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APPLICATION NUMBER:

21-411

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

Review of Mice Carcinogenicity Studies

NDA#:	**21-411**
APPLICANT:	**Eli Lilly and Company**
NAME OF DRUG:	**Atomoxetine Hydrochloride, LY139603**
INDICATION:	**Attention Deficiency Hyperactivity Disorder**
STUDIES REVIEWED:	**M03583 and M03683, two-year carcinogenicity studies in mice; Data were submitted electronically.**

PHARMACOLOGY REVIEWER: **Ikram Elayan, Ph.D. (HFD-120)**

STATISTICAL REVIEWER: **Mark Rothmann, Ph.D. (HFD-710)**

Sign off list: HFD-710/Ms. Kelly
Pre-clinical Coordinator

HFD-710/Dr. Chi
Division Director, DBI

Distribution: NDA 21-411
HFD-120/Homonnay Weikel
HFD-120/Elayan
HFD-120/Rosloff
HFD-710/Rothmann
HFD-710/Kelly
HFD-710/Jin
HFD-710/Chi
HFD-710/Anello

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Note on Levels of Statistical Significance:

Trends in inter-current mortality were tested at the 0.05 two-sided significance level. Positive linear trends in tumor incidence rates were tested at one-sided significance levels of 0.025 and 0.005 for rare and common tumors, respectively. It is believed that these levels of significance ensure an overall false positive rate of about 10 percent in the two-year two-species two-gender bioassay despite the multiplicity of testing.

1.0 Mice Studies M03583 and M03683

1.1 Introduction

These two-year carcinogenicity studies were conducted in 480 $B6C3F_1$ mice. According to the sponsor, these mice were "randomly distributed to replicate studies." For each study, there were 30 male mice and 30 female mice in each dose group. Mice were maintained for two years at dietary concentration of Atomoxetine of 0%, 0.03%, 0.1%, or 0.3%. These dietary levels provided average (time-weighted) daily doses of 0, 33.6, 120.1, or 436.0 mg/kg body weight for males and of 0, 33.7, 124.1, or 479 mg/kg body weight for females. The mg/kg equivalent doses of these concentrations represent approximately 34, 122 and 458 times the projected maximum dose of 1 mg/kg /day of atomoxetine to humans. The maximum dose of 0.3% is intended to represent the maximum tolerated dose (MTD) according to the selection criteria as defined in the Office of Science and Technology Policy document on chemical carcinogenesis. During these studies, mice were examined daily for general physical condition and behavior. Mice were submitted for necropsy when found dead or in extremis. Body weight and food consumption were determined weekly for the first 13 weeks and every other week for the remainder of the study.

To ensure an adequate number of mice, 264 mice of each sex were ordered from the supplier. Upon arrival, animals were grouped by sex into cages of five to ten animals and acclimated for seven days prior to initiation of treatment. Mice were then housed three per cage in 18 cm x 24 cm x 18 cm ventilated units constructed of stainless steel sheet metal. The mice were given free access to a standard mash diet ([redacted] Rodent Chow [redacted]) and city water was supplied through an automatic watering system.

These studies were conducted between November 1983 and November 1985. These studies were "re-opened" to perform further statistical analyses.

Reviewer's Comments:

1. It is standard to have at least 50 animals per treatment group per gender. Thirty mice per treatment group per gender may not have sufficient power to find real tumor or survival trends between groups.

2. The mean initial body weight and corresponding standard error for male mice in studies M03583 and M03683 were respectively, 17.9 grams and 0.1 grams, and 18.9

grams and 0.1 grams. The mean initial body weight and corresponding standard error for female mice in studies M03583 and M03683 were respectively, 14.9 grams and 0.1 grams, and 15.9 grams and 0.1 grams. For each gender, large sample normal tests for equality of theoretical mean initial body weight leads to p-values less than 0.0001. The sponsor's claim that atomoxetine "... was evaluated in 480 $B6C3F_1$ mice randomly distributed to two replicate studies," is suspect. While an analysis based on the pooled studies (60 mice per treatment group per gender) may have sufficient power to detect real tumor or survival trends between groups, the different initial body weight distributions between these two studies may make an analysis of the pooled data invalid.

3. The numbers 34, 122 and 458 are not in the same proportion as 0.03%, 0.1% and 0.3%.

1.2 Sponsor's Results

Statistical methodologies of Dunnett were used to analyze differences between control and treated groups for body weight and weight gain.

Survival data and tumor incidences were analyzed using Cochran-Armitage linear trend test statistics. All references of statistical significance in the applicant's report reflect p-values less than 0.05.

The sponsor reported no demonstrated increase in mortality. The respective two year survival rates for combined replicates were 73.3%, 76.7%, 85.0 %, and 68.3% for male mice and 75.0%, 71.7%, 85.0%, and 81.7% for female mice on doses of 0%, 0.03%, 0.1%, and 0.3% of atomoxetine. Overall respective two year survival rates for combined replicates were 74.2%, 74.2%, 85.0 %, and 75.0%.

Eleven male mice in the high dose treatment group died during the first six months of treatment. None of these eleven mice had clinically significant signs of toxicity – nine were normal and two had alopecia. Fighting among cage mates may have been associated with four of these deaths. For Study M03683, there was a decreased survival for high dose male mice compared to control male mice. Survival of low and mid dose male mice and all treated female mice seemed unaffected by the exposure to atomoxetine.

Five or more total occurrences appeared for at least one sex in six malignant tumor categories and four benign categories. For each of these tumor/sex combinations, the Cochran-Armitage linear trend test and a survival-adjusted trend test were both performed. The survival-adjusted trend test would adjust for any effect due to the early mortality in high-dose males. Malignant tumors found in animals which died prior to termination were classified as "fatal," while all other tumors were classified as "incidental." Hepatocellular carcinoma, alveolar/bronchiolar carcinoma and hepatocellular adenoma for males and pituary adenoma for females all resulted in two-tailed p-values smaller than 0.005. For these cases, there was a statistically significant dose-related decrease in tumor incidences. The sponsor concludes that the similarity in

results between the Cochran-Armitage test and the survival-adjusted test suggests that early deaths in high-dose males do not account for the reduction in tumors.

There was no increase the incidence of benign or malignant neoplasms among mice.

For mid and high dose males and females, statistically significant dose-related decreases in mean body weight and weight gain occurred. Mean body weight and weight gain of low dose males and females seemed unaffected by exposure to atomoxetine.

1.3 Reviewer's Results

There was no data provided for mouse #2006-A, a male mouse in study M03583 on 0.1% atomoxetine. For study M03683, there was a statistically significant dose-mortality trend (Cox p-value = 0.0283) among male mice. This result seems to be due to those aforementioned eleven early deaths in the highest dose group. For study M03583, there was not a statistically significant dose-mortality trend (Cox p-value = 0.9108) among male mice. For the pooled data, the Cox p-value for testing for a dose-mortality trend was 0.1669. For the female mice, there was no statistically significant dose-mortality trend. This reviewer's analyses confirmed that there were no statistically significant increases in the tumor findings of either gender.

2.0 Validity of Mice Studies

As there were no statistically significant (positive) tumor findings among either the female mice or the male mice, the validity of this study needs to be evaluated. 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?
Haseman[1,2], Chu, Cueto, and Ward[3], and Bart, Chu, and Tarone[4] proposed criteria to answer these questions. The adequacy of the length of exposure will be assessed using the proportions of animals surviving at 53 weeks, 81-91 weeks, and at termination (after 13 weeks, survival measurements were recorded every two weeks). All but two mice (a female mouse at dose 0.01% in study M03583 and a male mouse at dose 0.03% in study M03683) survived beyond 52 weeks. Table 1 below gives a summary of survival at 53 weeks, 81 weeks, 91 weeks and termination by dose x gender x study.

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[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

Table 1. Survival summary at 81 weeks, 91 weeks and termination

	Female mice – study M03583				Female mice – study M03683			
Dose	53 weeks	81 weeks	91 weeks	Termination	53 weeks	81 weeks	91 weeks	Termination
0%	29	28	25	24	29	26	25	21
0.01%	29	25	24	23	30	26	23	20
0.03%	29	29	29	25	28	28	26	26
0.1%	30	29	29	25	29	27	27	24
	Male mice – study M03583				**Male mice – study M03683**			
Dose	53 weeks	81 weeks	91 weeks	Termination	53 weeks	81 weeks	91 weeks	Termination
0%	30	26	23	19	30	30	29	25
0.01%	30	26	24	20	29	27	27	26
0.03%	30	29	29	27	29	28	27	24
0.1%	23	23	21	21	26	24	22	20

The respective two year survival rates for combined replicates were 73.3%, 76.7%, 85.0%, and 68.3% for male mice and 75.0%, 71.7%, 85.0%, and 81.7% for female mice on doses of 0%, 0.03%, 0.1% and 0.3% of atomoxetine. Overall respective two-year survival rates for combined replicates were 74.2%, 74.2%, 85.0 %, and 75.0%. The mice did have a sufficiently long enough exposure to atomoxetine.

Mean weight differences of up to 10% between high dosed versus control animals and slightly increased mortality compared to controls indicate that that dose may be close to the maximum tolerated dose (MTD). As mentioned previously, for only those male mice in study M03683, was there a statistically significant dose-mortality trend.

For the male mice (combining the studies), starting at day 21, the mean body weight was less for the high dose group compared to the control group by 10% (day 21) to 31% (day 350). The mean termination weight was less for the high dose group compared to the control group by 18%.

For study M03583, starting at day 28, the mean body weight was less for the high dose group compared to the control group from 10% (day 28) to 31% (day 329). The mean termination weight was less for the high dose group compared to the control group by 20%.

For study M03683, starting at day 21, the mean body weight was less for the high dose group compared to the control group from 8% (day 56) to 32% (day 343). The mean termination weight was less for the high dose group compared to the control group by 19%.

For female mice (combining the studies), starting at day 35, the mean body weight was less for the high dose group compared to the control group by 12% (day 35) to 37% (day 469). The mean termination weight was less for the high dose group compared to the control group by 32%.

For study M03583, starting at day 49, the mean body weight was less for the high dose group compared to the control group from 13% (days 49 and 63) to 40% (day 525). The mean termination weight was less for the high dose group compared to the control group by 36%.

For study M03683, starting at day 43, the mean body weight was less for the high dose group compared to the control group from 10% (day 49) to 35% (day 343). The mean termination weight was less for the high dose group compared to the control group by 28%.

In summary, there was a long enough exposure to atomoxetine. However, the mice in the high dose group weighed much less during the study and at termination than the mice in the control group, which may indicate that the high dose exceeded the MTD. The overall mortality reached statistical significance only for the male mice in study M03683.

3.0 Summary

These two-year carcinogenicity studies were conducted in 480 $B6C3F_1$ mice. According to the sponsor, these mice were "randomly distributed to replicate studies." For each study, there were 30 male mice and 30 female mice in each dose group. Mice were maintained for two years at dietary concentration of Atomoxetine of 0%, 0.03%, 0.1%, or 0.3%. Replicate studies were analyzed separately and were also combined for analyses. For each gender, large sample normal tests for equality of theoretical mean initial body weight leads to p-values less than 0.0001. The sponsor's claim that atomoxetine "... was evaluated in 480 $B6C3F_1$ mice randomly distributed to two replicate studies," is suspect. Therefore, the pooled results may not be appropriate, and with 30 mice per sex and dose in the individual studies, there may not be sufficient power to detect real tumor or survival trends between groups.

According to the applicant, the mg/kg equivalent doses of these concentrations represent approximately 34, 122 and 458 times the projected maximum dose of 1 mg/kg/day of atomoxetine to humans. The numbers 34, 122 and 458 are not in the same proportion as 0.03%, 0.1% and 0.3%.

Overall survival for both sexes appeared to be unrelated to dose level. However, there were eleven early deaths (before 200 days) in the high-dose male group. None of these eleven mice had clinically significant signs of toxicity – nine were normal and two had alopecia. Fighting among cage mates may have been associated with four of these deaths. For Study M03683, there was decreased survival for high dose male mice compared to control male mice. There was no apparent death pattern among female mice. Survival of low and mid dose male mice and all treated female mice seemed unaffected by the exposure to atomoxetine.

There was no increase in the incidence of benign or malignant neoplasms among mice.

For mid and high dose males and females, statistically significant dose-related decreases in mean body weight and weight gain occurred. Mean body weight and weight gain of low dose males and females seemed unaffected by exposure to atomoxetine.

In summary, there were no increases in benign or malignant neoplasms among either gender, but there were a sufficient number of mice exposed long enough to atomoxetine. The mice in the high dose control group weighed much less during the study and at termination than the mice in the control group, which may indicate that the MTD was exceeded. There was no observed shortened survival for the high dose group, except for the male mice in study M03683.

/S/

Mark Rothmann, Ph.D.
Mathematical Statistician
Date: July 12, 2002

Concur: Ms. Kelly
Pre-clinical Coordinator

Dr. Chi
Division Director, DBI

Cc:

HFD-120/Ms. Homonnay Weikel
HFD-120/Dr. Elayan
HFD-120/Dr. Rosloff
HFD-710/Dr. Rothmann
HFD-710/Ms. Kelly
HFD-710/Dr. Jin
HFD-710/Dr. Chi
HFD-710/Dr. Anello

This review consists of 28 pages of text
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APPENDIX MICE

(First all Tables and Graphs for Males, then all Tables and Graphs for Females)

For all tables and figures DOSE0, DOSE1, DOSE2, and DOSE3, respectively, represent the dietary concentrations of atomoxetine of 0%, 0.03%, 0.1%, and 0.3%. All tables and graphs include all four dose groups.

