0	1	IN	0.3333	0.0787
Spinal cord	0720	Metastas	0602	2%	1	0	IN	1.0000	0.7604
Lung	0930	A/B Aden	1528	.0%	0	1	IN	0.5375	0.1769
Lung	0930	Leuke-LG	1991	10%	5	4	IN	0.4710	0.2945
Eye	1010	Metastas	0602	2%	1	0	IN	N/A	N/A
Kidney	1110	Leuke-LG	1991	.0%	0	1	IN	0.3333	0.0787

Urinary bladder	1120	Trasit-P	1666	.0%	0	2	IN	0.2858	0.0934
Cranial cavity	1270	Osteo-Sa	1972	2%	1	0	IN	1.0000	0.7604
Liver	2150	Histio-S	0618	2%	1	0	IN	1.0000	0.8596
Liver	2150	H-C-Aden	1447	4%	2	2	IN	0.7470	0.5610
Liver	2150	Leuke-LG	1991	12%	6	4	IN	0.6483	0.4820
Glandular stomach	2182	Aden-pol	1730	.0%	0	1	IN	0.5375	0.1769
Glandular stomach	2182	Leuke-LG	1991	.0%	0	1	IN	0.3333	0.0787
Jejunum	2192	Leiomyom	0644	.0%	0	1	IN	0.3333	0.0787
Cecum	2201	Leuke-LG	1991	.0%	0	1	IN	0.3333	0.0787
Colon	2202	Leuke-LG	1991	.0%	0	1	IN	0.3333	0.0787
Pancreas	2230	Islet-ad	1773	.0%	0	1	IN	0.5375	0.1769
Mammary gland	2810	Adenoma	0632	6%	3	4	IN	0.5187	0.3643
Mammary gland	2810	Fibro-Ad	0634	6%	3	2	IN	0.7001	0.5284
Vagina	2900	Vaginal-	2446	2%	1	0	IN	1.0000	0.7604
Uterus	2910	EndometA	1874	2%	1	2	IN	0.5569	0.3248
Uterus	2910	EndometC	1875	2%	1	2	IN	0.5569	0.3248
Uterus	2910	EndometS	1876	.0%	0	2	IN	0.1667	0.0448
Uterus	2910	Uter_Pol	2062	8%	4	10	IN	0.1213	0.0733
Ovary	2930	Leuke-LG	1991	2%	1	0	IN	1.0000	0.7604
Ovary	2930	M_Grnl_C	2019	2%	1	0	IN	1.0000	0.8415
Clitoral gland	2950	Adenoma	0632	.0%	0	1	IN	0.5375	0.1769

Figure 1: Survival Curves for Male Rats

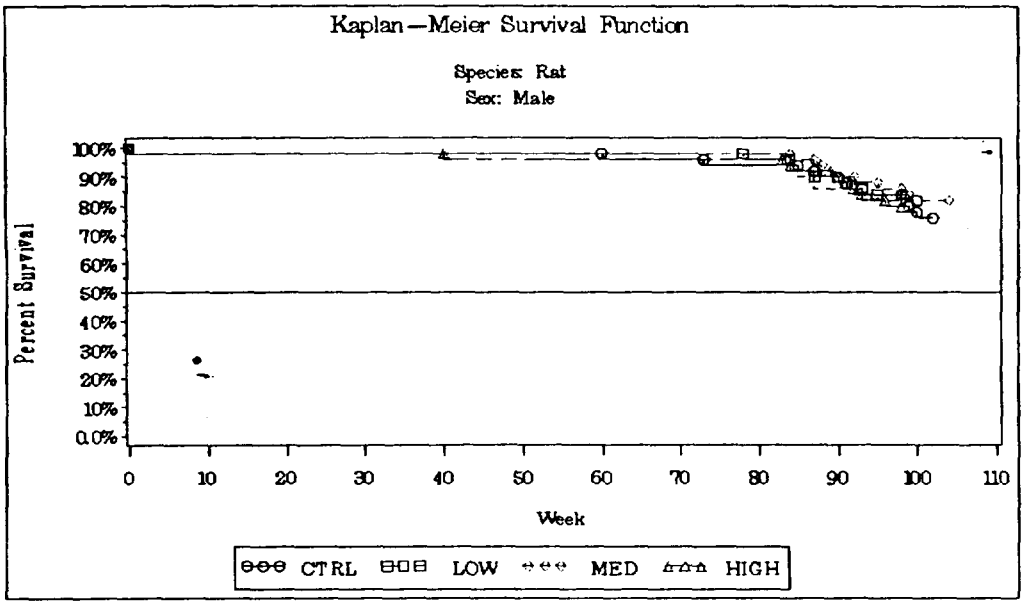
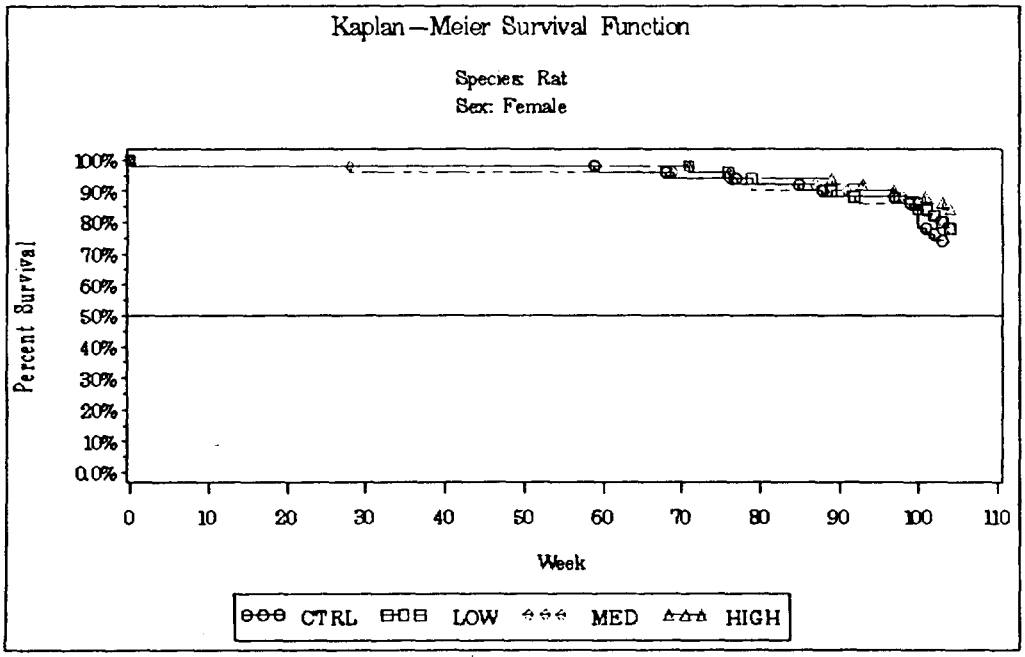


Figure 2: Survival Curves of Female Rats



/s/

Roswitha Kelly
3/6/01 03:39:37 PM
BIOMETRICS

Kooros Mahjoob
3/6/01 04:03:37 PM
BIOMETRICS

Full CAC - January 31, 2002
NDA 21,286 - olmesartan medoxomil, Sankyo Pharma

Attendees:
CDER:), Chuck Resnick (HFD-110), Gowra Jagadeesh (HFD-110), Belay Tesfamariam (HFD-110), Doug Throckmorton (HFD-110), Liz Hausner (HFD-110), Ed Fromm (HFD-110), Al DeFelice (HFD-110), Barry Rosloff (HFD-120), John Leighton (HFD-150), Dave Morse (HFD-150), Dave Bailey for Nakissa Sadrieh (HFD-160), Tim McGovern (HFD-170), Sushanta Chakder for Jasti Choudary (HFD-180), Jeri El Hage (HFD-510), Karen Davis-Bruno (HFD-510), James Farrelly (HFD-530), Paul Brown (HFD-540), Abby Jacobs (HFD-540), Terry Peters for Bob Osterberg (HFD-520/550), Robin Huff, (HFD-570), Joseph Sun (HFD-570), Suzanne Thornton for Alex Jordan (HFD-580), Ken Hastings (HFD-590), Frank Sistare (HFD-910), Roswitha Kelly (HFD-710), Karl Lin (HFD-715), Charles Anello (HFD-700), Adele Seifried (HFD-024), and Joseph Contrera (HFD-901).

Sankyo Pharma:
Kanichi Nakamura, Ph.D., Chairman of the Board
John Alexander, M.D., President
Bruce Dornseif, Ph.D., Senior Director, Biostatistics & Data Management
James Molt, Ph.D., V.P., Regulatory Affairs
Donald Hinman, Ph.D., Director, Clinical Research
Albert Yehaskel, M.S., M.B.A., Assoc. Director, Regulatory Affairs

Sankyo Co. Ltd.:
Sunao Manabe, D.V.M., Ph.D., V.P. Medical Safety Research Labs

Consultants:

Author of Draft: Adele Seifried

The following information reflects a summary of the Committee's discussion and its recommendations. Detailed study information can be found in the CDER background document.

Topic: NDA 21,286, olmesartan medoxomil

Background from FDA review division:

The angiotensin II receptor antagonist Benicar (olmesartan medoxomil, Sankyo), if approved, will be the 7th member of this class to be approved, all for the indication of hypertension. The potential for carcinogenicity has been considered by the division to be an approvability issue for an antihypertensive drug that has no unique clinical advantages over currently marketed members of its class.

The Carcinogenicity Studies

There were three carcinogenicity studies performed with olmesartan medoxomil (OM), a standard two year study in the Fischer rat, a 6 month p53(+/-) mouse study and a 6 month Hras2 mouse study. Although there were no statistically significant OM-related findings in any of these studies, there was a nominal increase in the incidence of renal tubular neoplasia in treated males in the two year rat study (adenomas and carcinomas which were not seen in the concurrent control rats and are relatively rare on the basis of historical control data for the strain (0.8%)). Because an Executive Committee of the CAC expressed concerns about the occurrence of renal tumors and renal tubular hyperplasia in OM-treated rats, the full CAC was asked to assess the evidence of carcinogenic potential for OM in the rat. A majority of the members of that committee felt that there was some evidence of treatment related renal neoplasia in male rats. There were no OM-associated increases in tumor incidence (renal or other) in the mouse studies. Because of a less than expected bladder tumor incidence in the positive control group in the p53(+/-) study, the committee was asked to assess the adequacy of that experiment and they found that study to be acceptable. In the sponsor's presentation to the CAC, they stressed the absence of atypical hyperplasia in the rats and argued that the renal tubular hyperplasia that was seen *should not* be considered pre-neoplastic. On the other hand, they claimed that the bladder hyperplasia observed in the positive control (p-cresidine) group in the p53(+/-) assay was atypical and *should* be considered pre-neoplastic.