Combined Studies - Male Mice Only

Number of Animals Dying in each Interval
Trend Tests for Mortality
Kaplan Meier Function Graphs
Trend Tests for Tumor Incidences

Study M03583 - Male Mice Only

Number of Animals Dying in each Interval
Trend Tests for Mortality
Kaplan Meier Function Graphs
Trend Tests for Tumor Incidences

Study M03683 - Male Mice Only

Number of Animals Dying in each Interval
Trend Tests for Mortality
Kaplan Meier Function Graphs
Trend Tests for Tumor Incidences

Combined Studies - Female Mice Only

Number of Animals Dying in each Interval
Trend Tests for Mortality
Kaplan Meier Function Graphs
Trend Tests for Tumor Incidences

Study M03583 - Female Mice Only

Number of Animals Dying in each Interval
Trend Tests for Mortality
Kaplan Meier Function Graphs
Trend Tests for Tumor Incidences

Study M03683 - Female Mice Only

Number of Animals Dying in each Interval
Trend Tests for Mortality
Kaplan Meier Function Graphs
Trend Tests for Tumor Incidences

Number of Animals dying in each Interval
Male Mice – Studies Combined

	Treatment Group				Total
	DOSE1	DOSE2	DOSE3	DOSE4	
	N	N	N	N	N
Week					
0-52	.	1	1	11	13
53-78	4	6	1	2	13
79-91	4	3	1	4	12
92-103	7	4	5	2	18
104-105	45	46	51	41	183
Total	60	60	59	60	239

Dose-Mortality Trend Tests

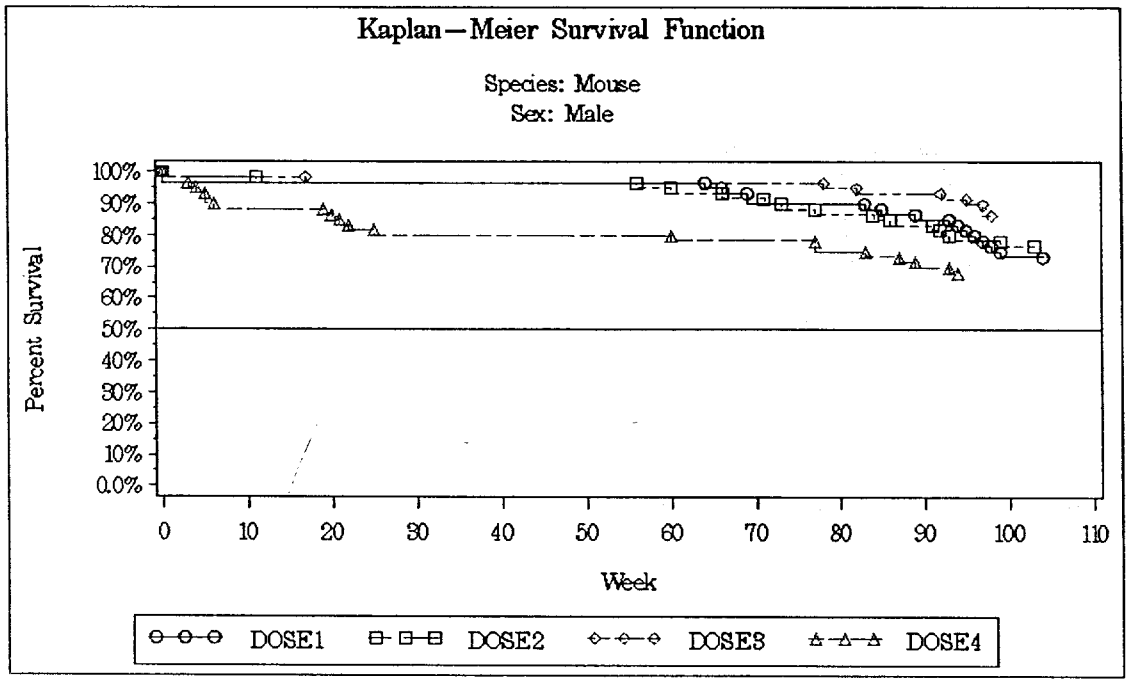
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data, Version 2.1 by Donald G. Thomas, National Cancer Institute

Species: Mouse, Sex: Male -Combined Studies

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.91	0.1669
	Depart from Trend	4.88	0.0871
	Homogeneity	6.79	0.0788
Kruskal-Wallis	Dose-Mortality Trend	2.87	0.0905
	Depart from Trend	5.17	0.0755
	Homogeneity	8.03	0.0453

Kaplan-Meier Survival Graph
Male Mice – Studies Combined

DOSE0: 0%
DOSE1: 0.03%
DOSE2: 0.1%
DOSE3: 0.3%



Test for Dose-Tumor Positive Linear Trend

Male Mice –Combined Studies

Organ Code	Organ Name	Tumor Code	Tumor Name	DOSE 1	DOSE 2	DOSE 3	DOSE 4	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
AC	ACCESSORY OCULAR	876	ADENOMA	2	2	4	2	0.8571	0.7299	2	3%	IN
AC	ACCESSORY OCULAR	902	ADENOCARCINOMA	0	0	1	0	0.8571	0.6758	0	0%	IN
AC	ACCESSORY OCULAR	948	MUCINOUS ADENOCARCINOMA	0	0	0	1	0.3333	0.0982	0	0%	FA
AD	ADRENAL	860	PHEOCHROMOCYTOMA	0	3	0	0	0.9700	0.9815	0	0%	IN
AD	ADRENAL	876	ADENOMA	0	2	0	0	0.8268	0.8570	0	0%	IN
DU	DUODENUM	902	ADENOCARCINOMA	0	0	1	0	0.4946	0.5187	0	0%	FA
EY	EYE	902	ADENOCARCINOMA	0	0	1	1	0.1119	0.0610	0	0%	IN
LI	LIVER	831	HEPATOCELLULAR ADENOMA	5	3	4	0	0.9835	0.9737	5	8%	MX
LI	LIVER	915	CHOLANGIOCARCINOMA	0	2	0	0	0.8162	0.8283	0	0%	IN
LI	LIVER	932	HEMANGIOSARCOMA	1	2	1	0	0.8648	0.8674	1	2%	MX
LI	LIVER	934	HEPATOCELLULAR CARCINOMA	9	10	6	3	0.9688	0.9627	9	15%	MX
LU	LUNG	803	ALVEOLAR/BRONCHIOLAR ADEN	6	5	4	3	0.8118	0.8120	6	10%	IN
LU	LUNG	904	ALVEOLAR/BRONCHIOLAR CARC	6	6	5	0	0.9955	0.9902	6	10%	MX
PA	PANCREAS	833	ISLET CELL ADENOMA	0	2	0	0	0.7522	0.7939	0	0%	IN
PR	PROSTATE	806	PAPILLOMA	1	0	0	0	1.0000	0.8318	1	2%	IN
SK	SKIN	805	HEMANGIOMA	0	1	0	0	0.7541	0.7550	0	0%	IN
SK	SKIN	806	PAPILLOMA	1	2	0	0	0.9406	0.9041	1	2%	IN
SK	SKIN	811	TRICHOEPITHELIOMA	1	0	0	0	1.0000	0.7866	1	2%	IN
SK	SKIN	821	FIBROMA	0	0	0	2	0.0492	0.0070	0	0%	IN
SK	SKIN	924	FIBROSARCOMA	2	0	0	1	0.5445	0.5102	2	3%	FA
SM	SKELETAL MUSCLE	924	FIBROSARCOMA	0	0	0	1	0.3333	0.0887	0	0%	IN
SM	SKELETAL MUSCLE	932	HEMANGIOSARCOMA	0	1	0	0	0.7527	0.7544	0	0%	IN
SM	SKELETAL MUSCLE	967	RHABDOMYOSARCOMA	0	0	1	0	0.5000	0.5270	0	0%	IN
SP	SPLEEN	932	HEMANGIOSARCOMA	1	3	0	0	0.9511	0.9263	1	2%	IN
TS	TESTIS	832	INTERSTITIAL CELL TUMOR	1	0	0	0	1.0000	0.8307	1	2%	IN
UB	URINARY BLADDER	805	HEMANGIOMA	0	1	0	0	0.7500	0.7496	0	0%	IN
UB	URINARY BLADDER	815	TRANSITIONAL CELL PAPILLO	1	0	0	0	1.0000	0.8276	1	2%	IN
WA	WHOLE ANIMAL	939	LYMPHOMA	3	5	1	3	0.5663	0.5792	3	5%	MX
WA	WHOLE ANIMAL	990	HISTIOCYTIC SARCOMA	1	1	2	0	0.7710	0.7931	1	2%	MX

Number of Animals dying in each Interval

Species: Mouse, Sex: Male Study M03583

	Treatment Group				Total
	DOSE1	DOSE2	DOSE3	DOSE4	
	N	N	N	N	N
Week					
0-52	.	.	.	7	7
53-78	4	4	.	.	8
79-91	3	3	.	2	8
92-103	4	3	2	.	9
104-105	19	20	27	21	87
Total	30	30	29	30	119

Dose-Mortality Trend Tests

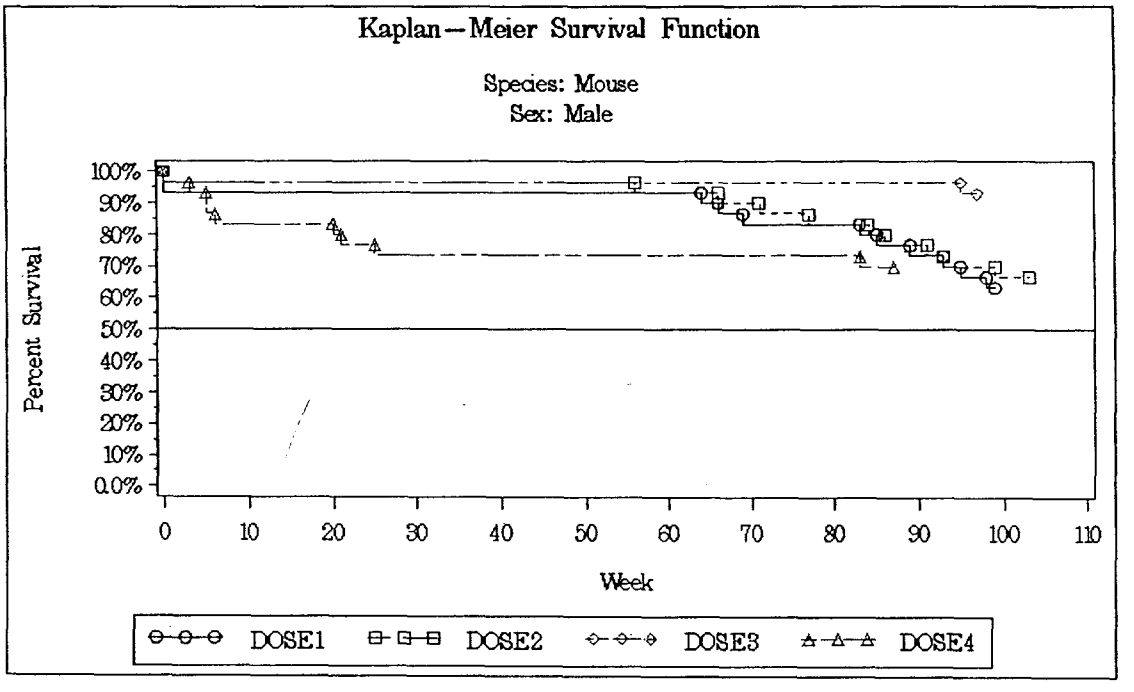
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data, Version 2.1 by Donald G. Thomas, National Cancer Institute

Species: Mouse, Sex: Male Study M03583

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.01	0.9108
	Depart from Trend	7.58	0.0226
	Homogeneity	7.60	0.0551
Kruskal-Wallis	Dose-Mortality Trend	0.05	0.8226
	Depart from Trend	7.91	0.0192
	Homogeneity	7.96	0.0469

Kaplan-Meier Survival Graph
Male Mice – Study M03583

DOSE0: 0%
DOSE1: 0.03%
DOSE2: 0.1%
DOSE3: 0.3%



Test for Dose-Tumor Positive Linear Trend

Source: Male Mouse Data Study M03583

Organ Code	Organ Name	Tumor Code	Tumor Name	DOSE 1	DOSE 2	DOSE 3	DOSE 4	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
AC	ACCESSORY OCULAR	876	ADENOMA	2	2	2	2	N/A	N/A	2	7%	IN
AD	ADRENAL	876	ADENOMA	0	2	0	0	0.8161	0.8370	0	0%	IN
LI	LIVER	831	HEPATOCELLULAR ADENOMA	3	2	2	0	0.9740	0.9593	3	10%	MX
LI	LIVER	915	CHOLANGIOCARCINOMA	0	1	0	0	0.7816	0.7742	0	0%	IN
LI	LIVER	932	HEMANGIOSARCOMA	1	1	1	0	0.8457	0.8379	1	3%	MX
LI	LIVER	934	HEPATOCELLULAR CARCINOMA	2	5	4	0	0.9482	0.9373	2	7%	MX
LU	LUNG	803	ALVEOLAR/BRONCHIOLAR ADEN	4	1	4	1	0.8632	0.8677	4	13%	IN
LU	LUNG	904	ALVEOLAR/BRONCHIOLAR CARC	3	3	2	0	0.9837	0.9711	3	10%	MX
PA	PANCREAS	833	ISLET CELL ADENOMA	0	1	0	0	0.4000	0.5103	0	0%	IN
PR	PROSTATE	806	PAPILLOMA	1	0	0	0	1.0000	0.8443	1	3%	IN
SK	SKIN	806	PAPILLOMA	0	2	0	0	0.8527	0.8507	0	0%	IN
SK	SKIN	811	TRICHOEPITHELIOMA	1	0	0	0	1.0000	0.8330	1	3%	IN
SK	SKIN	821	FIBROMA	0	0	0	1	0.2414	0.0517	0	0%	IN
SK	SKIN	924	FIBROSARCOMA	1	0	0	0	1.0000	0.8231	1	3%	FA
SM	SKELETAL MUSCLE	932	HEMANGIOSARCOMA	0	1	0	0	0.7816	0.7742	0	0%	IN
SM	SKELETAL MUSCLE	967	RHABDOMYOSARCOMA	0	0	1	0	0.5517	0.5538	0	0%	IN
SP	SPLEEN	932	HEMANGIOSARCOMA	1	2	0	0	0.9317	0.8961	1	3%	IN
UB	URINARY BLADDER	805	HEMANGIOMA	0	1	0	0	0.7765	0.7671	0	0%	IN
UB	URINARY BLADDER	815	TRANSITIONAL CELL PAPILLO	1	0	0	0	1.0000	0.8413	1	3%	IN
WA	WHOLE ANIMAL	939	LYMPHOMA	2	3	1	1	0.8204	0.8183	2	7%	MX
WA	WHOLE ANIMAL	990	HISTIOCYTIC SARCOMA	0	1	1	0	0.6648	0.7258	0	0%	IN

Number of Animals dying in each Interval

Species: Mouse, Sex: Male Study M03683

	Treatment Group				Total
	DOSE1	DOSE2	DOSE3	DOSE4	
	N	N	N	N	N
Week					
0-52	.	1	1	4	6
53-78	.	2	1	2	5
79-91	1	.	1	2	4
92-103	3	1	3	2	9
104-105	26	26	24	20	96
Total	30	30	30	30	120

Dose-Mortality Trend Tests

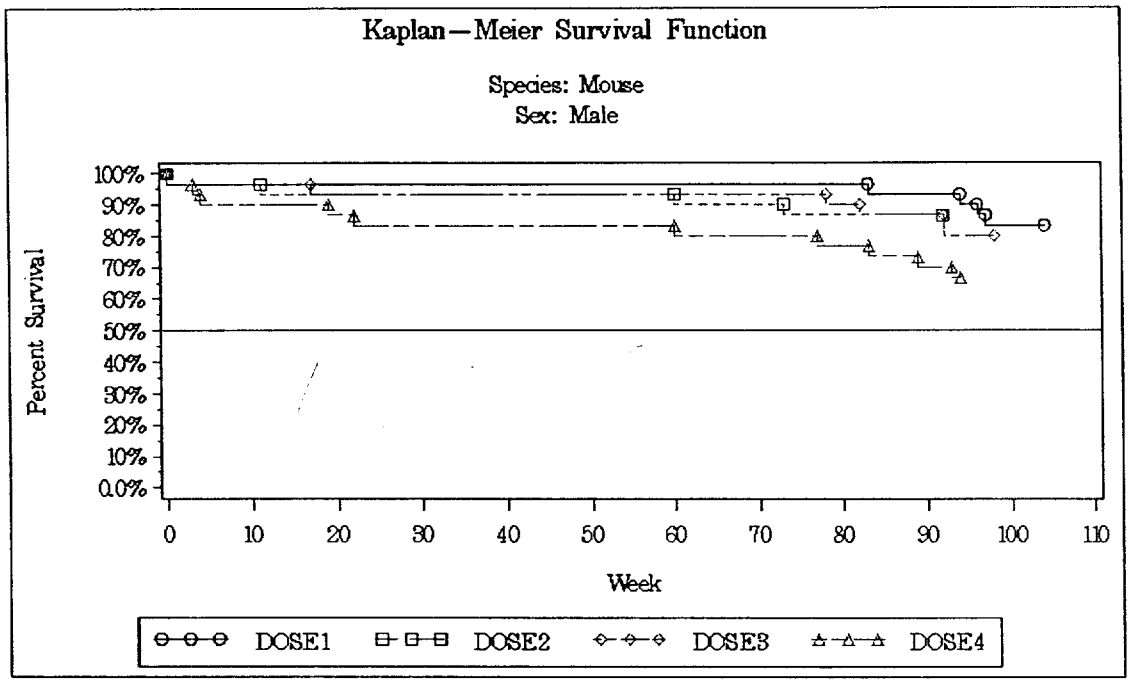
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data, Version 2.1 by Donald G. Thomas, National Cancer Institute

Species: Mouse, Sex: Male Study M03683

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	4.81	0.0283
	Depart from Trend	0.21	0.8998
	Homogeneity	5.02	0.1704
Kruskal-Wallis	Dose-Mortality Trend	5.37	0.0205
	Depart from Trend	0.14	0.9310
	Homogeneity	5.51	0.1381

Kaplan-Meier Survival Graph
Male Mice – Study M03683

DOSE0: 0%
DOSE1: 0.03%
DOSE2: 0.1%
DOSE3: 0.3%



Test for Dose-Tumor Positive Linear Trend

Male Mice - Study M03683

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	DOSE 1	DOSE 2	DOSE 3	DOSE 4	Tumor type	pValue (Exact)	pValue (Asymp)
ACCESSORY OCULAR	AC	ADENOMA	876	.0%	0	0	2	0	IN	N/A	N/A
ACCESSORY OCULAR	AC	ADENOCARCINOMA	902	.0%	0	0	1	0	IN	N/A	N/A
ACCESSORY OCULAR	AC	MUCINOUS ADENOCARCINOMA	948	.0%	0	0	0	1	FA	0.3333	0.0867
ADRENAL	AD	PHEOCHROMOCYTOMA	860	.0%	0	3	0	0	IN	0.9661	0.9665
DUODENUM	DU	ADENOCARCINOMA	902	.0%	0	0	1	0	FA	0.4687	0.5060
EYE	EY	ADENOCARCINOMA	902	.0%	0	0	1	1	IN	0.1667	0.1156
LIVER	LI	HEPATOCELLULAR ADENOMA	831	7%	2	1	2	0	MX	0.8381	0.8495
LIVER	LI	CHOLANGIOCARCINOMA	915	.0%	0	1	0	0	IN	0.7292	0.7375
LIVER	LI	HEMANGIOSARCOMA	932	.0%	0	1	0	0	IN	0.7292	0.7375
LIVER	LI	HEPATOCELLULAR CARCINOMA	934	23%	7	5	2	3	MX	0.8123	0.8129
LUNG	LU	ALVEOLAR/BRONCHIOLAR ADEN	803	7%	2	4	0	2	IN	0.5519	0.5656
LUNG	LU	ALVEOLAR/BRONCHIOLAR CARC	904	10%	3	3	3	0	IN	0.9442	0.9328
PANCREAS	PA	ISLET CELL ADENOMA	833	.0%	0	1	0	0	IN	0.7263	0.7362
SKIN	SK	HEMANGIOMA	805	.0%	0	1	0	0	IN	0.7292	0.7375
SKIN	SK	PAPILLOMA	806	3%	1	0	0	0	IN	1.0000	0.8174
SKIN	SK	FIBROMA	821	.0%	0	0	0	1	IN	0.2083	0.0364
SKIN	SK	FIBROSARCOMA	924	3%	1	0	0	1	FA	0.3967	0.2726
SKELETAL MUSCLE	SM	FIBROSARCOMA	924	.0%	0	0	0	1	IN	0.5000	0.1778
SPLEEN	SP	HEMANGIOSARCOMA	932	.0%	0	1	0	0	IN	0.7292	0.7375
TESTIS	TS	INTERSTITIAL CELL TUMOR	832	3%	1	0	0	0	IN	1.0000	0.8174
WHOLE ANIMAL	WA	LYMPHOMA	939	3%	1	2	0	2	MX	0.2448	0.2326
WHOLE ANIMAL	WA	HISTIOCYTIC SARCOMA	990	3%	1	0	1	0	MX	0.7079	0.7285

Number of Animals dying in each Interval

Species: Mouse, Sex: Female Combined Studies

	Treatment Group				Total
	DOSE1	DOSE2	DOSE3	DOSE4	
	N	N	N	N	N
Week					
0-52	2	1	3	1	7
53-78	3	6	.	2	11
79-91	5	7	2	1	15
92-103	3	2	4	7	16
104-105	47	44	51	49	191
Total	60	60	60	60	240

Dose-Mortality Trend Tests

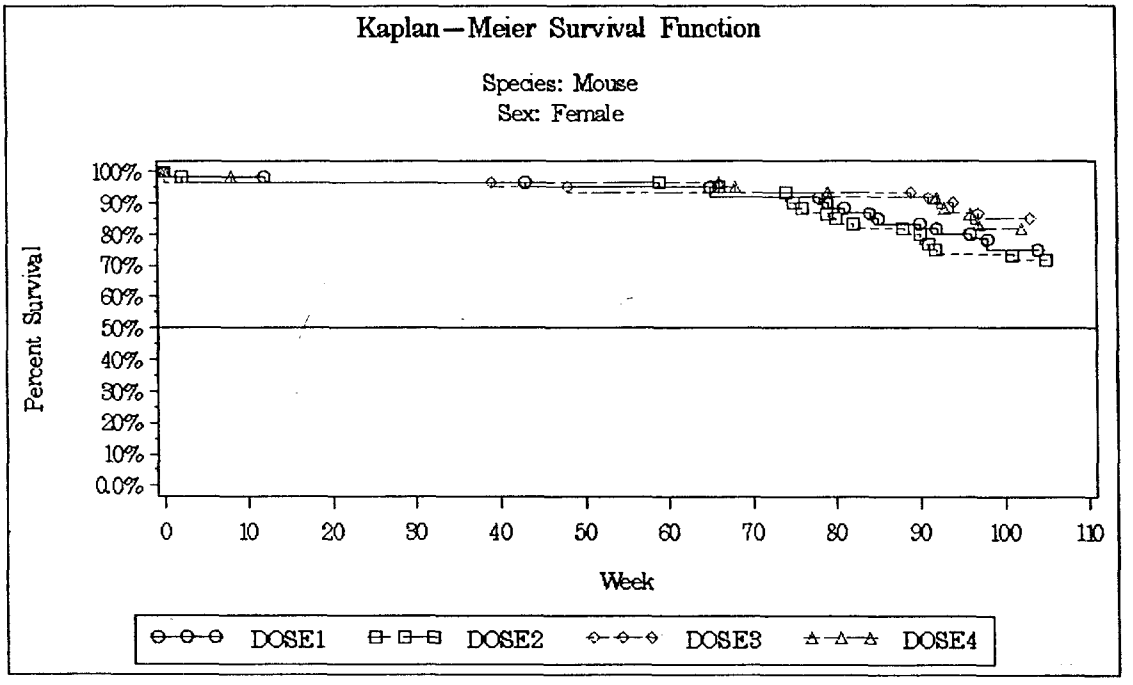
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data, Version 2.1 by Donald G. Thomas, National Cancer Institute

Species: Mouse, Sex: Female Combined Studies

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.32	0.2507
	Depart from Trend	2.25	0.3240
	Homogeneity	3.57	0.3114
Kruskal-Wallis	Dose-Mortality Trend	1.45	0.2278
	Depart from Trend	2.37	0.3062
	Homogeneity	3.82	0.2813

Kaplan-Meier Survival Graph
Female Mice – Studies Combined

DOSE0: 0%
DOSE1: 0.03%
DOSE2: 0.1%
DOSE3: 0.3%



Test for Dose-Tumor Positive Linear Trend
Female Mice – Combined Studies

Organ Code	Organ Name	Tumor Code	Tumor Name	DOSE 1	DOSE 2	DOSE 3	DOSE 4	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
AC	ACCESSORY OCULAR	876	ADENOMA	2	5	0	2	0.3333	0.2182	2	3%	IN
AC	ACCESSORY OCULAR	912	CARCINOMA, UNDIFFERENTIAT	1	0	0	0	1.0000	0.7446	1	2%	FA
AD	ADRENAL	860	PHEOCHROMOCYTOMA	1	2	0	1	0.7980	0.7873	1	2%	IN
AD	ADRENAL	924	FIBROSARCOMA	1	0	0	0	1.0000	0.7600	1	2%	IN
BO	BONE	856	OSTEOMA	0	0	0	1	0.4375	0.1458	0	.0%	IN
BO	BONE	989	OSTEOSARCOMA	1	1	0	1	0.5536	0.5232	1	2%	FA
DI	DIAPHRAGM	924	FIBROSARCOMA	1	0	0	0	N/A	N/A	1	2%	IN
LI	LIVER	831	HEPATOCELLULAR ADENOMA	1	1	1	0	0.8455	0.8470	1	2%	IN
LI	LIVER	932	HEMANGIOSARCOMA	1	0	0	0	1.0000	0.7595	1	2%	IN
LI	LIVER	934	HEPATOCELLULAR CARCINOMA	0	0	1	1	0.2025	0.1465	0	.0%	IN
LU	LUNG	803	ALVEOLAR/BRONCHIOLAR ADEN	2	3	0	1	0.8409	0.8372	2	3%	IN
LU	LUNG	904	ALVEOLAR/BRONCHIOLAR CARC	2	2	0	0	0.9832	0.9516	2	3%	MX
LU	LUNG	924	FIBROSARCOMA	1	0	0	0	1.0000	0.7574	1	2%	IN
ME	MESENTERY	924	FIBROSARCOMA	0	0	1	0	0.2593	0.2000	0	.0%	IN
MG	MAMMARY GLAND	902	ADENOCARCINOMA	0	1	0	1	0.3315	0.2710	0	.0%	MX
OV	OVARY	817	CYSTADENOMA	1	0	0	0	1.0000	0.8364	1	2%	IN
OV	OVARY	827	GRANULOSA-THECA TUMOR, BE	0	0	1	0	0.5185	0.5497	0	.0%	IN
OV	OVARY	858	PAPILLARY CYSTADENOMA	0	1	0	0	0.7513	0.7652	0	.0%	IN
OV	OVARY	924	FIBROSARCOMA	1	0	1	0	0.5667	0.6675	1	2%	IN
OV	OVARY	961	PAPILLARY CYSTADENOCARCIN	0	0	1	0	0.5185	0.5497	0	.0%	IN
PA	PANCREAS	817	CYSTADENOMA	0	1	0	0	0.7606	0.7711	0	.0%	IN
PA	PANCREAS	924	FIBROSARCOMA	1	0	0	0	1.0000	0.7715	1	2%	IN
PI	PITUITARY	876	ADENOMA	5	1	1	1	0.9233	0.9154	5	8%	IN
PY	PYLORUS	876	ADENOMA	1	0	1	0	N/A	N/A	1	2%	IN
SG	SALIVARY GLAND	902	ADENOCARCINOMA	0	1	0	0	0.6667	0.6182	0	.0%	IN
SK	SKIN	805	HEMANGIOMA	1	0	0	0	1.0000	0.8374	1	2%	IN
SK	SKIN	821	FIBROMA	0	1	0	0	0.7526	0.7669	0	.0%	IN
SK	SKIN	834	KERATOACANTHOMA	0	1	0	0	0.7526	0.7669	0	.0%	IN
SK	SKIN	924	FIBROSARCOMA	2	2	1	0	0.9514	0.9356	2	3%	MX
SK	SKIN	932	HEMANGIOSARCOMA	0	0	0	1	0.2663	0.0622	0	.0%	FA
SM	SKELETAL MUSCLE	924	FIBROSARCOMA	1	0	1	0	0.7743	0.7773	1	2%	IN
SM	SKELETAL MUSCLE	932	HEMANGIOSARCOMA	2	0	0	1	0.6186	0.5483	2	3%	IN
SM	SKELETAL MUSCLE	967	RHABDOMYOSARCOMA	2	0	0	0	1.0000	0.9143	2	3%	IN
SP	SPLEEN	932	HEMANGIOSARCOMA	2	0	0	1	0.7215	0.6667	2	3%	MX
TH	THYROID	823	FOLLICULAR CELL ADENOMA	0	0	0	1	0.2429	0.0520	0	.0%	IN