A few weeks after the CAC meeting, office and division representatives met with the sponsor to explore what further actions the sponsor might take to strengthen their position that the increased incidence of renal tubular neoplasia in the Fischer rat was not related to treatment with their drug. The FDA representatives suggested that a kidney step-sectioning protocol be carried out and that the original study kidney slides be sent to NIEHS for peer review. It was also suggested that the sponsor perform additional *in vivo* assays to assess the mutagenic effect of OM on the kidney (Mutamouse Assay) and to assess the potential for DNA damage in the kidney (Comet Assay in rats).

The peer review by NIEHS pathologists Gary Boorman and Bob Marinpot, and an independent peer review by the sponsor's expert consultant pathologist, [redacted] essentially confirmed the tumor findings of the original study pathologist. The original diagnosis of tubule hyperplasia was not confirmed by [redacted] who, instead, diagnosed renal

tubule hypertrophy. The sponsor provided further support for this diagnosis with PCNA staining, which showed no greater proliferation in the kidney sections (of OM-treated rats) originally diagnosed as hyperplastic than in kidney sections of control rats. The NIEHS pathologists concluded that the tubular hyperplasia observed by the original study pathologist reflected tubular regeneration secondary to nephropathy. None of the peer reviewers saw evidence of the atypical hyperplasia that is considered evidence of preneoplastic activity. [redacted] asserted that one of the tumors in each of the OM-treated groups had a phenotype consistent with a spontaneous origin.

The step sectioning of the kidneys (slides read blinded) resulted in four more tumor-bearing animals in comparison with the original (single section) evaluation. All of these additional occurrences were in OM-treatment groups. Whereas the single section evaluation resulted in incidences of 0, 2, 4 & 2 tumor bearing rats in the control, low-dose, mid-dose and high-dose groups, the step section evaluation resulted in corresponding incidences of 0, 3, 5 & 4 (all adenomas except for 1 carcinoma in the mid-dose group and 1 carcinoma in the high dose group). As with the single section evaluation, the step sectioning did not result in a statistically significant increasing trend in tumor incidence. Although a pairwise comparison of the mid-dose group (not the high dose group) and the control group resulted in a p value <0.05, and although a pairwise comparison of the combined treatment groups with the control group also resulted in a p value <0.05, FDA statisticians use a p value of 0.01 to determine statistical significance when dealing with a common tumor and although renal tubular neoplasia is uncommon (about 0.8%) when detection is based on single-sectioning, it is common (about 4.5%) when detection is based on step-sectioning.

Genetic Toxicity

OM and olmesartan have been shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung). OM was also positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay. Diacetyl, a side-chain cleaved by ester hydrolysis during the process of absorption from the gut, produced positive responses in both Ames and in vitro chromosomal aberration (Chinese hamster lung) assays[1]. (Olmesartan and diacetyl were not tested in the mouse lymphoma assay.) It was on the basis of these results that an executive committee of the CAC accepted the p53(+/-) assay as an alternative to the standard 2-year carcinogenicity bioassay in the mouse. Additional testing has generally been limited to OM, with equivocal *in vivo* findings in the MutaMouse intestine (LacZ and CII loci) and negative findings in the MutaMouse kidney (LacZ locus). Equivocal results were also obtained *in vivo* in the Fischer rat kidney (Comet Assay). OM tested negative for clastogenicity *in vivo* in the mouse bone marrow micronucleus test. Both OM and

[1] *Diacetyl occurs naturally in foods and drinks and is categorized as "Generally Regarded As Safe (GRAS)" by the FDA.*

olmesartan tested negative in vitro in the Syrian hamster embryo cell transformation assay.

Purpose of a Second Meeting of the CAC

On October 3rd, representatives of the Division and the Office again met with Sankyo. The company and their consultant, [redacted] outlined the reasons why they thought olmesartan medoxomil was not responsible for the renal tubular neoplasms that had been observed in the two-year rat study. Some of the material presented (results of the PCNA staining, and the views of Dr. Boorman, Marinpot and [redacted] had not been available at the time of the CAC meeting and a decision was made to reconvene that committee. Before taking this drug back to the CAC, it was agreed that a pathology working group (PWG) that included one or more members chosen by the Agency, along with other members selected by the sponsor, would be asked to consider the relationship of OM to the renal tumors seen in the 2-year rat study. The sponsor was told that although an approvable letter would issue, approval of their product would depend on the outcome of the CAC deliberations.

Findings of the Pathology Working Group

The report of the pathology working group (submitted to the Division in late December) confirms the presence of renal tubular neoplasms in all groups of OM-treated rats and the absence of such tumors in the concurrent control group.[2] It also confirms the absence of drug-associated renal tubular hyperplasia. The renal changes diagnosed as tubular cell hyperplasia by the original study pathologist were considered by the PWG to be tubular hypertrophy, a non-proliferative change associated with chronic nephropathy. The severity of nephropathy (which was seen in essentially all of the rats) was somewhat greater in all treated groups (not dose-dependent) than in the concurrent control group, but the PWG report is silent on whether the increased severity is related to the tubular neoplasia. The PWG was unable to determine, on the basis of morphology, whether the tumors seen in the OM-treated rats were spontaneous or drug-induced. They did conclude, on the basis of other factors ("lack of dose response and absence of increased incidence of hyperplastic lesions suggestive of preneoplastic changes") that "the few tubular cell neoplasms observed in this study" were not treatment related.

After reviewing all of the original male rat kidney slides and kidney slides from 4 male rats with tubular adenomas noted during the step-section study but not during the original single-section evaluation, the PWG agreed on the following incidences of tubular cell adenoma or carcinoma in the various study groups.

---

[2] The PWG confirmed only 3 of the 4 tumors diagnosed by the original study pathologist in the mid-dose group (4th tumor diagnosed by the PWG as a metastatic carcinoma, uncertain primary) and only 1 of the 2 additional tumors identified in the high-dose group by step sectioning (lesion originally diagnosed as a tubular cell adenoma was diagnosed by the PWG as a marked tubular cell hyperplasia).

Control: 0/50
Low Dose: 3/50 (2/50 before step sectioning)
Mid Dose: 4/50 (3/50 before step sectioning)
High Dose: 3/50 (2/50 before step sectioning)

Presentation by Sankyo Pharma:

Dr. James Molt introduced the presentation. He reminded everyone that on May 4, 2001, the CAC voted 12-8 that the compound tested positive in the rat carcinogenicity bioassay. There had also been concerns about the hyperplasia seen in association with tubular cell adenomas and carcinomas. Studies completed since the last meeting included:

Peer review of rat kidneys
Expert review of rat kidneys
PCNA staining for cell proliferation (hyperplasia)
Step-sectioning of rat kidneys
Comet assays to assess DNA damage
MutaMouse data to help address questions of genotoxicity.

[redacted] summarized his pathology evaluation of male rat kidneys, and compared his findings to those of the original study pathologist. He did not see hyperplasia, but did see (distal) tubule hypertrophy. He hypothesized that the hypertrophy was related to increased sodium excretion due to angiotension II receptor blockade. He saw 0, 2, 3, and 2 primary tumors in his analysis (control, LD, MD, HD, respectively, compared to 0, 2, 4, and 2 previously reported. He concluded that they were not related to treatment with CS-866 (olmesartan medoxomil) because of the absence of cellular change (cytotoxicity), absence of preneoplastic lesions (atypical tubule hyperplasia), and the presence of a tumor type consistent with spontaneous origin. He noted that the historical control incidence for renal tubule neoplasia is close to 1% in the laboratory that conducted the study.

[redacted] reviewed the findings of the pathology working group panel of experts, who scored coded slides using nomenclature from the NTP and the Society of Tox Path. Tubular cell hyperplasia was limited to 1 control, 1 LD, 0 MD, and 1 HD rat. The original study pathologist had reported incidences of 0,14,13,19. Tubular cell neoplasms were observed only in OM-treated rats, with incidence essentially the same in each treatment group. They saw no difference in severity of nephropathy with increasing dose. He concluded that there was:

- no treatment related increase in tubular cell hyperplasia,
- a low and similar incidence of tubular cell neoplasms across all treatment groups,
- minimal increase in severity of chronic nephropathy in treatment groups compared to control,
- no increase in severity of chronic nephropathy among groups dosed with CS-866,

• the tubular cell neoplasms were similar morphologically to spontaneously occurring tubular cell adenomas and carcinomas, and
• hyperplasia diagnosed by the study pathologist was considered by the PWG to be hypertrophy

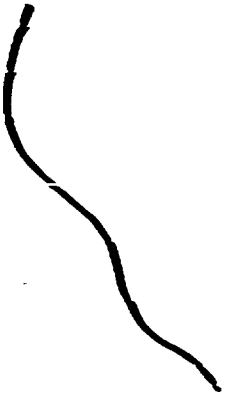
Dr. James Molt concluded the presentation. He asserted that the few tubular cell neoplasms observed in this study are not related to treatment with CS-866 because of the absence of hyperplastic lesions suggestive of preneoplastic changes, the relatively low incidence of neoplasms, the lack of statistical significance, and the lack of a dose-response. In addition, there was no relationship between renal neoplasia and chronic progressive nephropathy, and a lack of genotoxicity in the kidney as determined by kidney Comet and MutaMouse studies.