UB	URINARY BLADDER	815	TRANSITIONAL CELL PAPILLO	1	0	0	0	1.0000	0.8435	1	2%	IN
UT	UTERUS	805	HEMANGIOMA	0	1	0	0	0.7539	0.7673	0	0%	IN
UT	UTERUS	835	LEIOMYOMA	0	0	1	0	0.5236	0.5529	0	0%	IN
UT	UTERUS	921	ENDOMETRIAL STROMAL SARCO	1	0	0	0	1.0000	0.8379	1	2%	IN
WA	WHOLE ANIMAL	939	LYMPHOMA	7	7	8	10	0.2339	0.2333	7	12%	MX
WA	WHOLE ANIMAL	990	HISTIOCYTIC SARCOMA	3	4	3	1	0.9110	0.9044	3	5%	FA

Number of Animals dying in each Interval

Species: Mouse, Sex: Female Study M03583

	Treatment Group				Total
	DOSE1	DOSE2	DOSE3	DOSE4	
	N	N	N	N	N
Week					
0-52	1	1	1	.	3
53-78	1	2	.	1	4
79-91	3	3	.	.	6
92-103	1	.	4	4	9
104-105	24	24	25	25	98
Total	30	30	30	30	120

Dose-Mortality Trend Tests

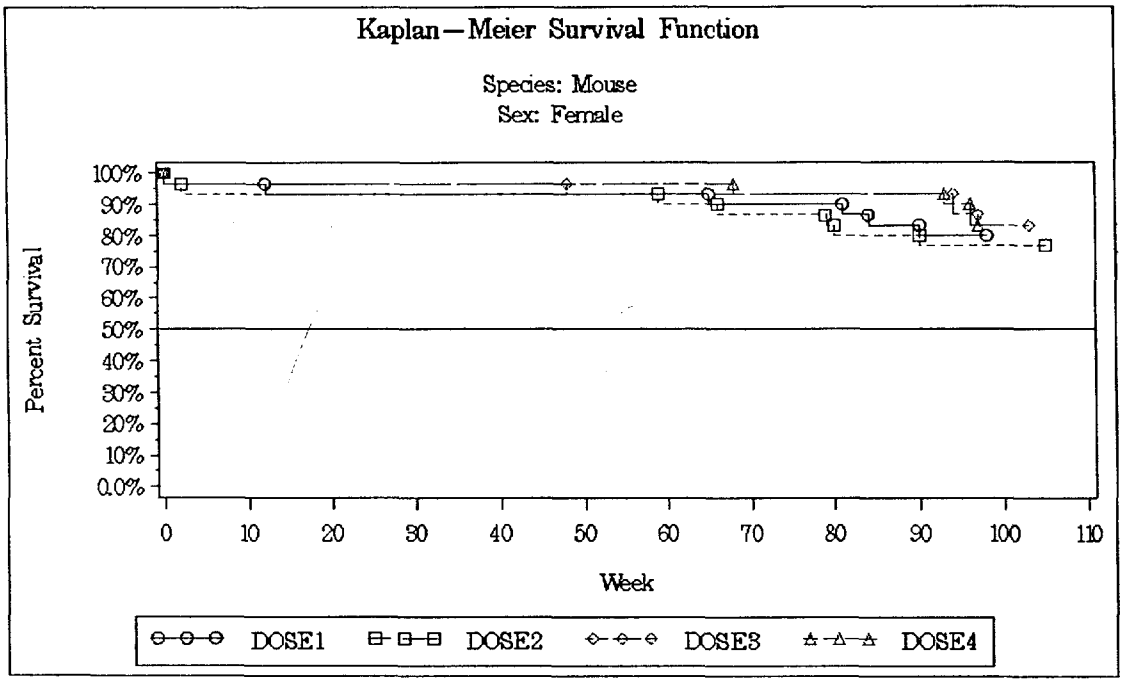
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data, Version 2.1 by Donald G. Thomas, National Cancer Institute

Species: Mouse, Sex: Female Study M03583

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.23	0.6328
	Depart from Trend	0.16	0.9210
	Homogeneity	0.39	0.9417
Kruskal-Wallis	Dose-Mortality Trend	0.32	0.5712
	Depart from Trend	0.25	0.8807
	Homogeneity	0.57	0.9022

Kaplan-Meier Survival Graph
Female Mice – Study M03583

DOSE0: 0%
DOSE1: 0.03%
DOSE2: 0.1%
DOSE3: 0.3%



Test for Dose-Tumor Positive Linear Trend

Female Mice Study M03583

Organ Code	Organ Name	Tumor Code	Tumor Name	DOSE 1	DOSE 2	DOSE 3	DOSE 4	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
AC	ACCESSORY OCULAR	876	ADENOMA	2	2	0	0	N/A	N/A	2	7%	IN
AD	ADRENAL	860	PHEOCHROMOCYTOMA	0	1	0	1	0.3208	0.2599	0	0%	IN
BO	BONE	989	OSTEOSARCOMA	0	1	0	0	0.7568	0.7685	0	0%	FA
LI	LIVER	831	HEPATOCELLULAR ADENOMA	1	1	1	0	0.8409	0.8438	1	3%	IN
LU	LUNG	803	ALVEOLAR/BRONCHIOLAR ADEN	0	1	0	0	0.7551	0.7640	0	0%	IN
LU	LUNG	904	ALVEOLAR/BRONCHIOLAR CARC	2	1	0	0	0.9867	0.9342	2	7%	IN
ME	MESENTERY	924	FIBROSARCOMA	0	0	1	0	0.3333	0.2745	0	0%	IN
MG	MAMMARY GLAND	902	ADENOCARCINOMA	0	1	0	1	0.3279	0.2702	0	0%	MX
OV	OVARY	827	GRANULOSA-THECA TUMOR, BE	0	0	1	0	0.5052	0.5425	0	0%	IN
OV	OVARY	858	PAPILLARY CYSTADENOMA	0	1	0	0	0.7526	0.7607	0	0%	IN
OV	OVARY	924	FIBROSARCOMA	0	0	1	0	0.5052	0.5425	0	0%	IN
OV	OVARY	961	PAPILLARY CYSTADENOCARCIN	0	0	1	0	0.5052	0.5425	0	0%	IN
PI	PITUITARY	876	ADENOMA	5	0	1	1	0.8856	0.8869	5	17%	IN
PY	PYLORUS	876	ADENOMA	1	0	1	0	N/A	N/A	1	3%	IN
SG	SALIVARY GLAND	902	ADENOCARCINOMA	0	1	0	0	0.5000	0.2525	0	0%	IN
SK	SKIN	805	HEMANGIOMA	1	0	0	0	1.0000	0.8352	1	3%	IN
SK	SKIN	924	FIBROSARCOMA	1	1	1	0	0.8381	0.8435	1	3%	MX
SK	SKIN	932	HEMANGIOSARCOMA	0	0	0	1	0.2692	0.0635	0	0%	FA
SM	SKELETAL MUSCLE	924	FIBROSARCOMA	0	0	1	0	0.5102	0.5488	0	0%	IN
SM	SKELETAL MUSCLE	932	HEMANGIOSARCOMA	0	0	0	1	0.4444	0.1504	0	0%	IN
SM	SKELETAL MUSCLE	967	RHABDOMYOSARCOMA	2	0	0	0	1.0000	0.9124	2	7%	IN
SP	SPLEEN	932	HEMANGIOSARCOMA	0	0	0	1	0.5000	0.1783	0	0%	IN
TH	THYROID	823	FOLLICULAR CELL ADENOMA	0	0	0	1	0.2184	0.0413	0	0%	IN
UB	URINARY BLADDER	815	TRANSITIONAL CELL PAPILLO	1	0	0	0	1.0000	0.8399	1	3%	IN
WA	WHOLE ANIMAL	939	LYMPHOMA	3	4	5	4	0.4412	0.4446	3	10%	MX
WA	WHOLE ANIMAL	990	HISTIOCYTIC SARCOMA	1	0	2	1	0.3932	0.4085	1	3%	FA

Number of Animals dying in each Interval

Species: Mouse, Sex: Female Study M03683

	Treatment Group				Total
	DOSE1	DOSE2	DOSE3	DOSE4	
	N	N	N	N	N
Week					
0-52	1	.	2	1	4
53-78	2	4	.	1	7
79-91	2	4	2	1	9
92-103	2	2	.	3	7
104-105	23	20	26	24	93
Total	30	30	30	30	120

Dose-Mortality Trend Tests

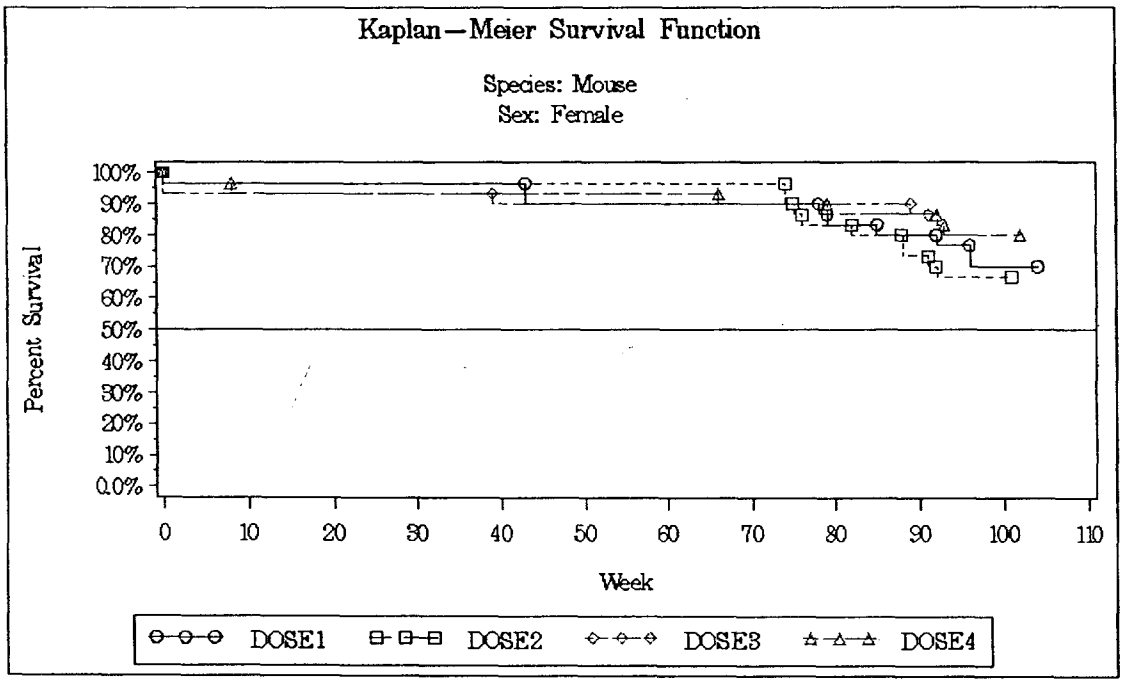
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data, Version 2.1 by Donald G. Thomas, National Cancer Institute

Species: Mouse, Sex: Female Study M03683

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.19	0.2762
	Depart from Trend	2.67	0.2625
	Homogeneity	3.86	0.2769
Kruskal-Wallis	Dose-Mortality Trend	1.12	0.2909
	Depart from Trend	2.44	0.2947
	Homogeneity	3.56	0.3132

Kaplan-Meier Survival Graph
Female Mice – Study M03583

DOSE0: 0%
DOSE1: 0.03%
DOSE2: 0.1%
DOSE3: 0.3%



Test for Dose-Tumor Positive Linear Trend

Female Mice – Study M03683

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	DOSE 1	DOSE 2	DOSE 3	DOSE 4	Tumor type	pValue (Exact)	pValue (Asymp)
ACCESSORY OCULAR	AC	ADENOMA	876	0%	0	3	0	2	IN	0.3333	0.2182
ACCESSORY OCULAR	AC	CARCINOMA, UNDIFFERENTIAT	912	3%	1	0	0	0	FA	1.0000	0.7715
ADRENAL	AD	PHEOCHROMOCYTOMA	860	3%	1	1	0	0	IN	0.9524	0.9138
ADRENAL	AD	FIBROSARCOMA	924	3%	1	0	0	0	IN	1.0000	0.7456
BONE	BO	OSTEOMA	856	0%	0	0	0	1	IN	0.4286	0.1323
BONE	BO	OSTEOSARCOMA	989	3%	1	0	0	1	FA	0.4599	0.3384
DIAPHRAGM	DI	FIBROSARCOMA	924	3%	1	0	0	0	IN	N/A	N/A
LIVER	LI	HEMANGIOSARCOMA	932	3%	1	0	0	0	IN	1.0000	0.7975
LIVER	LI	HEPATOCELLULAR CARCINOMA	934	0%	0	0	1	1	IN	0.2104	0.1491
LUNG	LU	ALVEOLAR/BRONCHIOLAR ADEN	803	7%	2	2	0	1	IN	0.7864	0.7873
LUNG	LU	ALVEOLAR/BRONCHIOLAR CARC	904	0%	0	1	0	0	FA	0.7579	0.7725
LUNG	LU	FIBROSARCOMA	924	3%	1	0	0	0	IN	1.0000	0.7446
OVARY	OV	CYSTADENOMA	817	3%	1	0	0	0	IN	1.0000	0.8398
OVARY	OV	FIBROSARCOMA	924	3%	1	0	0	0	IN	1.0000	0.9615
PANCREAS	PA	CYSTADENOMA	817	0%	0	1	0	0	IN	0.7582	0.7756
PANCREAS	PA	FIBROSARCOMA	924	3%	1	0	0	0	IN	1.0000	0.7446
PITUITARY	PI	ADENOMA	876	0%	0	1	0	0	IN	0.7416	0.7647
SKIN	SK	FIBROMA	821	0%	0	1	0	0	IN	0.7500	0.7700
SKIN	SK	KERATOACANTHOMA	834	0%	0	1	0	0	IN	0.7500	0.7700
SKIN	SK	FIBROSARCOMA	924	3%	1	1	0	0	FA	0.9354	0.8782
SKELETAL MUSCLE	SM	FIBROSARCOMA	924	3%	1	0	0	0	IN	1.0000	0.8408
SKELETAL MUSCLE	SM	HEMANGIOSARCOMA	932	7%	2	0	0	0	IN	1.0000	0.8969
SPLEEN	SP	HEMANGIOSARCOMA	932	7%	2	0	0	0	FA	1.0000	0.9142
UTERUS	UT	HEMANGIOMA	805	0%	0	1	0	0	IN	0.7527	0.7708
UTERUS	UT	LEIOMYOMA	835	0%	0	0	1	0	IN	0.5376	0.5571
UTERUS	UT	ENDOMETRIAL STROMAL SARCO	921	3%	1	0	0	0	IN	1.0000	0.8408
WHOLE ANIMAL	WA	LYMPHOMA	939	13%	4	3	3	6	MX	0.1921	0.1868
WHOLE ANIMAL	WA	HISTIOCYTIC SARCOMA	990	7%	2	4	1	0	FA	0.9771	0.9635