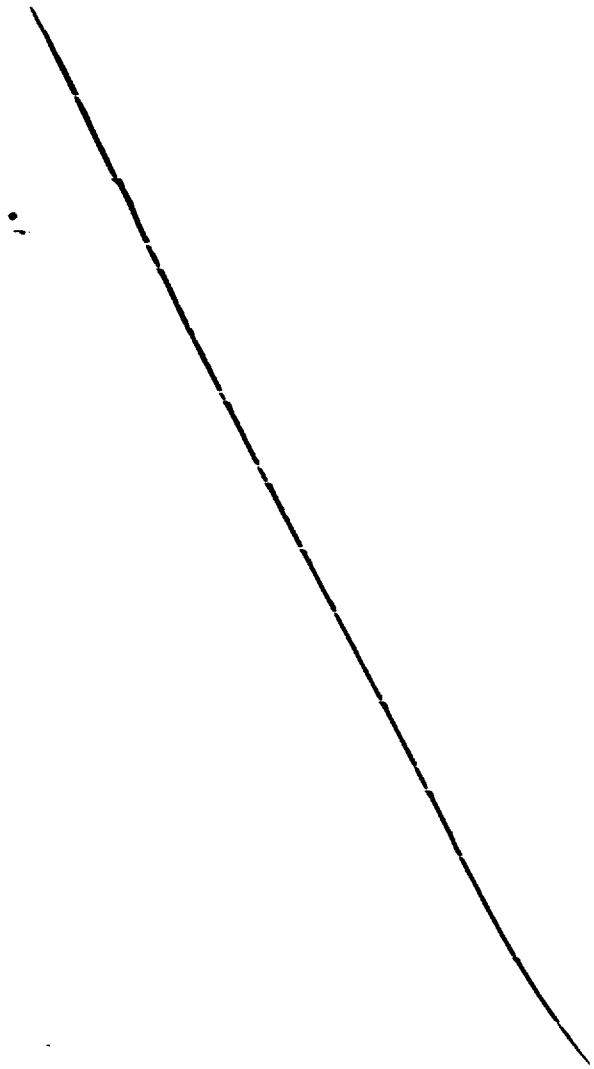
Presentation by FDA:
The division did not make a formal presentation.

General Discussion:

The results of the kidney Comet assay were discussed. The kidney Comet assay for DNA damage was negative. The sponsor stated that based on dispersion analysis, there is no evidence of increased heterogeneity suggestive of sub-populations of kidney cells with significantly increased levels of DNA damage. Combined with the lack of a significant increase in mean tail length, there is no evidence that CS-866 induces DNA damage in kidney cells.

Closed Discussion:





Conclusion:
A clear majority of the committee did not think that the olmesartan-renal tumor association observed in the 2-year study in the Fischer 344 rat provided evidence of carcinogenic potential sufficient to label that study positive. They based their decision primarily on the lack of proliferative lesions (hyperplasia), the absence of a dose relationship, and the absence of statistical significance. A minority of the members still had a concern that the tumors were seen only in the treated animals, with none seen in the controls, but 3 of 4 did not believe that this poses a risk for humans.

/S/

Joseph Contrera
Acting Chair, Carcinogenic Assessment Committee

cc:
HFD-110/NDA 21,286
GJagadeesh/HFD-110
CResnick/HFD-110
EFromm/HFD-110
ASeifriedHFD-024

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joe Contrera
2/13/02 09:40:24 AM

Full CAC - May 4, 2001
NDA 21,286 - olmesartan medoxomil, Sankyo Pharma

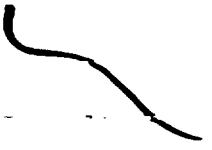
Attendees:

CDER: Joseph DeGeorge (HFD-024), Adele Seifried (HFD-024), Chuck Resnick (HFD-110), Gowra Jagadeesh (HFD-110), Tim Link for Al DeFelice (HFD-110), Barry Rosloff (HFD-120), John Leighton (HFD-150), Dave Morse (HFD-150), Dave Bailey for Nakissa Sadrieh (HFD-160), Kathy Haberny for Tom Papoian (HFD-170), Sushanta Chakder for Jasti Choudary (HFD-180), Jeri El Hage (HFD-510), Karen Davis-Bruno (HFD-510), James Farrelly (HFD-530), Abby Jacobs (HFD-540), Bob Osterberg (HFD-520/550), Robin Huff, (HFD-570), Joseph Sun (HFD-570), Steve Hundley for Ken Hastings (HFD-590), Joseph Contrera (HFD-901), Frank Sistare (HFD-910), and Roswitha Kelly for Charles Anello (HFD-700).

Sankyo Pharma:
Kanichi Nakamura, Ph.D., Chairman of the Board
John Alexander, M.D., President
Tom Robinson, M.D., V.P., Development
Jim Molt, Ph.D., V.P., Regulatory Affairs
Harvey Masonson, M.D., Sr. Dir, Clinical Research
Antonia Wang, Ph.D., Dir, Biostatistician
Donald Hinman, Ph.D., Director, Clinical Research
Albert Yehaskel, M.S., M.B.A., Assoc. Director, Regulatory Affairs
Hisashi Nakagaki, M.S., R.Ph., Asst. Dir, Liaison & Project Coordinator
John Cargiulo, Commercial Operations

Sankyo Co. Ltd.:
Sunao Manabe, D.V.M., Ph.D., V.P. Medical Safety Research Labs
Shinya Sehata, D.V.M., Assoc. Researcher, Medicinal Safety Research Labs

Consultants:



Author of Draft: Adele Seifried

The following information reflects a summary of the Committee's discussion and its recommendations. Detailed study information can be found in the CDER background document.

Topic: NDA 21,286, olmesartan medoxomil

Background from FDA review:

Olmesartan medoxomil (OM) is an angiotensin II receptor antagonist that has been shown to possess mutagenic and clastogenic activity. Three carcinogenicity studies have been carried out. The executive committee of the CAC had previously accepted the dosage levels employed in the 2-year rat study and 6 month p53(+/-) mouse study but was not offered the opportunity to comment on the protocol for the Hras2 mouse study (a non-GLP study). The division was in agreement with the sponsor that none of the carcinogenicity studies conducted with OM provided evidence of OM-related carcinogenicity but questioned the adequacy of the P53 (+/-) study in which administration of the positive control (p-cresidine) resulted in only 1 urinary bladder tumor (transitional cell carcinoma), although urinary bladder transitional cell hyperplasia was seen in all members of the positive control group. (Urinary bladder transitional cell carcinoma is the expected response to p-cresidine in this assay.)

In a meeting on March 20, 2001, the Exec CAC discussed the adequacy of the positive control response in the p53(+/-) mouse, but did not reach agreement. In the evaluation of the 2-year rat study, it was noted that hyperplasia was observed in the renal tubules of males and females and was accompanied, in males, by nominal (but not statistically significant or dose dependent) increases in the incidence of renal tubular neoplasia. Another concern was the identification of mesotheliomas, in treated rats only. The committee concluded that additional information would be needed to reach resolution. Where not already provided, the committee wanted the division to compare combined incidences of tumors of the same cell type (e.g. endometrial adenomas and sarcomas) across treated and control groups of rats.

The division agreed to follow-up on these concerns by reviewing group incidences of hyperplasia for all organs where a nominal increase in tumor incidence was observed. Where incidences of hyperplasia and tumors of the same cell type were both found to be increased, the division was to ask the sponsor to provide historical control data for each of those tumors. The division was also to ask the sponsor for the background incidence for mesothelioma in the Fisher rat, and compare the incidences of treated and control Fisher rats bearing a) uterine endometrial stromal polyps *or* uterine endometrial stromal sarcomas, (b) uterine endometrial adenomas *or* uterine endometrial sarcomas and (c) renal tubular adenomas *or* renal tubular carcinomas. It was recommended that the olmesartan medoxomil carcinogenicity studies be brought to the full CAC when the additional information was available.

By the time of the full CAC meeting that is the subject of these minutes, the division had determined that the incidence of mesothelioma observed in olmesartan medoxomil treated rats was within the sponsor's laboratory control range for Fisher 344 rats, but that the incidence of renal tubular cell neoplasia (combined incidence of adenomas and carcinomas) exceeded the upper limit of the sponsor's laboratory control range as well the upper limit of the NTP historical control range in this same strain of rat. The full CAC was asked to assess the evidence of

carcinogenic potential for olmesartan medoxomil in the Fisher 344 rat and the adequacy of both the p53(+/-) and Hras2 assays.

Presentation by Sankyo Pharma:

[redacted] presented the rat carcinogenicity study data and addressed the concerns that had been raised by the Executive CAC regarding the results of that study. He noted that the exposures (AUCs for olmesartan medoxomil) at the highest and lowest doses evaluated in that study were, respectively, 31.9 and 6.8 times the human exposure at the recommended dose of 40 mg/day and that, although there were renal tubular adenomas or carcinomas in each treated group and none in the concurrent control group, the difference relative to concurrent control was neither statistically significant nor dose-related. Furthermore, neither the adenoma incidence nor the carcinoma incidence in any of the treated groups was outside the historical control range for the Fisher 344 rat. Regarding the occurrence of tubular cell hyperplasia, which was dose-related (and significantly higher than concurrent control at all dose levels), he noted that the finding was graded as slight in all cases but for one of 19 high dose males, which received a grade of moderate. He further noted the observations of the study pathologist and consultant expert reviewers that there was no nuclear pleomorphism, no increased mitosis, and no cellular atypia, leading them to conclude that the lesions were not pre-neoplastic. In the company's view, the Fisher 344 rat study did not provide evidence of carcinogenic potential sufficient to label that study positive. The presentation also noted that two other angiotensin II receptor blockers, telmisartan and candesartan, were also associated with nominal increases over concurrent control incidences of renal tubular cell adenoma (telmisartan) or carcinoma (candesartan) and that those studies had been described in product labeling as providing "no evidence of carcinogenicity".

[redacted] discussed the short-term carcinogenicity tests and the genotoxicity assays. Regarding the p53 (+/-) mouse study, he argued that the high incidence of transitional cell hyperplasia and the low incidence of transitional cell carcinoma in the urinary bladders of mice treated with para cresidine (the positive control) have been observed and reported previously for this assay system. When one also considers a diagnosis of "atypia" for the tubular hyperplasia in at least one of the non-tumor bearing positive control mice, it was considered that this was an adequate study. Regarding the Hras2 mouse study, in which only a single dose level of OM was evaluated, it was argued that although that single dose level had not been approved by the CAC, the criteria used for selecting it were the same as used for the p53(+/-) study (reduction in blood pressure in parent strain). It was further noted that the systemic exposure to olmesartan medoxomil (AUC) was 6 times (males) or 8.4 times (females) the systemic exposure at the MRHD. This study, in which OM tested negative and the positive control tested clearly positive, should be described in product labeling. As for the genotoxicity assays, the sponsor's position was that angiotensin II receptor antagonists, as a

class, are positive *in vitro* for clastogenicity and negative in the Ames Test. While agreeing with the assertion that the Ames Test has been consistently negative for these agents, the division disagreed with the generalization regarding other studies; although some other members of the class may have tested positive *in vitro* for clastogenicity, there is insufficient data to consider this a class effect. In addition, CS-866 (olmesartan medoxomil) presented a more disturbing profile than the other members of the class since it also tested positive in the mouse lymphoma assay and the *in vivo* mutamouse assay. stated that in evaluating potential for mutagenicity, the lowest weight should be given the in vitro genotoxicity studies, greater weight given to the *in vivo* genotoxicity studies, and the highest weight be given to the short-term carcinogenicity studies. He concluded that CS-866 is not a genotoxic carcinogen.

presented the sponsor's overall conclusions that there were no findings from the F344 Rat Bioassay or the p53 (+/-) and Hras2 Transgenic Mice Bioassays that are suggestive of a genotoxic carcinogen. He emphasized the absence of atypical tubular hyperplasia (a preneoplastic tubular change) in the rat bioassay.