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/s/

Mark Rothmann
7/12/02 04:57:59 PM
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Roswitha Kelly
7/15/02 02:36:28 PM
BIOMETRICS

George Chi
7/16/02 08:54:11 AM
BIOMETRICS

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

STATISTICAL REVIEW AND EVALUATION

Medical Division: Division of Neuropharm Drug Products (HFD-120)
Biometrics Division: Division of Biometrics I (HFD-710)

STATISTICAL KEY WORDS:	Repeated Measurement, LOCF
NDA NUMBER:	21-411
SERIAL NUMBER:	0
DATE RECEIVED BY CENTER:	10/11/01
DRUG NAME:	Atomoxetine Hydrochloride
INDICATION:	ADHD
SPONSOR:	Lilly
DOCUMENTS REVIEWED:	NDA submission
STATISTICAL REVIEWER:	Ning Li (HFD-710)
STATISTICAL TEAM LEADER:	Kun Jin (HFD-710)
BIOMETRICS DIVISION DIRECTOR:	George Chi (HFD-710)
CLINICAL REVIEWER:	Roberta Glass (HFD-120)
PROJECT MANAGER:	Anna Marie Homonnay (HFD-120)

Distribution: NDA 21-411
HFD-120/Anna Marie Homonnay
HFD-120/Roberta Glass
HFD-120/Tom Laughren
HFD-120/Russell Katz
HFD-710/Ning Li
HFD-710/Kun Jin
HFD-710/George Chi
HFD-700/Chuck Annello

File Directory: C:/DATA/NDA/ADHD/NDA21411.doc

I. Background

In this NDA submission, Atomoxetine hydrochloride (Atomoxetine) is being studied as a treatment for Attention-Deficit/Hyperactivity Disorder (ADHD) in children, adolescents, and adults. Atomoxetine [benzenepropanamine, N-methyl-© -(2-methylphenoxy), hydrochloride, (-)] is a potent inhibitor of the presynaptic norepinephrine transporter with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. The sponsor submitted 7 (seven) double blinded controlled studies and 4 (four) open label studies to support the claim on Attention-Deficit/Hyperactivity Disorder (ADHD):

Study HFBD was a randomized, acute, double-blind, placebo-controlled study conducted in 147 enrolled children at 7 study sites in the United States. The primary comparison was between atomoxetine (titrated up to 2.0 mg/kg/day, administered in equally divided doses in the early morning and late afternoon/early evening) and placebo. A small methylphenidate treatment group (titrated up to 1.5 mg/kg/day, administered in the early morning and at noon) was included primarily to validate the study design. Doses were titrated based on clinical responses.

Study HFBK was a randomized, acute, double-blind placebo-controlled study conducted in 144 enrolled children at 10 study sites in the United States. The primary comparison was between atomoxetine (titrated up to 2.0 mg/kg/day, administered in equally divided doses in the early morning and late afternoon/early evening) and placebo. A small methylphenidate treatment group (titrated up to 1.5 mg/kg/day, administered in the early morning and at noon) was included primarily to validate the study design. Doses were titrated based on clinical responses. The study design for Study HFBK was identical to Study HFBD.

Study LYAC is a randomized, acute and long-term, double-blind, placebo-controlled study being conducted in 297 enrolled children and adolescents at 13 study sites in the United States. The 2 primary comparisons are between an intermediate dose (1.2 mg/kg/day) of atomoxetine and placebo, and between a high dose (1.8 mg/kg/day) of atomoxetine and placebo during an approximately 8-week acute treatment period. Atomoxetine is administered in equally divided doses in the early morning and late afternoon/early evening. A report of the analyses of the acute phase of the study was completed 5 June 2001, while the long-term phase of the study is ongoing.

Study LYAT was a randomized, double-blind, placebo-controlled study conducted with 171 enrolled children and adolescents at 9 study sites in the United States. The primary comparison was between atomoxetine administered as a single daily dose in the morning compared with placebo. The initial single-daily dose was determined by patients' weights (minimum dose of 0.5 mg/kg/day); subsequent doses were not to exceed 100 mg/day (1.5 mg/kg/day). Doses were titrated based on clinical responses.

Study LYAA was a randomized, double-blind, placebo-controlled study conducted in 280 enrolled adults at 14 study sites in the United States and 3 in Canada. The primary comparison was between atomoxetine, at total daily doses of 60 mg to 120 mg for up to 10 weeks, and placebo. Atomoxetine was administered in equally divided doses in the early morning and late afternoon/early evening. Doses were titrated based on clinical responses.

Study HFBE was a randomized, double-blind, placebo-controlled, variable discontinuation study conducted in 228 enrolled children and adolescents at 23 study sites in the United States. After a 10-week, open label, active therapy-controlled period where patients were randomized to either atomoxetine or methylphenidate; atomoxetine responders were then randomly and variably discontinued from atomoxetine (switched to placebo) using double-blind methodology. The primary comparison was between the time to relapse for atomoxetine-treated ADHD responders randomized to continue treatment with atomoxetine versus the time to relapse for those randomized to placebo.

Study HFBC was an acute, open-label, dose-titration study conducted in 30 enrolled children and adolescents at 1 study site in the United States. This study was completed early in the ADHD clinical development program and the primary objective was to evaluate the safety, effectiveness, and pharmacokinetics of atomoxetine in child and adolescent patients who met DSM-IV criteria for ADHD.

Study HFBF is a long-term, open-label, dose-titration, ongoing study being conducted in 325 enrolled children and adolescents at 22 study sites in the United States. This study included patients who had previously been enrolled in other atomoxetine studies (mainly Study HFBD, Study HFBE, and Study HFBK) and then "rolled over" into Study HFBF to examine the long-term safety of treatment with atomoxetine. The primary assessments were of the safety and tolerability of atomoxetine. Secondary assessments were of the efficacy of atomoxetine for ADHD.

Study LYAB is an acute and long-term, open-label, dose-titration, ongoing study conducted in 914 enrolled children and adolescents at 52 study sites in the United States, 1 in Puerto Rico, and 4 in Canada. Patients and investigators are blind to Cytochrome P450 2 D6 (CYP2D6) metabolic status. The primary assessments are of the safety and tolerability of atomoxetine. Secondary assessments are of the efficacy of atomoxetine for ADHD, and comparison of the safety, tolerability and efficacy of atomoxetine in CYP2D6 extensive metabolizer (EM) and poor metabolizer (PM) patients.

Study LYBB is an acute, open-label, dose-titration, ongoing study conducted in 357 enrolled children and adolescents at 39 study sites in the United States and 1 in Puerto Rico. Patients and investigators are blind to CYP2D6 metabolizer status. The primary assessments are of the safety and tolerability of atomoxetine. Secondary assessments are of the efficacy of atomoxetine for ADHD, and comparison of the safety, tolerability and efficacy of atomoxetine in CYP2D6 EM patients and PM patients.

In this review, we are going to focus on the first 7 controlled trials.

II. Study HFBD

This pediatric ADHD study was conducted between November 19, 1998 to February 17, 2000. The protocol was amended three times and approved during study. No statistical related changes were made during the study.

II.1 Study Design

Study HFBD was a Phase 2 stratified, randomized, double-blind, parallel, outpatient study of 147 pediatric outpatients, aged 7 through 12 years, who met diagnostic criteria for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) Attention-Deficit/Hyperactivity Disorder (ADHD). Prior to randomization at Visit 3, patients were stratified into 2 groups that were determined by their prior exposure to psychostimulants. The first stratum included patients who had no prior history of treatment with psychostimulants (stimulant-naïve stratum). Patients in stimulant-naïve stratum were randomized to double-blind treatment with tomoxetine, placebo, or methylphenidate hydrochloride (randomization ratio: 3:3:2). The second stratum included children who had been treated at any time with a psychostimulant (stimulant-prior-exposure stratum). Children in this second stratum were randomized to double-blind treatment with tomoxetine or placebo (randomization ratio 1:1). There was no methylphenidate treatment arm in the stimulant- prior-exposure stratum.

II.2 Objectives

The primary objective of this study was to evaluate the efficacy of tomoxetine compared with placebo in the combined strata of pediatric patients who met DSM-IV criteria for attention-deficit/hyperactivity disorder (ADHD). Efficacy was determined by a comparison of mean change from baseline to endpoint using an intent-to-treat analysis of the primary outcome measure, the investigator administered and scored Attention-Deficit/ Hyperactivity Disorder Rating Scale-IV-Parent Version (ADHDRS-IV-Parent:Inv) total score, for tomoxetine- and placebo-treated patients.

II.3 Efficacy Variables

The primary efficacy measure for this study was ADHDRS-IV-Parent: Inv score (Attention-Deficit/Hyperactivity. This scale was administered at every visit. The ADHDRS-IV-Parent:Inv is an 18-item scale with 1 item for each of the 18 symptoms contained in the DSM-IV diagnosis of ADHD. Each item is scored on a 0 to 3 scale (0 = never or rarely; 1 = sometimes; 2 = often; 3 = very often;). The rating scale was used to assess the symptom for each week. The scale was administered and scored by qualified personnel at the investigative site. The total score was computed as the sum of the scores on each of the 18 items.

The total score was considered the primary efficacy measure, while the subscale scores were considered secondary measures.

II.4 Sample Size

Total of 199 patients entered the study. 147 of these 199 patients were stratified and randomized into the study. The sample size for the study was to provide approximately 80% power for the

primary analysis of detecting a pairwise treatment difference of 8.0 points in mean ADHDRS-IV-Parent:Inv total score between tomoxetine and placebo. This assumed a standard deviation of 14.0, using a 2-sided, 0.05 level test, with approximately 5% of enrolled patients having no postbaseline measurement.

II.5 Population and Statistical Analysis

The primary analysis was based on ITT population that was defined as all randomized patients who took at least one post baseline measurement. The primary efficacy measure was the ADHDRS-IV-Parent:Inv total score. This scale was administered at every visit. The primary analysis of the primary measure was an analysis of variance (ANOVA) on change from baseline to Study Period II endpoint scores for tomoxetine and placebo patients in the combined strata. Change was computed using a last observation carried forward approach and the ANOVA model contained terms for treatment, stimulant-prior-exposure stratum, and investigational site. All patients who were randomized to tomoxetine or placebo and who had a baseline and at least 1 postbaseline measurement were included in the analysis. Secondary analyses using the primary efficacy variable included an analysis of T-scores, analysis of percentage of responders, subgroup analyses including analyses by investigational site, analyses of changes over time using repeated measures mixed models, analyses within stimulant-exposure stratum (ANOVA model with terms for treatment and investigational site), and changes in scores during Study Period III.

For efficacy analyses, all investigational sites with fewer than 10 patients who qualified for the primary efficacy analysis were pooled and considered as a single site. If the 'pooled site' still had fewer than 10 patients, then this group was pooled with the site with the next smallest number of patients in the analysis. All statistical tests were performed using a 2-sided, .05 significance level.

II.6 Sponsor's Results and Statistical Reviewer's Findings/Comments

II.6.1. Patient Deposition

A total of 147 patients were randomized into this study (n=65, 20, and 65 for tomoxetine, Methyl, and placebo respectively). In the patient disposition summary, the percentages of patients who completed the study were similar across treatment arms. Total of 72.8% of the randomized patient completed the period II study.

The demographics and patient characteristics are compatible between treatment groups. 81.0% were boys; 83.0% were Caucasian; 52.4% had no prior stimulant exposure; and 91.8% were in the 2nd to 6th elementary school grades (US). The mean age was 9.7 years (range of 7.0 to 12.9), and the mean IQ was 106.0 (range 71 to 144).

The most common comorbid diagnoses (confirmed by clinical assessment) were oppositional defiant disorder (ODD) (38.1%), phobias (12.2%), elimination disorders (10.2%), major depressive disorder (MDD) (4.8%), dysthymia (4.1%), and conduct disorder (2.7%). All other comorbid diagnoses were found in less than 2% of the patients.

No statistically significant differences were seen in patient characteristics at baseline between tomoxetine and placebo in the combined strata.

II.6.2. Primary Endpoint

The primary efficacy variable was the ADHDRS-IV-Parent:Inv total score. The total score is the sum of the scores for each of the 18 items, with higher scores indicating greater severity of ADHD symptoms. Table II. 6.2.1 summarized the primary efficacy analysis results for the study.

Table II.6.2.1 ADHDRS-IV-Parent:Inv Total Score Change from Baseline to Endpoint – Study Period II

		Baseline		Endpoint		Change		p-value vs. placebo
Treatment	n	Mean	SD	Mean	SD	Mean	SD	
Combined:								
TMX	64	41.2	8.9	25.6	14.6	-15.6	13.7	0.0001
Placebo	61	41.4	7.9	35.9	13.3	-5.5	11.6	
Stimulant-Naïve stratum								
TMX	30	39.4	9. 0	24.3	13.9	-15.1	11.8	0. 0015
Placebo	27	39.6	8. 3	35.4	12.6	-4.2	10.8	
Prior-Exposure stratum								
TMX	34	42.8	8. 7	26.9	15.3	-16.0	15.3	0. 0091
Placebo	34	42.9	7. 4	36.3	14.1	-6.6	12.3	

Reviewer Comment:

1. In Table II.6.2.1, the between treatment group p-values are from pairwise tests of treatment differences in mean change from baseline to endpoint scores versus placebo using least squares means from an ANOVA model with terms for investigator and treatment (in each strata) or terms for investigator, treatment and strata (combined group).
2. The missing values are handled using LOCF method.
3. In addition to the analysis in Table II.6.2.1, the sponsor also performed some analysis on the primary endpoint as secondary efficacy analysis, these analysis includes an analysis of T-scores (representing transformation of the ADHDRS total scores to allow for interpretation relative to normative data), analysis of percentage of responders, subgroup analyses including analyses by investigational site, analyses of changes over time using repeated measures mixed models and changes in scores during Study Period III. All of these analysis shows consistent results in favor of the tomoxetine treatment arm.
4. There was an internal audit that the sponsor conducted and found that one site (site #21) for study HFBD had incorrect dates and omissions in the case report forms. There was also a

lack of complete verification of the physician notes by the monitor for the site. This reviewer performed an analysis by taking out of the patients from the site. The difference in the total score change between TMX and placebo is –6.30, favoring the TMX arm. The resulting p-value for comparing TMX vs. placebo is 0.013.