The division did not make a formal presentation.

General Discussion:

The following points were raised:

There is only 1 metabolite in man, olmesartan, although olmesartan glucuronide is made in rats.

There is greater urinary excretion (as % of dose administered) in man than in rat.

Survival was slightly higher in dosed rats than in control rats.

The current NTP rates for adenomas and carcinomas seem to be lower than the older historical rates presented by Sankyo.

Although there is no trend for the increased incidence of renal tubular neoplasms, and no statistically significant difference between the incidence in treated and concurrent control groups, what is the likelihood of seeing such incidences (4-8%) in each of the treated groups?

The sponsor noted that three mutamouse studies have been done.

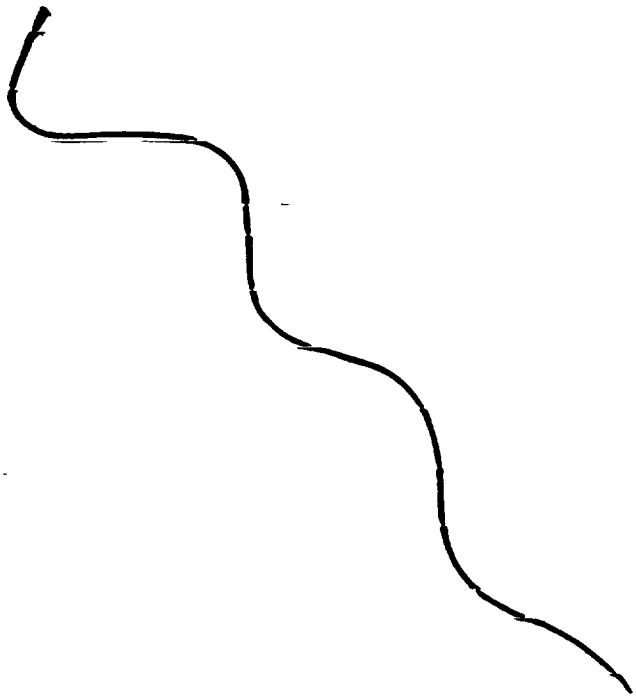
The committee was interested in whether the kidney showed evidence of mutation. The sponsor did not look at kidneys in any of those studies and can not do so now as kidneys were not preserved.

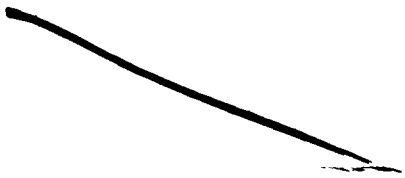
Regarding the P53: What would one expect to see at 6 months with a carcinogen? In a C57 black mouse, what would you see with p-cresidine at 6 months? (Very little change in bladder). What about the hypercellularity at the expected target site, the renal tubule? What were the criteria used to distinguish between the various grades of non-neoplastic and of neoplastic findings in this study? [The sponsor did not answer this, but discussed general criteria and focused on the distinctions between adenoma and carcinoma.]
The sponsor will see if they can find additional data on p-cresidine responses in the wild type animals and supply that to FDA.

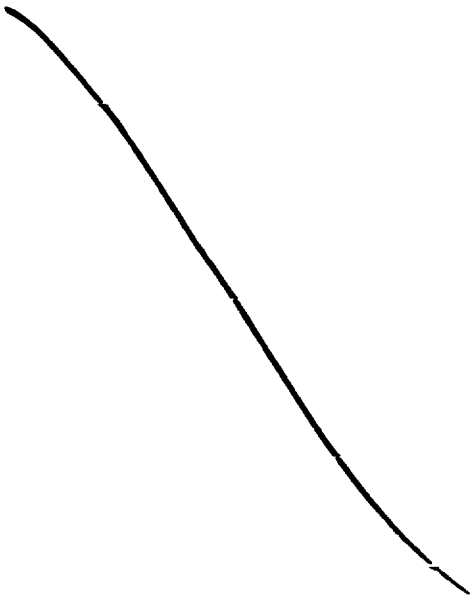
If the study in the Hras2 was considered adequate for dose selection it was noted that it could be included in the label provided the sponsor could say how it deviated from GLP and what impact that would have on it's interpretation and reliability.

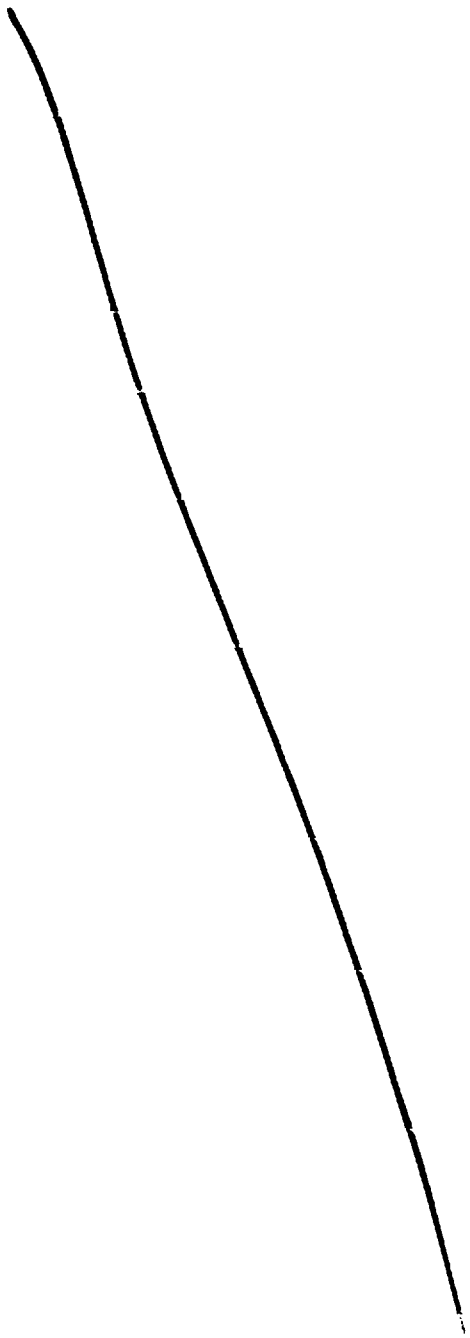
In addressing the MTD question for the Hras2 study, the sponsor stated that although there were significant effects on serum chemistry values, hematology values and organ weights, dose selection was based on the hypotensive effects of the drug, one of the criteria used by the ExecCAC in accepting the P53 study protocol.

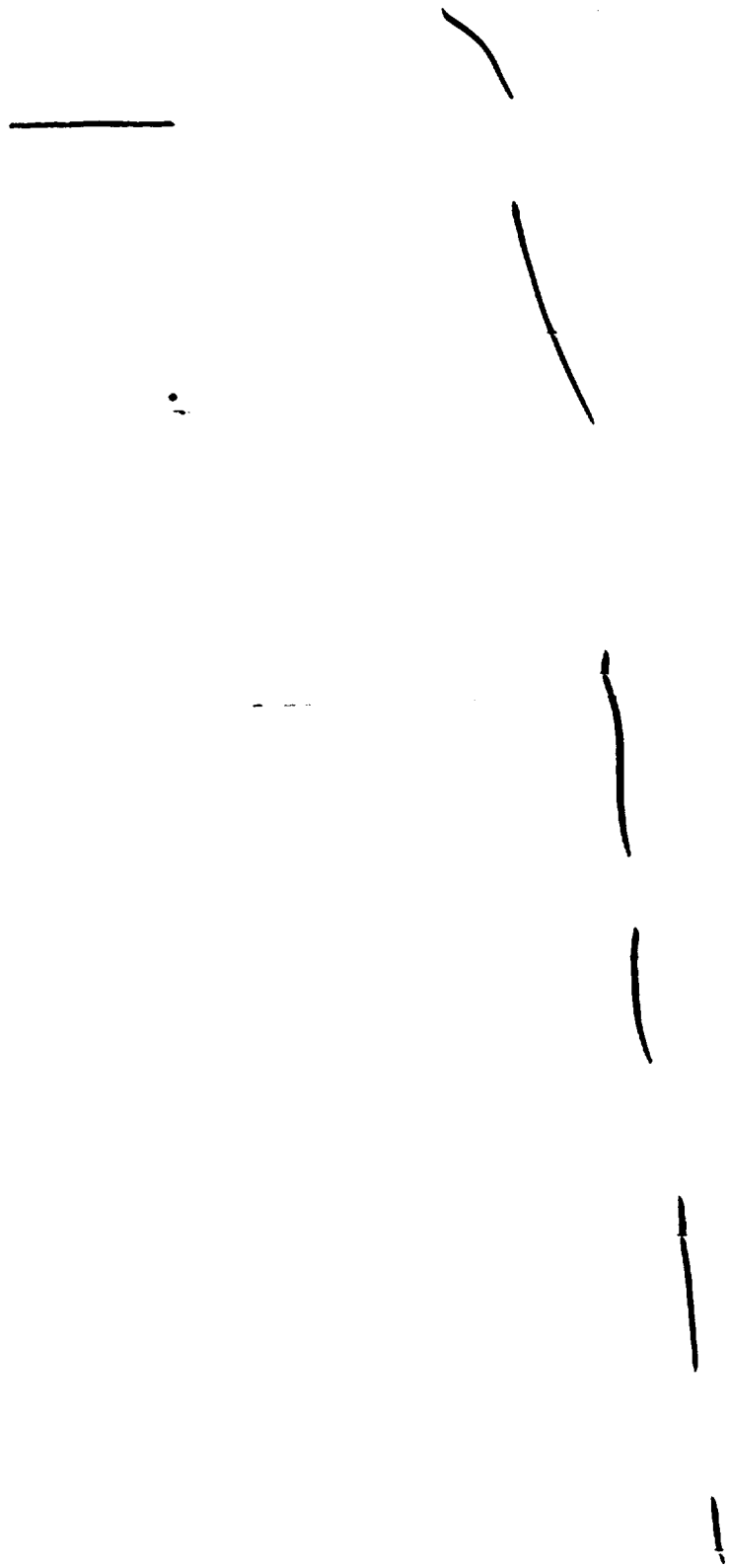
Closed Discussion:











Conclusion:

A majority of the members believed that the drug appears positive in the rat carcinogenicity assay, most of these unable to conclude that it does not pose a risk for humans. Further clarification of the renal response observed by reevaluation of the renal histopathology by a third party chosen by the agency and possibly additional step sectioning of the kidney were recommended. A majority believed that the p53 assay was probably an adequate test, although they would like to have access to historical data on what response would be seen in six months in the wild type mouse to the positive control. Many also had concerns about the lack of tumors in the positive control, suggesting that this reflected either a failure or a low sensitivity of the assay and perhaps a capability of detecting only potent carcinogens which may not be relevant to omlesartan. It was almost unanimous that the dose administered in the Hras2 assay was adequate to provide an acceptable test of carcinogenic potential, because they felt the maximum tolerated dose had been reached based on an acceptable pharmacodynamic endpoint of substantially lowered blood pressure. A majority felt that information from this assay non-GLP Hras2 assay should be described in the product labeling,

/S/

Joseph J. DeGeorge
Chair, Carcinogenic Assessment Committee

cc:
HFD-110/NDA 21,286
GJagadeesh/HFD-110
CResnick/HFD-110
EFromm/HFD-110
ASeifriedHFD-024

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph DeGeorge
6/19/01 04:43:37 PM

STATISTICAL REVIEW AND EVALUATION

NDA #: 21-286
Applicant: Sankyo Pharma Inc.
Drug Name: Olmesartan medoxomil
Indication: Anti-hypertension
Document Reviewed: Vols. 1.337, 1.170, Electronic study reports, SAS database

1. INTRODUCTION

This document contains a review of three US studies (866-204, 866-305, and 866-306) that are large studies in terms of sample size, if not the largest, in this NDA application, and a brief summary of two European studies (SE-866/09, SE-866/11). Study 866-204 focused primarily on ABPM blood pressures and the other two studies on cuff blood pressures. The two European studies are briefly summarized for the effect of the 2.5 mg dose of olmesartan. In the sponsor's analyses, small centers were pooled to construct a set of pooled centers and treatment by center interaction and treatment by baseline blood pressure interaction were included in the ANCOVA models. In my view these processes added little value to the primary analyses but might make interpretation more difficult. Thus this reviewer did analyses using the model that does not contain the interaction terms. The reviewer's results are generated from the SAS database the sponsor's provided and are very similar to the sponsor's results. Only the reviewer's results will be presented in this review.

2. REVIEWER'S OVERVIEW AND EVALUATION OF STUDIES 866-204, 866-305 AND 866-306

Study 866-204

This 35-center, randomized, double-blind, placebo-controlled, parallel-group study was designed to study the efficacy of 5 mg, 20 mg, 80 mg olmesartan QD, as compared to placebo in patients with essential hypertension.

During a 14-day single-blind placebo run-in period, the patients must have their two daily average sitting DBPs >= 100 mmHg but <= 115 mmHg, with no more than a 7 mm Hg difference between the daily averages at the two visits before they could undergo an ABPM measurement on the last day of the run-in period. Patients who had a mean daytime DBP >= 90 mm Hg determined by ABPM were randomized in equal allocation and in a double-blind fashion to one of seven treatment groups: 5, 20, or 80 mg olmesartan QD, 2.5

mg, 10, or 40 mg olmesartan BID, or placebo. The number of black patients randomized at each center was to be limited to 20% of the total number of randomized patients at the center. The active treatment period was 8 weeks.

The primary efficacy analysis compared the change from baseline in mean 24-hour DBP as measured by ABPM at Week 8 for the placebo and olmesartan QD dose groups. The goal was to look for a monotone non-decreasing antihypertensive effect in mean DBP. The statistical hypotheses to be tested were: H_0: $\mu_{placebo} = \mu_{5mg} = \mu_{20mg} = \mu_{80mg}$ versus H_1: $\mu_{placebo} \leq \mu_{5mg} \leq \mu_{20mg} \leq \mu_{80mg}$ with at least one strict inequality and where μ was the mean change in 24-hour ABPM DBP from baseline to Week 8 or the last available post placebo run-in measurement. Secondary efficacy assessments include the change from baseline at Week 8 in mean 24-hour DBP and SBP for the placebo and olmesartan BID dose groups, change from baseline in mean daytime and nighttime DBP, and SBP comparison of cuff blood pressure.

Bartholomew's test for order alternatives in the one-way ANOVA was used for the primary efficacy comparison. A lot of supplemental and exploratory analyses were proposed, such as, regression analysis for dose response.

The sample size of 50 patients per group (40 non-black and 10 black patients) was planned so that the study would have 71% power to detect a 5 mm Hg difference and 100% power for 10 mm Hg difference in mean DBP between 80 mg and placebo. The trial was thought to have at least 92% power to detect a 10 mm Hg difference in mean SBP.

Disposition of patients

A total of 334 patients (302 non-Black, 32 Black) were randomized into the study. The number of patients appeared to be evenly distributed among the seven treatment groups. Thirty-six patients (about 10%) discontinued from the study before Week 8. The most frequent reasons for discontinuations were: patient request (25%), adverse event (22%), investigator judgement (19%), and protocol violation (11%).

Efficacy evaluation

The intent-to-treat (ITT) population consists of patients who were randomized, received at least one dose of randomized study medication, and had at least one evaluation of blood pressure after baseline. ITT for ABPM consists of 289 non-Black and 28 Black patients and ITT for cuff BP consists of 299 non-Black and 29 Black patients. The treatment groups appeared to be similar

with respect to demographic characteristics and baseline blood pressures.

1) ABPM Blood Pressure and Heart Rate

There was highly statistically significant monotone trend for increasing DBP reduction with higher dose for QD dosing ($p < 0.0001$, Bartholomew's test). So was for BID dosing and combined QD plus BID dosing. The results of ANCOVA not using monotone trend assumption were also in agreement with Bartholomew's test results.

There was also highly statistically significant monotone trend for increasing SBP reduction with higher dose for QD dosing ($p < 0.0001$, Bartholomew's test). So was for BID dosing and combined QD plus BID dosing. The results of ANCOVA not using monotone trend assumption were also in agreement with Bartholomew's test results.

In most centers there were one or two patients in the treatment groups; thus, the results by center will not be displayed. There was no evidence of treatment by site interaction ($p > 0.20$). Change of heart rate appeared to be very small in all the treatment groups. There was no significant difference.

Table 204-1. Mean change in ABPM DBP (ITT patients)

Treatment Group	N	Mean change ±se in 24-hr DBP (mm Hg)	Mean change ±se in daytime DBP (mm Hg)	Mean change ±se in nighttime DBP (mm Hg)
Placebo	46	0.9±0.8	-0.0±1.0	1.8±0.9
5 mg QD	43	-8.7±1.2	-10.2±1.3	-7.3±1.3
20 mg QD	41	-11.3±1.2	-12.8±1.3	-9.8±1.3
80 mg QD	45	-9.3±1.4	-10.0±1.6	-8.6±1.5
2.5 mg BID	49	-7.7±0.8	-8.1±0.9	-7.4±1.0
10 mg BID	48	-10.0±1.1	-10.6±1.2	-9.4±1.2
40 mg BID	46	-10.6±1.3	-12.9±1.3	-8.4±1.3

Table 204-2. Mean change in ABPM SBP (ITT patients)

Treatment Group	N	Mean change ±se in 24-hr SBP (mm Hg)	Mean change ±se in daytime SBP (mm Hg)	Mean change ±se in nighttime SBP (mm Hg)
Placebo	46	1.3±1.2	0.5±1.4	2.1±1.3
5 mg QD	43	-13.6±1.8	-15.6±1.9	-11.6±2.0
20 mg QD	41	-15.3±1.7	-17.5±1.9	-13.2±1.8
80 mg QD	45	-13.4±1.8	-14.8±2.0	-11.9±2.0
2.5 mg BID	49	-10.8±1.2	-11.5±1.3	-10.0±1.5
10 mg BID	48	-14.4±1.7	-15.0±1.7	-13.8±1.8
40 mg BID	46	-15.9±1.8	-19.1±1.9	-12.7±1.9

Table 204-3. Mean change in ABPM heart rate (ITT patients)

Treatment Group	N	Mean change ±se in 24-hr HR (bpm)	Mean change ±se in daytime HR (bpm)	Mean change ±se in nighttime HR (bpm)
Placebo	46	-0.4±1.0	0.1±1.5	-0.9±1.0
5 mg QD	43	-0.3±0.8	0.4±1.0	-1.0±0.9
20 mg QD	41	0.5±1.0	0.3±1.3	0.7±1.0
80 mg QD	45	2.1±0.8	2.3±1.0	1.9±1.1
2.5 mg BID	49	0.3±0.8	1.1±1.0	-0.5±0.9
10 mg BID	48	-0.6±1.0	0.1±1.2	-1.4±1.0
40 mg BID	46	1.0±1.0	1.4±1.2	0.5±1.0

The sponsor performed separate analyses for non-Black and Black patients. The results of non-Black patients are similar to all patient results (the sponsor's Tables 7.5.1.1-1, 7.5.1.1-2, 7.5.1.1-3 on pages 97-99 of the 866-204 Clinical Trial Report). There was no evidence indicating that the effect of olmesartan in Black patients was very different from that in non-Black patients. In my view, the sponsor's separate by-race analyses offer little help in attempting to find the potential between-race difference in drug effect.

Dose response on ABPM BPs

It is clear from Tables 204-4, 204-5, 204-6, and 204-7 that there is a positive dose response indicating that the greater the daily dose the greater blood pressure decreases are. Highly statistically significant quadratic term (i.e., dose square term) indicates that increases in blood pressure reduction appear to

start leveling off at some dose approximately between 46 and 52 mg.

Table 204-4. Dose response analysis for DBP (ITT patients)

Parameter	24-hr DBP p-value	Daytime DBP p-value	Nighttime DBP p-value
Dose (QD)	< 0.0001	< 0.0001	< 0.0001
Dose^2 (QD)	< 0.0001	< 0.0001	< 0.0001

Table 204-5. Dose response analysis for SBP (ITT patients)

Parameter	24-hr SBP p-value	Daytime SBP p-value	Nighttime SBP p-value
Dose (QD)	< 0.0001	< 0.0001	< 0.0001
Dose^2 (QD)	< 0.0001	< 0.0001	< 0.0001

Table 204-6. Dose response analysis for DBP (ITT patients)

Parameter	24-hr DBP p-value	Daytime DBP p-value	Nighttime DBP p-value
Dose (BID)	< 0.0001	< 0.0001	< 0.0001
Dose^2 (BID)	< 0.0001	< 0.0001	< 0.0001

Table 204-7. Dose response analysis for SBP (ITT patients)

Parameter	24-hr SBP p-value	Daytime SBP p-value	Nighttime SBP p-value
Dose (BID)	< 0.0001	< 0.0001	< 0.0001
Dose^2 (BID)	< 0.0001	< 0.0001	< 0.0001

Subgroup results on ABPM BPs

No subgroup showed a drastically different trend compared to the overall results (Tables 204-8, 204-9).

Table 204-8. Mean change (Δ) in ABPM 24-hour DBP by subgroups (ITT patients)

Treatment Group	Male Δ, n	Female Δ, n	Non-Black Δ, n	Black Δ, n	<65 yrs Δ, n	65+ yrs Δ, n
Placebo	0.4, 27	1.5, 19	0.8, 41	1.4, 5	1.0, 35	0.6, 11
5 mg QD	-9.7, 28	-6.9, 15	-9.3, 39	-2.7, 4	-7.8, 26	-10.2, 17
20 mg QD	-11.5, 27	-10.8, 14	-11.2, 39	-12.8, 2	-11.4, 33	-10.6, 8
80 mg QD	-10.0, 31	-7.8, 14	-9.9, 41	-3.1, 4	-9.9, 37	-6.4, 8
2.5 mg BID	-6.8, 33	-9.7, 16	-7.9, 43	-6.3, 6	-7.5, 37	-8.3, 12
10 mg BID	-10.6, 27	-9.1, 18	-10.7, 41	-3.2, 4	-10.1, 35	-9.6, 10
40 mg BID	-11.5, 33	-8.8, 15	-10.7, 45	-9.5, 3	-10.1, 29	-11.5, 19

n: sample size

Table 204-9. Mean change (Δ) in ABPM 24-hour SBP by subgroups (ITT patients)

Treatment Group	Male Δ, n	Female Δ, n	Non-Black Δ, n	Black Δ, n	<65 yrs Δ, n	65+ yrs Δ, n
Placebo	0.8, 27	2.0, 19	1.1, 41	2.9, 5	1.5, 35	0.7, 11
5 mg QD	-14.5, 28	-11.9, 15	-14.3, 39	-6.4, 4	-11.8, 26	-16.3, 17
20 mg QD	-16.1, 27	-13.9, 14	-15.2, 39	-17.4, 2	-15.4, 33	-15.1, 8
80 mg QD	-13.4, 31	-13.4, 14	-14.8, 41	0.8, 4	-14.0, 37	-10.4, 8
2.5 mg BID	-9.7, 33	-13.0, 16	-11.2, 43	-7.9, 6	-10.6, 37	-11.4, 12
10 mg BID	-15.3, 27	-13.0, 18	-15.3, 41	-4.9, 4	-14.2, 35	-15.1, 10
40 mg BID	-16.7, 33	-14.3, 15	-16.1, 45	-13.4, 3	-14.1, 29	-18.6, 19

n: sample size

2) Cuff BP and Heart Rate

The reviewer's analyses (given in Table 204-10) based on the database VITALS.SD2 provided by the sponsor give the results similar to, though not identical to, the sponsor's results for the entire ITT patients (i.e., combining Black patients and non-Black patients, Tables 29A, 29B, 29C, 129A, 129B, 129C). The differences are small. The level of statistical significance is the same (i.e., $p < 0.0001$) for all the treatment differences between olmesartan dose and placebo.

Table 204-10. Mean change in cuff measurements (ITT patients)

Treatment Group	N	Mean change ±se in sitting DBP (mm Hg)	Mean change ±se in sitting SBP (mm Hg)	Mean change ±se in sitting HR (bpm)
Placebo	47	-0.7±1.0	-0.1±1.7	-1.0±1.3
5 mg QD	45	-6.5±1.7	-8.3±2.7	-0.1±1.5
20 mg QD	45	-9.7±1.5	-12.8±2.3	1.1±1.3
80 mg QD	46	-11.4±1.6	-12.8±2.7	0.8±1.2
2.5 mg BID	49	-8.2±1.8	-8.9±2.7	0.7±1.2
10 mg BID	48	-10.2±1.2	-14.6±2.0	0.8±1.0
40 mg BID	47	-11.4±1.3	-17.1±2.6	1.4±1.3

1) Baseline value is the average of the day -1 and the day 1 values, if at least one of them is not missing. If one of them is missing, then the non-missing value is taken as the baseline value. The day 1 value is taken to be the first of the two day 1 values in the database VITALS.SD2.
2) Endpoint value is the last available value of weeks 1, 2, 4, or 6 values or early termination value (ET) from the database VITALS.SD2

Dose response on Cuff BPs

The cuff blood pressures showed consistent results on dose response as compared to ABPM blood pressures, as illustrated in Tables 204-11, 204-12. There is a positive dose response

indicating that the greater the daily dose the greater blood pressure decreases are. Highly statistically significant quadratic term (i.e., dose square term) indicates that increases in blood pressure reduction appear to start leveling off at some dose approximately between 46 and 52 mg.

Table 204-11. Dose response analysis for Cuff BPs (ITT patients)

Parameter	SiDBP p-value	SiSBP p-value
Dose (QD)	0.0002	< 0.0001
$Dose^2$ (QD)	0.0019	0.0007

Table 204-12. Dose response analysis for Cuff BPs (ITT patients)

Parameter	SiDBP p-value	SiSBP p-value
Dose (BID)	< 0.0001	< 0.0001
$Dose^2$ (BID)	0.0005	0.0002

Study 866-305

This 54-center, randomized, double-blind, placebo-controlled, parallel-group study was designed to study the efficacy of 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg olmesartan QD, after 8 weeks of treatment, as compared to placebo in patients with essential hypertension. In addition, the study was to assess the long-term safety of olmesartan after one year of treatment, with and without HCTZ.

In order to qualify for randomization, during a 4-week single-blind placebo run-in period, the patients must have their two daily average sitting DBPs >= 100 mm Hg but <= 115 mm Hg, with no more than a 7 mm Hg difference between the daily averages at the Week 3 and Week 4 visits (at least 4 full intervening calendar days between these two visits and at least 80% compliance with the study drug regimen during the run-in period). Qualified patients were randomized in equal allocation and in a double-blind fashion to one of seven treatment groups: 2.5, 5, 10, 20 or 40 mg olmesartan QD, or placebo.

The primary efficacy analysis compared the change from baseline in mean trough sitting DBP at Week 8. Secondary efficacy assessments include the change from baseline at Week 8 in mean sitting DBP and SBP at Weeks 1, 2, 4, and 8 and the proportion of patients achieving a successful response (mean sitting DBP < 90 mm Hg or >= 10 mm Hg decrease from baseline).

ANCOVA with baseline as covariate and treatment and center as main effects, including baseline-by-treatment and treatment-by-

center interaction terms, will be used in the primary efficacy analysis. The step-down procedure used to handle multiple comparisons is one that begins by comparing the highest dose group with placebo. If the one-sided p-value < 0.025 then 40 mg is claimed to be more effective than placebo and the next highest dose is tested against placebo. Otherwise, no further testing is performed and no dose group is claimed to have superior efficacy over placebo. Proceed the procedure in this manner until the first comparison is not significant or until the lowest dose group is tested against placebo. This step-down procedure is certainly valid in the sense that it protects the overall experiment-wise type I error rate at 1-sided 0.025 level. Regression analysis would be used to explore dose response to test whether the slope is greater than zero.

The sample size of 70 patients per group was planned so that the study would have 90% power to detect a 5 mm Hg, assuming a standard deviation of 9 mm Hg. According to the study report, it turned out that at the time the study was closed to additional patient screening, there were enough patients already screened or in the placebo run-in period to allow for an actual randomized cohort of 526 patients as a result of the sustained rapid enrollment rate at many sites.

Disposition of patients

A total of 526 patients were randomized into the study. The number of patients appeared to be evenly distributed among the six treatment groups. Forty-six patients (about 9%) discontinued from the study before Week 8. The most frequent reasons for discontinuation were: patient request (6%), uncontrolled blood pressure (7%), adverse event (2%), investigator judgement (2%), and protocol violation and others (0.6%). Three hundred seventy patients completed 1-year study period.

Efficacy evaluation

Site #07 was excluded from the primary analysis because aneroid manometers rather than mercury manometers were used to determine blood pressure at this site. From the SAS database, the reviewer found that one of the 526 randomized patient did not have baseline sitting DBP. The sponsor explained that this patient inadvertently received randomized active study drug instead of placebo during the placebo run-in period. Moreover, the intent-to-treat (ITT) population should consist of 517 patients but the data sets include only 511 patients with at least one visit regularly scheduled visits at Week 1, 2, 4, or 8. In the response of Feb 5, 2001 to the inquery of this reviewer, the sponsor explained that the missing 6 patients were discontinued from the study before the Week 1 visit and their available blood

pressures were recorded for their early termination visits prior to the Week 1 time point.

The treatment groups appeared to be similar with respect to demographic characteristics and baseline blood pressures.

In the sponsor's analyses, small centers were pooled according to some predetermined algorithm. The ANCOVA models contain treatment by center interactions and treatment by baseline interactions. Inclusion of treatment by baseline interactions makes little sense and inclusion of treatment by center interactions also makes little sense. According to this reviewer's analysis, there was no evidence for treatment by site interaction. In the primary analysis, this reviewer used ANCOVA model that contains treatment, original center and baseline blood pressure. The reviewer's results on sitting DBP, sitting SBP, standing DBP and standing SBP are summarized in Tables 305-1 and 305-2. They are similar to the sponsor's results (sponsor's Tables 7.4.1a and 7.4.1c, Volume 1.170). Clearly, all the olmesartan doses give statistically significant reductions in sitting and standing blood pressures.