5. To verify the validity of the LOCF, a OC analysis was performed. The p-values for the primary comparison (TMX vs. placebo) is 0.0013, which is consistent with the LOCF analysis.
6. In summary of the primary efficacy analyses, the primary and secondary analyses of the primary measure, an analysis of variance (ANOVA) on change from baseline to Study Period II endpoint scores for tomoxetine and placebo patients in the combined strata and other pre-specified secondary analysis was statistically significant. The results support the efficacy claim for this study population.

II.6.3. Secondary Endpoints

One of the major secondary endpoints that the sponsor mentioned in the proposed labeling is the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S). The CGI-ADHD-Severity (CGI-ADHD-S) is a single-item clinician rating of the clinician's assessment of the severity of the ADHD symptoms in relation to the clinician's total experience with ADHD patients. Severity was rated on a 7-point scale (1 = normal, not at all ill; 7 = among the most extremely ill patients). The sponsor's result for the combined-strata LOCF Study Period II endpoint and change from baseline to endpoint scores is summarized in Table II6.3.1.

Table II 6.3.1. CGI-ADHD-Severity and CGI-ADHD-Severity:Evening Summary of Endpoint and Change Values –Study Period II – Combined Strata B4Z-MC-HFBD

	Endpoint Scores - All Enrolled Patients							Endpoint	Change	
Measure	1	2	3	4	5	6	7	Mean(SD)	Mean (SD)	p-Value
CGI-ADHD-Severity										
Tomoxetine	4	8	19	12	16	2	3	3.7 (1.5)	-1.2 (1.4)	.0032
Placebo	0	5	7	19	23	5	2	4.4 (1.2)	-0.5 (1.0)	
CGI-ADHD-Severity:Evening										
Tomoxetine	3	9	17	15	14	3	3	3.8 (1.4)	-1.2 (1.4)	.0028
Placebo	0	5	7	20	20	7	2	4.4 (1.2)	-0.5 (1.1)	

Reviewer Comment:

1. In Table II.6.3.1, the p-values are from least square mean comparisons of change scores using an ANOVA model with terms for therapy, pooled investigator, and strata.

2. The missing values are handled using LOCF method for this analysis.
3. The results showed that for the two measures: CGI-ADHD-Severity and CGI-ADHD-Severity:Evening scores, there are statistically significantly different between the Tomoxetine and placebo groups with p-values of 0.0032 , 0.0028 respectively. In favor of the Tomoxetine treatment.
4. The Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S) was collected only for patients who were in school for the duration of the study, who had 2 or fewer classroom teachers, and for whom a classroom teacher was available to complete the questionnaire. A total of 28 questionnaires were collected on 24 patients. No patients were able to provide valid baseline and postbaseline data. Due to the small amount of CTRS-R:S data collected, statistical analyses were not performed.
5. Other secondary endpoints that are not mentioned in the labeling are not reviewed at this time.

II.7 Sponsor's Conclusion and Reviewer's Conclusion/Comments

The protocol-specified primary analysis was a treatment comparison of mean change from baseline to endpoint ADHDRS-IV-Parent:Inv total scores between tomoxetine and placebo in the combined strata using an ANOVA model. Both sponsor's and this reviewer's analysis demonstrated statistically significantly greater reduction in severity of ADHD symptoms for tomoxetine-treated patients as compared with placebo-treated patients (mean changes: tomoxetine –15.6, placebo –5.5; p=.0001, Table II.6.2.1).

III. Study HFBK

This pediatric ADHD study was conducted between Feb. 17, 1999 to Oct. 21, 1999. The protocol was amended once and approved on February 28, 2000. The change in the amendment included a justification of the use of the high dose (1.8 mg/kg/day, instead of 1.9 mg/kg/day), testing for treatment differences using a very small significance level at the interim, adding safety assessment, modify exclusion criterion, correcting the typographical error in the event schedule, etc.

III.1 Study Design

Similar to Study HFBD, Study HFBK was a Phase 2 stratified, randomized, double-blind, parallel, outpatient study of 144 pediatric outpatients, aged 7 through 12 years, who met diagnostic criteria for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) Attention-Deficit/Hyperactivity Disorder (ADHD). Prior to randomization at Visit 3, patients were stratified into 2 groups that were determined by their prior exposure to psychostimulants. The first stratum included patients who had no prior history of treatment with psychostimulants (stimulant-naïve stratum). Patients in stimulant-naïve stratum were randomized to double-blind treatment with tomoxetine, placebo, or methylphenidate hydrochloride (randomization ratio: 3:3:2). The second stratum included children who had been treated at any time with a psychostimulant (stimulant-prior-exposure stratum). Children in this second stratum

were randomized to double-blind treatment with tomoxetine or placebo (randomization ratio 1:1). There was no methylphenidate treatment arm in the stimulant- prior-exposure stratum.

III.2 Objectives

The primary objective of this study was to evaluate the efficacy of tomoxetine compared with placebo in the combined strata of pediatric patients who met DSM-IV criteria for attention-deficit/hyperactivity disorder (ADHD). Efficacy was determined by a comparison of mean change from baseline to endpoint using an intent-to-treat analysis of the primary outcome measure, the investigator administered and scored Attention-Deficit/ Hyperactivity Disorder Rating Scale-IV-Parent Version (ADHDRS-IV-Parent:Inv) total score, for tomoxetine- and placebo-treated patients.

III.3 Efficacy Variables

The primary efficacy measure for this study was ADHDRS-IV-Parent: Inv score (Attention-Deficit/Hyperactivity. This scale was administered at every visit. The ADHDRS-IV-Parent:Inv is an 18-item scale with 1 item for each of the 18 symptoms contained in the DSM-IV diagnosis of ADHD. Each item is scored on a 0 to 3 scale (0 = never or rarely; 1 = sometimes; 2 = often; 3 = very often;). The rating scale was used to assess the symptom for each week. The scale was administered and scored by qualified personnel at the investigative site. The total score was computed as the sum of the scores on each of the 18 items.

The total score was considered the primary efficacy measure, while the subscale scores were considered secondary measures.

III.4 Sample Size

Total of 144 patients entered the study and were stratified and randomized into the study. 74 prior stimulant exposure patients and 70 stimulant naïve patients were stratified. The sample size for the study was to provide approximately 80% power for the primary analysis of detecting a pairwise treatment difference of 8.0 points in mean ADHDRS-IV-Parent:Inv total score between tomoxetine and placebo. This assumed a standard deviation of 14.0, using a 2-sided, 0.05 level test, with approximately 5% of enrolled patients having no postbaseline measurement.

III.5 Population and Statistical Analysis

The primary analysis was based on ITT population that was defined as all randomized patients who took at least one post baseline measurement. The primary efficacy measure was the ADHDRS-IV-Parent:Inv total score. This scale was administered at every visit. The primary analysis of the primary measure was an analysis of variance (ANOVA) on change from baseline to Study Period II endpoint scores for tomoxetine and placebo patients in the combined strata. Change was computed using a last observation carried forward approach and the ANOVA model contained terms for treatment, stimulant-prior-exposure stratum, and investigational site. All patients who were randomized to tomoxetine or placebo and who had a baseline and at least 1 postbaseline measurement were included in the analysis. Secondary analyses using the primary

efficacy variable included an analysis of T-scores, analysis of percentage of responders, subgroup analyses including analyses by investigational site, analyses of changes over time using repeated measures mixed models, analyses within stimulant-exposure stratum (ANOVA model with terms for treatment and investigational site), and changes in scores during Study Period III.

For efficacy analyses, all investigational sites with fewer than 10 patients who qualified for the primary efficacy analysis were pooled and considered as a single site. If the 'pooled site' still had fewer than 10 patients, then this group was pooled with the site with the next smallest number of patients in the analysis. All statistical tests were performed using a 2-sided, .05 significance level.

III.6 Sponsor's Results and Statistical Reviewer's Findings/Comments

III.6.1. Patient Deposition

A total of 144 patients were randomized into this study (n=64, 18, and 62 for tomoxetine, Methyl, and placebo respectively). In the patient disposition summary, the percentages of patients who completed the study were similar across treatment arms. Total of 78.5% of the randomized patient completed the period II study.

The demographics and patient characteristics are compatible between treatment groups (trt vs. placebo). 80.0% vs. 80.6% were boys; 76.6% vs. 87.1% were Caucasian; 48.6% had no prior stimulant exposure; and total of 91.0% were in the 2nd to 6th elementary school grades (US). The mean age was 9.8 vs. 9.9 years (range of 7.0 to 12.8), and the median IQ was 100.0 vs. 105(range 81 to 148).

In the combined strata, the tomoxetine treatment group had statistically significantly lower mean Wechsler Intelligence Scale for Children-3 rd Editiov-Revised (WISC-III-R) total score (tomoxetine 101.4, placebo 107.7, p = .018) and Wide Range Achievement Test 3 arithmetic standard scores (tomoxetine 91.0, placebo 97.5, p = .007) than the placebo treatment group. No other statistically significant differences were seen in patient characteristics at baseline between tomoxetine and placebo.

III.6.2. Primary Endpoint

The primary efficacy variable was the ADHDRS-IV-Parent:Inv total score. The total score is the sum of the scores for each of the 18 items, with higher scores indicating greater severity of ADHD symptoms.

The analysis of the primary efficacy variable, the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) total score, included all randomized patients who had a baseline and at least 1 postbaseline measurement. Of the 144 randomized patients, 140 met the criteria to be included in the primary efficacy analysis. Four patients were enrolled, but did not have postbaseline efficacy measurements. According to the protocol analysis plans, these patients were excluded from the

primary efficacy analysis. All of the patients in the primary efficacy analysis took at least 1 dose of study medication.

Table III. 6.2.1 summarized the primary efficacy analysis results for the study.

Table III.6.2.1 ADHDRS-IV-Parent:Inv Total Score Change from Baseline to Endpoint – Study Period II-Study HFBK

Treatment	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-value vs. placebo
Combined:								
TMX	63	37.8	7.9	23.3	14.3	-14.4	13.0	0.0005
Placebo	60	37.6	8.0	31.7	14.4	-5.9	13.0	
Stimulant-Naïve stratum								
TMX	25	36.6	7.4	18.6	14.9	-18.0	13.2	0.094
Placebo	24	35.9	7.0	26.8	14.0	-9.1	11.7	
Prior-Exposure stratum								
TMX	38	38.6	8.2	26.5	13.1	-12.1	12.4	0.0059
Placebo	36	38.7	8.5	35.0	13.9	-3.7	13.5	

Reviewer Comment:

1. In Table 1, the between treatment group p-values are from pairwise tests of treatment differences in mean change from baseline to endpoint scores versus placebo using least squares means from an ANOVA model with terms for investigator and treatment (in each strata) or terms for investigator, treatment and strata (combined group).
2. The missing values are handled using LOCF method. In the combined strata for the protocol-specified primary analysis, tomoxetine treatment resulted in a statistically significantly greater mean reduction in ADHDRS-IV-Parent:Inv total score than placebo. The mean changes for the tomoxetine and placebo treatment groups were -14.4 and –5.9 (p = .0005, the sponsor's p-value reported in the NDA study report is 0.0003.)
3. In addition to the analysis in Table 1, the sponsor also performed some analysis on the primary endpoint as secondary efficacy analysis, these analysis includes an analysis of T-scores (representing transformation of the ADHDRS total scores to allow for interpretation relative to normative data), analysis of percentage of responders, subgroup analyses including analyses by investigational site, analyses of changes over time using repeated measures mixed models and changes in scores during Study Period III. All of these analysis shows consistent results in favor of the tomoxetine treatment arm.
4. There was no statistically significant difference between the treatment arm and the placebo arm for the stimulant naïve stratum (p=0.094) although the score reduction is in favor of the tomoxetine arm.

5. In summary of the primary efficacy analyses, the primary and secondary analyses of the primary measure, an analysis of variance (ANOVA) on change from baseline to Study Period II endpoint scores for tomoxetine and placebo patients in the combined strata and other pre-specified secondary analysis was statistically significant. The results support the efficacy claim for this study population as a whole.

III.6 Sponsor's Conclusion and Reviewer's Conclusion/Comments

The protocol-specified primary analysis was a treatment comparison of mean change from baseline to endpoint ADHDRS-IV-Parent:Inv total scores between tomoxetine and placebo in the combined strata using an ANOVA model. Both sponsor's and this reviewer's analysis demonstrated statistically significantly greater reduction in severity of ADHD symptoms for tomoxetine-treated patients as compared with placebo-treated patients (mean changes: tomoxetine –14.4, placebo –5.9; p=.0005, Table III.6.2.1). However, in a subgroup analysis, there was no statistically significant difference between the treatment arm and the placebo arm for the stimulant naïve stratum (p=0.094) although the score reduction is in favor of the tomoxetine arm.

IV. Study LYAC

This pediatric ADHD study was conducted between April 24, 2000 to December 22, 2000. The protocol was amended once and approved on February 28, 2000. The change in the amendment included a justification of the use of the high dose (1.8 mg/kg/day, instead of 1.9 mg/kg/day), testing for treatment differences using a very small significance level at the interim, adding safety assessment, modify exclusion criterion, correcting the typographical error in the event schedule, etc.

IV.1 Study design

Patients aged 8 to 18 years old who met the entry criteria and passed the screening period were randomized to four dose groups : low-dose (0.5 mg/kg/day), intermediate-dose (1.2 mg/kg/day), high-dose (1.8 mg/kg/day) and placebo in a 1:2:2:2 ratio. Patient randomization was stratified by CYP2D6 status and for EMs patients, by patients' prior history of stimulant treatment. Due to the low number of PMs patients, no further stratification of prior stimulant treatment was performed for the PMs patients. To ensure unbiased evaluation, metabolizer status was remain blinded to both parents and investigators. Five study periods were included in this study :

- Study Period I (10-28 days): including visits 1 to 3. It was a washout, screening and assessment period. At the end of visit 3, patients who were eligible to be enrolled will be randomized to treatments.
- Study Period II (8-week): including visits 4 to 9. It was an acute treatment period. Patients received study drug BID before and after school.
- Study Period III (4-week): including visits 10 to 13. It was an assessment period for non-responder. Patients who did not meet the response criteria at visit 9 entered this period and

received tomoxetine dose adjustment. Placebo patients were switched to receive tomoxetine.

- Study Period IV (40-week): including visits 14 to 24. It was a double-blind, long-term responder extension period. Patients who met the response criteria either at visit 9 or at visit 13 will enter this period. All patients received tomoxetine BID before and after school.
- Study Period V (4 to 28 days): including visits 25 and 26. It was a discontinuation period. Patients who completed study period IV and all patients who were non-responders at visit 13 entered this period during which patients were randomized to either tomoxetine tapered or abruptly discontinued groups.

IV.2 Objectives

The primary objective of this study was to test the hypothesis that an 8-week acute treatment at low (0.5 mg/kg/day), median (1.2 mg/kg/day) and high dose (1.8 mg/kg/day) was statistically significantly more effective in reducing the severity of ADHD symptoms, as compared with placebo.

IV.3 Efficacy Variables

The primary efficacy measure for this study was ADHDRS-IV-Parent: Inv score (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV Parent Version: Investigator Administered and Scored) which was measured at every visits. The ADHDRS-IV-Parent: Inv is an 18-item scale with one item corresponding to each symptom contained in the DSM-IV diagnosis of ADHD. Each item was scored on a 0 to 3 scale where higher score indicated more severe symptom. . Half of these items are inattention subscales and half of them are hyperactivity-impulsivity subscale. Total score was the sum of the 18 items and was considered as the primary efficacy measure.

The primary endpoint was the change in the primary efficacy measure from baseline (last measurement taken on or before visit 3) to endpoint (the last measurement taken from visit 4 to 9). There were two primary efficacy comparisons:

- Between the mid-dose tomoxetine and placebo,
- Between the high-dose tomoxetine and placebo.

The secondary efficacy endpoints included inattention and hyperactivity-impulsivity subscales of ADHDRS-IV-Parent: Inv scale and the following measures :

1. Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S) : A 7-point, single-item clinician assessment of the severity of the ADHD symptoms;
2. Clinical Global Impressions-Anxiety-Severity (CGI-A-S) and Clinical Global Impressions-Depression-Severity (CGI-D-S) scales : Similar to CGI-ADHD scales;

3. Children's Depression Rating Scale-Revised (CDRS-R): This scale was modeled after the Hamilton Depression Rating Scale (HAMD) for adults. This is a clinician-rated instrument measure of severity of depression. The scale consists of 17 items scored from 1 to 5 or 1 to 7;
4. Clinical Global Impressions-efficacy Index (CGI-EI) : This scale combines a therapeutic effect rating and a side effect rating (both scored from 1 to 4);
5. Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) This is a 27-item rating scale completed by parents. The Oppositional, Cognitive problems and ADHD index subscale scores were computed from CPRS-R:S.

IV.4 Sample Size

Dunnett's test was used to adjust for the significance level for these two primary comparisons. Approximately 259 patients were enrolled in this study. This sample size provided 86% power for the two primary comparisons, assuming treatment difference of 7 in mean change from baseline of ADHDRS-IV-Parent:Inv total score, a 13.5 standard deviation, a two-sided 0.05 test level and 5% of patients would not have the post-baseline information.

IV.5 Population and Statistical Analysis

The primary analysis was based on ITT population that was defined as all enrolled patients who took at least one dose of study medication at phase II and who had both a baseline and at least one post baseline ADHDRS-IV-Parent:Inv measure. The treatment difference in mean change from baseline score was evaluated based on analysis of covariance model (ANCOVA). The ANCOVA model contained treatment group, investigational site, CYP2D6 metabolism status and the baseline ADHDRS-IV-parent:Inv total score. Treatment comparison was based on least square means. In the protocol, a site-pooling scheme was proposed based on whether the site has more than 1 ITT patient in each treatment group or not. If the site/combined sites had no more than 1 ITT patient in each treatment group, the sites would be combined. But in the report, since all 13 sites had at least 1 randomized patient per treatment, no pooling sites was performed.

In the analysis, if more than 1 item was missing in a subscale, the subscale (or the total) score was considered as missing. For a single missing item, the mean score was used to impute the missing item and then to compute the subscale or total scores. Last observation carried forward approach was used for the primary analysis. All tests were based on 2-sided 0.05 significance level. The primary efficacy analysis used adjusted p-values from Dunnett's test to preserve the overall type I error rate of 0.05. All secondary statistical tests used a 2-sided (unadjusted) 0.05 significance level.

Subgroup analysis was performed based on various subgroups : metabolic status, investigational site, prior stimulant use strata, ADHD subtype, gender, age, comorbidity groups.

One interim analysis was planned for this protocol. This would occur after approximately 150 patients completed the study period II. The interim analysis result was not to terminate the study for declaring the efficacy of tomoxetine. But in the protocol, it stated that the study may be terminated for reasons of safety and lack of efficacy. The sponsor proposed 0.0001 level to

adjust for the significance level. Again, 0.05 level was used for the final analysis since the study did stop to declare efficacy. In addition to one interim analysis, periodical data monitoring for safety reason was performed under the auspices of the Data Monitoring Board assigned to this study.

IV.6 Sponsor's Results and Statistical Reviewer's Findings/Comments

A total of 297 patients were randomized into this study (n=84, 44, 84 and 85 for placebo, tomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day and 1.8 mg/kg/day, respectively). In the patient disposition summary, the percentages of patients who completed the study were similar across treatment arms (85.7%, 77.3%, 82.1% and 85.9% for placebo, tomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day and 1.8 mg/kg/day, respectively). The most common reason for discontinuation was personal conflict or other patient decision (5.7%, overall).

The demographics and patient characteristics are compatible between treatment groups. Over 70% of these patients were boys. The majority of the patients were Caucasian (75%, overall). The mean age was approximately 11 years old. The majority of patients were extended CYP2D6 metabolizers (approximately 94%, overall). The majority of patients were mixed subtype (67%, overall); the next were inattentive subtype (31%, overall) and then hyperactivity/impulsivity subtype (1.7% overall). Approximately 23 or 24% patients had family history of ADHD in father or sibling. Over 70% patients had prior stimulant exposure. There were about 76% patients, overall, in grades 3 to 7. The overall mean age at onset of ADHD symptoms was 4.58 years old.

The most common present comorbid diagnosis (based on K-SADS-PL) was oppositional defiant disorder (ODD) found in 38% of randomized patients. All other diagnoses were seen in less than 2% of the randomized population.

Of the 253 patients randomized to treatment arms included in the primary comparison (i.e. placebo, 1.2mg/kg/day, 1.8mg/kg/day), 249 patients had both the baseline and postbaseline efficacy measures. All patients included in the primary efficacy analysis took at least 1 dose of study medication except 1 patient (LYAC-13-7179) who was randomized to 1.8mg/kg.day and had some post baseline efficacy measures without taking study drug.

APPEARS THIS WAY
ON ORIGINAL

Table IV.6.1 ADHD Rating Scale IV-Parent Version: Investigator Scored (ADHDRS-IV-Parent:Inv) Total Score Change from Baseline to Endpoint –

Study Period II, B4Z-MC-LYAC

Treatment	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	p-value TMX v.s. placebo adjusted	(UnAdjusted)
Placebo	83	38.3	8.9	32.5	13.8	-5.8	10.9		
TMX0.5	43	40.2	9.6	30.3	15.2	-9.9	14.6		(.155)
TMX1.2	84	39.2	9.2	25.5	13.8	-13.6	14.0	<.001	(<.001)
TMX1.8	82	39.7	8.7	26.2	14.8	-13.5	14.5	<.001	(<.001)

Reviewer Comment:

1. In Table IV.6.1. 1, Unadjusted p-values are from pairwise tests in mean change from baseline to endpoint(last visit carried forward) scores using least squares means from an ANOVA model including baseline, investigator, treatment and CYP2D6 status in the model. Adjusted p-values are computed using Dunnett's procedure.
2. In the primary analysis, the overall treatment effect was significant based on the ANCOVA model adjusted for baseline, investigator and CYP2D6 status. Observed mean reduction were –5.8, -9.9, -13.6 and –13.5 for placebo, tomoxetine 0.5 mg/kg/day, 1.2mg/kg/day, 1.8 mg/kg/day, respectively (Table IV.6.1). The primary comparison showed significant improvement of tomoxetine 1.2 mg/kg/day /1.8mg/kg/day compared with placebo (adjusted p-value 0.001). The improvement of 0.5mg/kg/day showed numerically, but no statistically significant improvement.

IV.6. Secondary Analyses

The secondary efficacy endpoints included inattention and hyperactivity-impulsivity subscales of ADHDRS-IV-Parent: Inv scale and the following measures :

1. Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Severity (CGI-ADHD-S) : A 7-point, single-item clinician assessment of the severity of the ADHD symptoms;
2. Clinical Global Impressions-Anxiety-Severity (CGI-A-S) and Clinical Global Impressions-Depression-Severity (CGI-D-S) scales : Similar to CGI-ADHD scales;
3. Children's Depression Rating Scale-Revised (CDRS-R): This scale was modeled after the Hamilton Depression Rating Scale (HAMD) for adults. This is a clinician-rated instrument measure of severity of depression. The scale consists of 17 items scored from 1 to 5 or 1 to 7;
4. Clinical Global Impressions-efficacy Index (CGI-EI) : This scale combines a therapeutic effect rating and a side effect rating (both scored from 1 to 4);
5. Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) This is a 27-item rating scale completed by parents. The Oppositional, Cognitive problems and ADHD index subscale scores were computed from CPRS-R:S.

Since the secondary endpoints analysis results are consistent with the primary analysis and there are no claims included in the labeling claim, according to medical division's suggestion, these secondary analyses are not reviewed.

IV.7 Sponsor's Conclusion and Reviewer's Conclusion/Comments

Based upon the analysis for the primary endpoints, this study met the primary objective of this study: to test the hypothesis that acute treatment for approximately 8 weeks with tomoxetine, either 1.2 mg/kg/day or 1.8 mg/kg/day, would be statistically significantly more effective in reducing the severity of Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms than placebo. Symptom reduction in both the 1.2 mg/kg/day and 1.8 mg/kg/day groups was statistically superior to that observed in the placebo group on the primary outcome efficacy measure. The 0.5 mg/kg/day group was not statistically significantly different from placebo as assessed by the ADHDRS-IV-Parent:Inv although it is not the protocol specified comparison.

V. Study LYAT

Study LYAT was a randomized, double-blind, placebo-controlled study conducted with 171 enrolled children and adolescents at 9 study sites in the United States. The study started on Febuary 6, 2001 and ended on May 18, 2001. The primary comparison was between atomoxetine administered as a single daily dose in the morning compared with placebo.

V.1 Study Design

LYAT was a child and adolescent placebo-controlled study conducted with 171 enrolled patients aged 6 to 16 years who met the Diagnostic criteria for Attention-Deficit/Hyperactivity Disorder (ADHD). Patients were randomized to either placebo or once daily (QD) dosing of atomoxetine. The study included three treatment periods. Patients who met entry criteria completed an initial evaluation period of 3 to 20 days (Study Period I; Visits 1 and Visit 2), that included full clinical assessment, diagnostic assessment, and a washout phase. At the end of Visit 2, patients were randomized. During the 6-week, double-blind, acute treatment phase (Study Period II; Visits 3 through Visit 6), dose was titrated according to prespecified response criteria.

V.2 Objective

The primary objective of this study is to test the hypothesis that tomoxetine administered as a single-daily dose provides superior efficacy compared with placebo in children with Attention-Deficit/Hyperactivity Disorder (ADHD). Assessment is measured by reduction from baseline-to-endpoint by the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) total score in the once-daily and placebo-treated groups.

The secondary objectives of the study are as follows:

- To compare the improvement in symptoms associated with ADHD in children achieved by once-daily dosing of tomoxetine or placebo as defined by a >25% reduction in the ADHDRS-IV-Parent:Inv score and by mean reductions in the Conners'-Revised: Short Form (CPRS-R:S) and ADHDRS-IV-Parent:Inv subscale scores.
- To compare the reduction in non-school related symptoms between tomoxetine and placebo as assessed by the Daily Parent Ratings of Evening and Morning Behavior (DPREMB) and the Social Skills Rating System–Parent Questionnaire (SSRS-P).
- To compare the reduction in school-related symptoms between tomoxetine and placebo as assessed by the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S).
- To assess the safety and tolerability of once-daily dosing of tomoxetine.

V.3 Efficacy Variables

The primary efficacy measure for this study was the ADHDRS-IV-Parent:Inv. This scale was administered at Visit 1 through Visit 6. The ADHDRS-IV-Parent:Inv is an 18-item scale with 1 item for each of the 18 symptoms contained in the DSM-IV diagnosis for ADHD. Each item is scored on a 0- to 3-point scale (0=never or rarely; 1=sometimes; 2=often; 3=very often. The rating scale was used to assess the symptom severity over each past week. The scale was administered and scored by qualified personnel at the investigative site. The total score was computed as the sum of the scores on each of the 18 items.

The secondary efficacy measures include (1) the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S); (2) Daily Parent Ratings of Evening and Morning Behavior (DPREMB); (3) Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S); (4) the Social Skills Rating System-Parent Questionnaire (SSRS-P); and (5) the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S).

V.4 Sample Size

171 patients were enrolled into the study. This sample size would provide approximately 82% power for the treatment comparison between QD tomoxetine and placebo. This calculation assumes a treatment difference of 6.0 points in the mean change in ADHDRS-IV-Parent:Inv total score, a standard deviation of 12.5, a 2-sided, 0.05 level test, and that at most 5% of the enrolled subjects will provide no postbaseline information.

V.5 Population and Statistical Analysis

At the end of Visit 2, 86 patients were randomized to placebo (60 male, 26 female); 85 were randomized to atomoxetine (59 male, 26 female). One patient discontinued after randomization and never took study drug. Of the 171 patients randomized, 148 completed Study Period II.

The primary efficacy scale was the ADHDRS-IV-Parent:Inv. The primary analysis variable was the total score of the 18 items from the ADHDRS-IV-Parent:Inv. Treatment differences were assessed with a repeated measures mixed model . The dependent variable in the model was the ADHDRS-IV-Parent:Inv total scores (from Visit 3 through Visit 6; all Study Period II postbaseline data). The model contained fixed class effect terms for treatment, investigator, and

visit, and contained an interaction term between treatment and visit. The model also included a random subject effect and baseline (Visit 2) ADHDRS-IV-Parent:Inv total score as a covariate.

V.6. Sponsor's Results and Statistical Reviewer's Findings/Comments

V.6.1. Patient Deposition

A total of 171 patients were randomized into this study (n=86, 85 for tomoxetine, placebo respectively). One patient (LYAT-005-3077) who was enrolled in the study was randomized to a treatment group, and did not take study drug.