Table 305-1. Mean change at Week 8 in diastolic blood pressures (ITT patients)

Treatment Group	N	Mean$ change ±se in SiDBP#, p-value		Mean$ change ±se in StDBP, p-value	
Placebo	88	-5.1±0.9	---	-4.4±0.9	---
2.5mg QD	91	-8.6±0.8	0.0028	-7.0±0.9	0.033
5mg QD	80	-8.6±0.9	0.0042	-7.8±0.9	0.0067
10mg QD	85	-12.0±0.9	<0.0001	-10.3±0.9	<0.0001
20mg BID	85	-11.4±0.9	<0.0001	-9.8±0.9	<0.0001
40mg BID	88	-11.9±0.9	<0.0001	-11.4±0.9	<0.0001

$ Adjusted mean obtained from ANCOVA containing unpooled site, baseline BP
# primary efficacy variable
p-value is nominal p-value comparing active dose with placebo

Table 305-2. Mean change at Week 8 in systolic blood pressures (ITT patients)

Treatment Group	N	Mean$ change ±se in SiSBP, p-value		Mean$ change ±se in StSBP, p-value	
Placebo	88	-4.2±1.4	---	-4.4±1.4	---
2.5mg QD	91	-9.4±1.3	0.0052	-8.6±1.4	0.029
5mg QD	80	-10.6±1.4	0.0010	-9.3±1.5	0.013
10mg QD	85	-13.2±1.4	<0.0001	-14.5±1.4	<0.0001
20mg BID	85	-12.5±1.4	<0.0001	-11.7±0.4	<0.0001
40mg BID	88	-16.2±1.4	<0.0001	-16.2±1.4	<0.0001

$ Adjusted mean obtained from ANCOVA containing unpooled site, baseline BP
p-value is nominal p-value comparing active dose with placebo

Dose response

As illustrated in Table 305-3, there is a positive dose response indicating that the greater the daily dose the greater blood pressure decreases are. Highly statistically significant quadratic term (i.e., dose square term) indicates that increases in blood pressure reduction appear to start leveling off at some dose approximately between 26 and 32 mg.

Table 305-3. Dose response analysis of BPs (ITT patients)

Parameter	SiDBP p-value	SiSBP p-value	StDBP p-value	StSBP p-value
Dose (QD)	<0.0001	<0.0001	<0.0001	<0.0001
$Dose^2$ (QD)	<0.0001	0.0078	0.0019	0.0055

Subgroup results

Subgroup results are given in the tables below. No subgroup showed a drastically different trend compared to the overall results except for the subgroups with very small number of patients.

Table 305-4. Mean change (Δ) in siDBP by subgroups (ITT patients)

Treatment Group	Male Δ, n	Female Δ, n	<65 yrs Δ, n	65+ yrs Δ, n
Placebo	-5.5, 64	-4.5, 24	-3.7, 60	-8.6, 28
2.5 mg QD	-7.6, 47	-10.2, 44	-8.6, 64	-9.4, 27
5 mg QD	-8.8, 48	-9.0, 32	-7.9, 58	-11.6, 22
10 mg QD	-10.6, 51	-15.0, 34	-12.4, 60	-12.5, 25
20 mg QD	-11.0, 49	-12.3, 36	-10.6, 57	-13.3, 28
40 mg QD	-12.7, 56	-11.2, 32	-12.4, 61	-11.4, 27

n: sample size

Table 305-5. Mean change (Δ) in siDBP by race (ITT patients)

Treatment Group	Caucasians Δ, n	Blacks Δ, n	Asians Δ, n	Hispanics Δ, n	Others Δ, n
Placebo	-4.8, 71	-8.2, 7	---, 0	-7.6, 9	-3.0, 1
2.5 mg QD	-9.0, 71	-6.2, 8	-1.0, 1	-10.4, 11	---, 0
5 mg QD	-9.2, 69	-12.6, 6	---, 0	-0.1, 5	---, 0
10 mg QD	-13.0, 60	-7.7, 9	-5.0, 1	-13.3, 14	-9.5, 1
20 mg QD	-12.6, 57	-8.6, 12	-17.3, 1	-10.6, 14	8.5, 1
40 mg QD	-11.9, 62	-13.4, 12	-1.5, 1	-12.9, 13	---, 0

n: sample size

Table 305-6. Mean change (Δ) in siSBP by subgroups (ITT patients)

Treatment Group	Male Δ, n	Female Δ, n	<65 yrs Δ, n	65+ yrs Δ, n
Placebo	-3.6, 64	-5.6, 24	-2.1, 60	-8.6, 28
2.5 mg QD	-10.8, 47	-8.5, 44	-10.4, 64	-8.0, 27
5 mg QD	-10.9, 48	-9.0, 32	-9.2, 58	-12.8, 22
10 mg QD	-12.8, 51	-16.2, 34	-11.8, 60	-19.8, 25
20 mg QD	-13.1, 49	-13.7, 36	-13.3, 57	-13.6, 28
40 mg QD	-17.1, 56	-15.9, 32	-17.1, 61	-15.7, 27

n: sample size

Table 305-7. Mean change (Δ) in siSBP by race (ITT patients)

Treatment Group	Caucasians Δ, n	Blacks Δ, n	Asians Δ, n	Hispanics Δ, n	Others Δ, n
Placebo	-2.8, 71	-12.6, 7	---, 0	-8.7, 9	-0.0, 1
2.5 mg QD	-9.2, 71	-9.3, 8	-6.0, 1	-13.5, 11	---, 0
5 mg QD	-9.7, 69	-18.2, 6	---, 0	-7.4, 5	---, 0
10 mg QD	-14.4, 60	-10.7, 9	-10.0, 1	-15.9, 14	-9.5, 1
20 mg QD	-13.5, 57	-5.3, 12	-11.5, 1	-20.1, 14	-12.0, 1
40 mg QD	-16.5, 62	-19.4, 12	-4.3, 1	-16.0, 13	---, 0

n: sample size

Long-term effect

After Week 8, patients continued on their randomly assigned study drug treatment for an additional 10-month period. The patient whose blood pressure was not sufficiently controlled (average daily siDBP >= 95 mm Hg at any two consecutive office visits, average daily siDBP >= 105 mm Hg at any one office visit) could be given HCTZ 12.5 mg and up to 25 mg. A total of 110 patients (29 placebo, 81 olmesartan) discontinued study drug during the long-term phase (Week 8 through Month 12) for the following reasons: patient request (5 placebo, 25 olmesartan), uncontrolled blood pressure (16 placebo, 22 olmesartan), adverse event (2 placebo, 6 olmesartan), investigator judgment (3 placebo, 7 olmesartan), lost to follow up (2 placebo, 5 olmesartan), noncompliance/lack of cooperation (1 placebo, 13 olmesartan), protocol violation (0 placebo, 1 olmesartan), other (0 placebo, 2 olmesartan).

With or without addition of HCTZ, the blood pressure reduction associated with 10 mg, 20 mg, and 40 mg was greater than that observed for the 2.5 mg and 5 mg doses (see the sponsor's table 7.4.3 of Volume 1.170).

Study 866-306

This 50-center, randomized, double-blind, placebo-controlled, parallel-group, dose-titration study was designed to study the efficacy of olmesartan QD, after 8 weeks of treatment, as compared to placebo in patients with essential hypertension. In addition, the study was to assess the effect of dose titration in patients with blood pressure uncontrolled after 5 mg olmesartan, and the tolerance to long-term treatment (up to 6 months) with olmesartan, alone or in combination with HCTZ.

In order to qualify for randomization, during a 4-week single-blind placebo run-in period, the patients must have their two daily average sitting DBPs >= 100 mm Hg but <= 115 mm Hg, with no more than a 7 mm Hg difference between the daily averages at the Week 3 and Week 4 visits. Qualified patients were randomized in equal allocation and in a double-blind fashion to one of two treatment groups: 5 olmesartan QD, or placebo. After 4 weeks of treatment, patients with a mean sitting DBP >= 90 mmHg were to have dose randomly titrated in double-blind fashion to 5 mg, 10 mg, or 20 mg olmesartan or matching placebo for another 4 weeks. After completion of 8 weeks randomized treatment, patients entered the open-label period and received 20 mg olmesartan for safety assessment.

The primary efficacy was the change from baseline in mean trough sitting DBP at Week 8. Secondary efficacy assessments include the change from baseline at Week 8 in mean sitting DBP and SBP at Weeks 1, 2, 4, 6, and 8.

ANCOVA with baseline as covariate and treatment and center as main effects, including baseline-by-treatment and treatment-by-center interaction terms, will be used in the primary efficacy analysis.

A total sample size of 400 patients (in a randomization ratio of 1:3 for placebo, 5 mg, 10 mg, 20 mg (titrated doses) of olmesartan) was planned so that the study would have more than 99% power to detect a 5 mm Hg difference, assuming a standard deviation of 9 mm Hg.

Disposition of patients

A total of 457 patients were randomized into the study. Fifty patients (about 9%) discontinued from the study before Week 8. The most frequent reasons for discontinuation were: patient request (4%), uncontrolled blood pressure (2%), adverse event (2%), investigator judgment (1%). Four hundred and seven patients completed double-blind phase. Three hundred sixty six patients completed 6-month long term open-label study period.

Efficacy evaluation

The intent-to-treat (ITT) population consists of patients who were randomized, received at least one dose of randomized study medication, and had at least one usable blood pressure observation after baseline. According to the study report, ITT consists of 451 patients. The two treatment groups appeared to be similar with respect to demographic characteristics and baseline blood pressures. However, as explained in this reviewer's inquiry of 2/21/01, there were 454 patients who had baseline and double-blind phase blood pressures (including site 08 in which some of the patients were excluded in the sponsor's analyses).

In what follows, this reviewer reports the results of these 454 patients. As in Study 866-305, in the sponsor's analyses, small centers were pooled according to some predetermined algorithm. The ANCOVA models contain treatment by center interactions and treatment by baseline interactions. Inclusion of treatment by baseline interactions makes little sense and inclusion of treatment by center interactions also makes little sense. According to this reviewer's analysis, there was no evidence for treatment by site interaction. In the primary analysis, this reviewer used ANCOVA model that contains treatment, original center and baseline blood pressure. The reviewer's results on sitting DBP, sitting SBP, standing DBP and standing SBP are summarized in Tables 306-1 and 306-2. They are similar to the sponsor's results (sponsor's Tables 7.4.1a and 7.4.1b). Clearly, olmesartan gives statistically significant reductions in sitting and standing blood pressures.

Table 306-1. Mean change at Week 8 in diastolic blood pressures (all patients with available baseline and DB phase BPs)

Treatment Group	N	Mean change ±se in SiDBP#, p-value		Mean change ±se in StDBP, p-value	
Placebo	115	-7.0±0.9	---	-5.3±0.8	---
Olmesartan	339	-9.9±0.6	0.0017	-8.2±0.6	0.0007

primary efficacy variable
p-value is nominal p-value

Table 306-2. Mean change at Week 8 in systolic blood pressures (all patients with available baseline and DB phase BPs)

Treatment Group	N	Mean change ±se in SiSBP, p-value		Mean change ±se in StSBP, p-value	
Placebo	115	-2.9±1.5	---	-3.9±1.5	---
Olmesartan	339	-10.2±1.0	<0.0001	-9.8±1.0	0.0002

p-value is nominal p-value

Effect of Dose Titration

In the sponsor's exploratory analyses on the patients who were treated with 5 mg olmesartan and had sitting DBP >= 90 mm Hg at Week 4, there appeared to be a monotonic relationship between dose and the amount of blood pressure reduction (adjusted mean Bp reductions were -6.2 mm Hg for 5 mg, -7.9 for 10 mg, -10.0 for 20 mg). A similar pattern was seen in other blood pressures.

Subgroup results

Subgroup results are given in the tables below. No subgroup showed a drastically different trend compared to the overall results except for the subgroups with small number of patients.

Table 306-3. Mean change (Δ) in siDBP by subgroups (all patients with available baseline and DB phase BPs)

Treatment Group	Male Δ, n	Female Δ, n	<65 yrs Δ, n	65+ yrs Δ, n
Placebo	-6.6, 68	-7.1, 47	-6.2, 79	-7.9, 36
Olmesartan	-9.4, 192	-10.5, 147	-9.4, 235	-11.0, 104

n: sample size

Table 306-4. Mean change (Δ) in siDBP by race (all patients with available baseline and DB phase BPs)

Treatment Group	Caucasins Δ, n	Blacks Δ, n	Asians Δ, n	Hispanics Δ, n	Others Δ, n
Placebo	-6.1, 85	-9.2, 14	1.0, 1	-10.2, 13	-1.5, 2
Olmesartan	-10.7, 235	-6.5, 47	-12.5, 6	-9.0, 49	-8.0, 2

n: sample size

Table 306-5. Mean change (Δ) in siSBP by subgroups (all patients with available baseline and DB phase BPs)

Treatment Group	Male Δ, n	Female Δ, n	<65 yrs Δ, n	65+ yrs Δ, n
Placebo	-4.7, 68	-4.9, 47	-4.0, 79	-6.5, 36
Olmesartan	-11.0, 192	-9.0, 147	-10.4, 235	-9.6, 104

n: sample size

Table 306-6. Mean change (Δ) in siSBP by race (all patients with available baseline and DB phase BPs)

Treatment Group	Caucasins Δ, n	Blacks Δ, n	Asians Δ, n	Hispanics Δ, n	Others Δ, n
Placebo	-4.6, 85	-4.8, 14	-10.5, 1	-6.6, 13	-0.3, 2
Olmesartan	-11.2, 235	-4.1, 47	-18.0, 6	-10.0, 49	-1.0, 2

n: sample size

A BRIEF SUMMARY OF SOME OTHER STUDIES ABOUT 2.5 MG DOSE

Two European studies, SE-866/09 and SE-866/11, were also available for assessing the effect of a daily dose of 2.5 mg olmesartan.

Study SE-866/09 was a Phase II, double-blind, randomized, placebo-controlled, dose-finding study. The primary objective of the trial was the determination of the sitting diastolic blood pressure lowering effect of olmesartan at trough level (approximately 24 hours after last administration) at dosages of 2.5, 5, 10, 20, 40, and 80 mg once daily after 12 weeks of treatment in patients with mild and moderate essential hypertension. A total of 792 patients were randomized and allocated in equal proportion to seven treatment groups. Of them, 790 patients are ITT patients according to the sponsor's definition of ITT. The treatment groups were comparable with respect to demographic and baseline characteristics. Table 09-1 presents the results of the reviewer's analyses on all randomized patients using ANCOVA models that contains treatment, original site, and baseline blood pressure. Using the pre-specified simultaneous confidence interval method for multiple comparison adjustment, it is clear that the effect of 2.5 mg dose is not statistically significant. This study shows that the dose >= 10 mg resulted in a statistically significantly greater reduction in blood pressure than placebo. There is a positive dose response indicating that the greater the daily dose the greater blood pressure decreases are (Table 09-2). Highly statistically significant quadratic term (i.e., dose square term) indicates that increases in blood pressure reduction appear to start leveling off at some point approximately between 55 and 62 mg.

Table 09-1. Mean change at Week 12 in sitting blood pressures (all randomized patients)

Treatment Group	N	Mean[$] change ±se in SiDBP[#], p-value		Mean[$] change ±se in SiSBP, p-value	
Placebo	110	-9.2±0.7	---	-8.1±1.2	---
2.5mg QD	117	-10.0±0.7	0.38	-11.8±1.2	0.020
5mg QD	113	-11.0±0.7	0.059	-12.6±1.2	0.0056
10mg QD	116	-12.2±0.7	0.003	-14.5±1.2	<0.0001
20mg QD	112	-12.7±0.7	0.0015	-15.7±1.2	<0.0001
40mg QD	107	-14.4±0.7	<0.0001	-18.5±1.2	<0.0001
80mg QD	117	-14.9±0.7	<0.0001	-18.3±1.2	<0.0001

$ Adjusted mean obtained from ANCOVA containing unpooled site, baseline BP
# primary efficacy variable
p-value is nominal p-value comparing active dose with placebo

Table 09-2. Dose response analysis of sitting BPs (all randomized patients)

Parameter	SiDBP p-value	SiSBP p-value
Dose (QD)	<0.0001	<0.0001
Dose^2 (QD)	0.0019	<0.0001

Study SE-866/11 was a Phase III, randomized, double-blind, placebo-controlled, parallel-group study in patients with mild to moderate hypertension. A total of 292 patients were randomized to either placebo, 2.5 mg, 5 mg or 10 mg olmesartan once daily. The primary objective was the assessment of the efficacy of olmesartan at these doses using diastolic blood pressure evaluated by 24-hour ABPM after 12 weeks of treatment compared to baseline. The treatment groups were comparable with respect to demographic and baseline characteristics. Table 11-1 presents the results of the reviewer's analyses on all randomized patients using ANCOVA models that contains treatment, original site, and baseline blood pressure. Using the pre-specified simultaneous confidence interval method for multiple comparison adjustment, all the doses of olmesartan resulted in a statistically significantly greater reduction in ABPM blood pressure than placebo.

Table 11-1. Mean change at Week 12 in ABPM diastolic blood pressures (ITT patients)

Treatment Group	N	Mean$ change ±se in mean daytime DBP#, p-value		Mean$ change ±se in mean 24-hr DBP, p-value	
Placebo	68	-3.3±1.5	---	-3.0±1.3	---
2.5mg QD	73	-7.0±1.5	0.012	-7.3±1.3	0.0011
5mg QD	71	-7.8±1.5	0.0028	-8.1±1.3	<0.0001
10mg QD	74	-9.7±1.4	<0.0001	-9.9±1.2	<0.0001

$ Adjusted mean obtained from ANCOVA containing unpooled site, baseline BP
# primary efficacy variable
p-value is nominal p-value comparing active dose with placebo

The SAS database also contains cuff BP data. Tables 11-2 and 11-3 summarizes the results of this reviewer's analyses. The 2.5 mg QD dose resulted in a statistically significantly greater reduction in cuff blood pressures as compared to placebo.

Table 11-2. Mean change at Week 12 in cuff diastolic blood pressures (all randomized patients)

Treatment Group	N	Mean$ change ±se in sitting DBP, p-value		Mean$ change ±se in standing DBP, p-value	
Placebo	70	-8.0±1.2	---	-6.4±1.3	---
2.5mg QD	74	-11.0±1.1	0.012	-9.7±1.2	0.0099
5mg QD	72	-13.4±1.2	<0.0001	-11.7±1.3	<0.0001
10mg QD	74	-14.2±1.1	<0.0001	-13.7±1.2	<0.0001

$ Adjusted mean obtained from ANCOVA containing unpooled site, baseline BP
p-value is nominal p-value comparing active dose with placebo

Table 11-3. Mean change at Week 12 in cuff systolic blood pressures (all randomized patients)

Treatment Group	N	Mean$ change ±se in sitting DBP, p-value		Mean$ change ±se in standing DBP, p-value	
Placebo	70	-10.1±2.1	---	-7.7±2.4	---
2.5mg QD	74	-15.6±2.0	0.0099	-14.5±2.3	0.0044
5mg QD	72	-17.8±2.1	0.0004	-14.1±2.4	0.0076
10mg QD	74	-19.5±2.0	<0.0001	-16.4±2.3	0.0003

$ Adjusted mean obtained from ANCOVA containing unpooled site, baseline BP
p-value is nominal p-value comparing active dose with placebo

3. CONCLUSIONS

The three US studies show that olmesartan at a daily dose >= 5 mg resulted in a statistically significantly greater reduction in blood pressures as compared to placebo. Study 866-305 also shows that the 2.5 mg dose resulted in a statistically significantly greater reduction in cuff blood pressure as compared to placebo. Study SE-866/11 shows that 2.5 mg dose also resulted in a statistically significantly greater reduction in ABPM diastolic blood pressure and cuff blood pressures as compared to placebo.

Based on the results of Studies 866-204 and 866-305, there is a positive dose response indicating that the greater the daily dose the greater blood pressure decreases are. Increases in blood pressure reduction appear to start leveling off at some dose in the range of 25 to 52 mg. Study SE-966/09 also showed a positive dose-response and the blood pressure reduction effect seems to level off in the dose range of 55 to 62 mg.

No subgroup showed a drastically different trend compared to the overall results except for the subgroups with small number of patients.

/S/

H.M. James Hung, Ph.D.
Acting Team Leader

This review consists of 18 pages of text.

Concur: Dr. Chi

cc: NDA 21-286
HFD-110/Dr. Lipicky
HFD-110/Dr. Stockbridge
HFD-110/Dr. Targum
HFD-110/Dr. Roden
HFD-110/Dr. Williams
HFD-110/Mr. Fromm
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/chron

JHung/594-5436/DB1/CS-866.doc/03-08-2001