Baseline demographic and other characteristics were examined, these including age, gender, race, CYP2D6 status, weight, family history of ADHD, prior stimulant exposure. No statistically significant differences were found in the comparison of the two treatment arms (at the level of 0.05).

V.6.2. Primary Endpoint

The primary efficacy endpoint was the ADHDRS-IV-Parent:Inv. The primary analysis variable was the total score of the 18 items from the ADHDRS-IV-Parent:Inv. Treatment differences were assessed with a repeated measures mixed model . The dependent variable in the model was the ADHDRS-IV-Parent:Inv total scores (from Visit 3 through Visit 6; all Study Period II postbaseline data). The model contained fixed class effect terms for treatment, investigator, and visit, and contained an interaction term between treatment and visit. The model also included a random subject effect and baseline (Visit 2) ADHDRS-IV-Parent:Inv total score as a covariate. The result of the analysis is showed on Table V.6.1.

Table V.6.1.1. ADHRS- IV- Parent: Inv Total Score Repeated Measures Least Squares Means Study Period II - B4Z- MC- LYAT

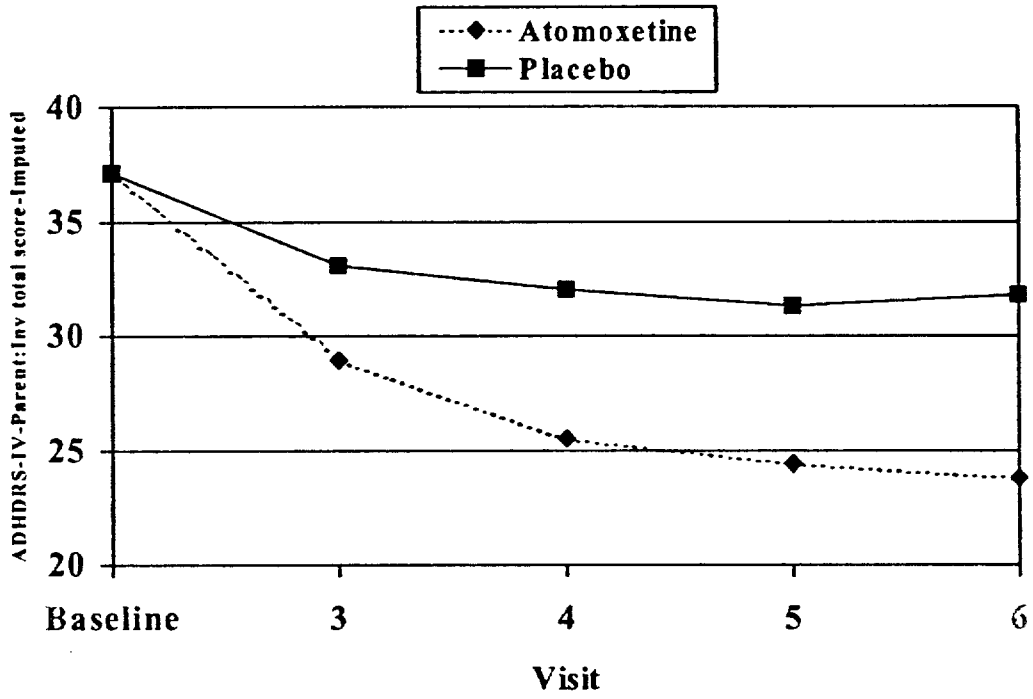
	TMX		Placebo		Change		p-value TMX v.s. placebo
Visit	Mean	SE	Mean	SE	Mean	SE	
3	28.91	0.94	33.09	0.95	-4.18	1.27	.001
4	25.52	1.14	32.00	1.15	-6.48	1.56	<.001
5	24.45	1.22	31.29	1.23	-6.84	1.69	<.001
6	24.45	1.22	31.29	1.23	-6.84	1.69	<.001

Reviewer Comment:

1. In Table V.6.1.1, p-values are from tests for a treatment difference in least squares means at the given visit.
2. Results are based on a mixed model with a term for visit, (treated as a class variable) baseline, treatment and treatment by visit interaction using an unstructured covariance matrix to model correlations within patient across visits.

3. The analysis at Visit 6 is the primary analysis. Both groups showed an overall improvement (decrease) from baseline in mean ADHDRS-IV-Parent:Inv total score at each visit. Mean reductions for atomoxetine were statistically significantly larger compared with placebo. The FigureV.6.6.1 showed the overall change of the mean ADHDRS-IV-Parent:Inv total score at each visit.

FigureV.6.6.1 Overall change of the mean ADHDRS-IV-Parent:Inv total score at each visit.



4. However, the missing value is not treated using the last observation carried forward (LOCF) method for the primary analysis (visit 6 comparison). To confirm the efficacy showed in the modeling results, a LOCF method was used to test the differences between the two treatment arms. Table V.6.1.2 showed the result using LOCF for the primary analysis.

Table V.6.1.2 ADHD Rating Scale IV-Parent Version: Investigator Scored (ADHDRS-IV-Parent:Inv) Total Score Change from Baseline to Endpoint-Study Period II) LOCF

Disorder-Severity score) <=3 at visit 8 can continue **to receive the same study medication as period II** during this period. Dosage can be adjusted according to symptoms or tolerability.

- Study period IV (3-week): This is a double-blind discontinuation phase in which patients are either randomized to abruptly drug stopped group or gradual drug reduction group.

The sponsor indicated that the timing and criteria for study entry, randomization as well as dose increase during study period II were kept blinded for primary outcome efficacy raters and patients. However, principal investigators and study coordinators can have access to the protocol and to details of the study design.

VI.2 Objective

The primary objective of this study was to test the hypothesis that, compared with placebo, administration of atomoxetine at total daily doses of 60 mg to 120 mg for up to 10 weeks would result in a statistically significantly greater reduction in mean Total ADHD Symptom Score on the investigator-administered and scored Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV).

The secondary objectives of the study were:

(1) To compare percentages of responders among atomoxetine-treated and placebo-treated patients who have completed a minimum of 3 visits following randomization. Determination of clinical response was based on the CAARS-Inv:SV and the Clinical Global Impressions-ADHD-Severity CGI-ADHD-S scores.
(2) To compare improvement of neurocognitive function during treatment with atomoxetine to improvement during treatment with placebo using the Stroop Color Word Test.
(3) To compare the safety of atomoxetine with placebo in a population of adult patients who meet DSM-IV criteria for ADHD
(4) To assess changes in health outcomes.

VI.3 Efficacy Variables

The primary efficacy measure is Conners Adult ADHD Rating Scale-Investigator rated: Screening Version (CAARS-INV:SV). The CAARS-INV:SV is a 30-item scale containing 3 subscales: the 9-item inattention subscale and the 9-item hyperactivity/impulsivity subscale, and the 12-item ADHD index. The 18-item total ADHD symptom score (sum of the inattention subscale and the hyperactivity/impulsivity subscale) is considered to be the primary efficacy measure.

VI.4 Sample Size

A total of 280 patients were enrolled and randomized into two studies with 141 patients in TMX arm and 139 in the placebo arm. The 280 sample size would provide 82% power for treatment comparison, assuming 0.42 effect size of the 18-item CAARS-INV:SV total ADHD symptom

score, using 2-sided , 0.05 level test. The sample size calculation is also based on the assumption that 5% patients might not have post-baseline information from each study.

VI.5 Population and Statistical Analysis

The primary analysis is the intent-to-treat analysis (ITT) which includes all enrolled patients who take at least one dose of study medication at phase II and who have both a baseline and at least one post baseline CAARS-INV:SV total ADHD symptom score.
The site pooling scheme is similar to LYAC. A site-pooling scheme was proposed by the sponsor based on whether the site has more than 1 ITT patient in each treatment group or not. If the site/combined sites has no more than 1 ITT patient in each treatment group, the sites would be combined.

The primary efficacy analysis is based on the repeated measures mixed effect model in which the change from baseline in CAARS-INV:SV total ADHD symptom scores (at visits 4 to 9) will be the dependent variable. The model included fixed class effect terms for treatment, investigator, visit, CYP2D6 status, and an interaction term of treatment by visit. The model also included a random subject effect and the baseline (visit 3) CAARS-INV:SV total ADHD symptom score as covariates. Four different within patient covariance structures were considered: unstructured, heterogeneous toeplitz, heterogeneous autoregressive of order 1, and heterogeneous compound symmetry. The covariance structure which provide the largest Akaike's information criteria score was used for the primary analysis. The primary efficacy comparison was performed at Visit 9 using a contrast from the repeated measures mixed effect model. If more than 1 item is missing in a subscale, the subscale (or the total) score was considered as missing. For a single missing item, the mean score was used to impute the missing item and then to compute the subscale or total scores.

All statistical tests will be two-sided at the 0.05 level.

Subgroup analysis were performed based on various subgroups : metabolic status, investigational site, prior stimulant use strata, ADHD subtype, gender, age, comorbidity groups. The influence of missing data on the treatment effect were evaluated using several methods that account for missing data: repeated measures mixed effect model, last observation carried forward approach, subset analysis for patients who completed at least 2 post-baseline visits as well as missing data imputation method such as multiple imputation. The repeated measures mixed effect model is used for the primary analysis.

One interim analysis was planned for this study. The interim analysis occurred after 150 patients had completed the period II visits.

VI.6. Sponsor's Results and Statistical Reviewer's Findings/Comments

VI.6.1. Patient Deposition

Of the 280 enrolled patients, 63.6% were male; 87.5% were Caucasian, 53.6% had no prior stimulant exposure, and 6.8% were determined to be poor metabolizers (PMs). The

mean age for these patients was 40.3 years (range of 18.2 to 67.5).

Baseline demographic and other characteristics were examined, these including age, gender, race, height, weight, family history of ADHD, prior stimulant exposure. No statistically significant differences were found in the comparison of the two treatment arms (at the level of 0.05).

VI. 6.2. Primary Endpoint

The primary efficacy endpoint was the Total ADHD Symptom Score on the investigator-administered and scored Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV). The analysis of the primary efficacy variable included all randomized patients who had a baseline and at least 1 postbaseline measurement. Of the 280 patients randomized to either atomoxetine or placebo, 267 met the criteria to be included in the primary efficacy analysis. 13 patients who were enrolled, but did not have postbaseline efficacy measurements.

The primary analysis of the primary efficacy measure assessed treatment difference between atomoxetine and placebo using a repeated measures mixed model on the CAARS-Inv:SV Total ADHD Symptom scores across all postbaseline visits during Study Period II. The model used contained fixed class effect terms for treatment, investigational site, visit, cytochrome P450 2D6, and an interaction term between treatment and visit. The model also included baseline (Visit 3) CAARS-Inv:SV Total ADHD Symptom Score as a covariate. A random patient effect was used to determine the within patient covariance structure for the model. The primary efficacy analysis was the comparison of atomoxetine and placebo at Visit 8. The result of the analysis is showed on Table VI.6.1.1.

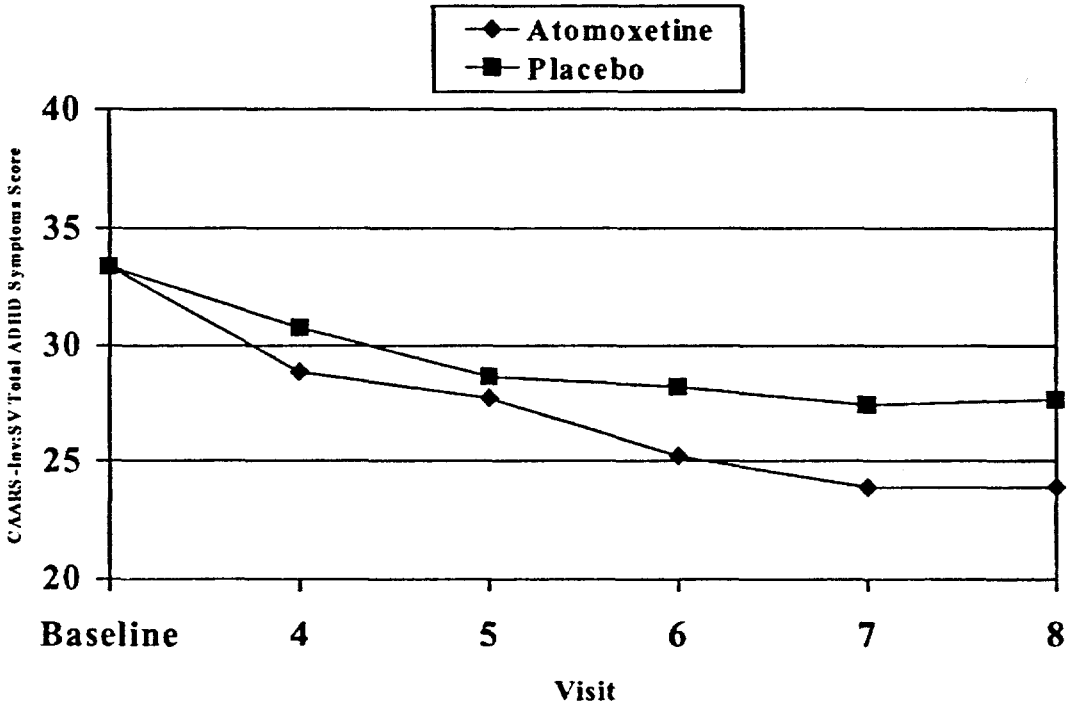
Table VI.6.1.1. CAARS-INV:SV Total Score Repeated Measures Least Squares Means Study Period II – LYAA

	TMX		Placebo		Change		p-value
							TMX v.s. placebo
Visit	Mean	SE	Mean	SE	Mean	SE	
4	28.82	0.90	30.76	0.93	-1.94	0.82	.020
5	27.67	0.99	28.62	1.02	-0.95	1.00	.342
6	25.23	1.00	28.18	1.03	-2.94	1.02	.004
7	23.90	1.10	27.44	1.12	-3.54	1.21	.004
8	23.88	1.13	27.60	1.15	-3.72	1.26	.004

Reviewer Comment:

1. In Table VI.6.1.1, p-values are from tests for a treatment difference in least squares means at the given visit.
2. Results are based on a mixed model with a term for visit, (treated as a class variable) baseline, treatment and treatment by visit interaction using an unstructured covariance matrix to model.
3. The analysis at Visit 8 is the primary analysis. Both groups showed an overall improvement (decrease) from baseline total score at each visit. Mean reductions for atomoxetine were statistically significantly larger compared with placebo. The FigureVI.6.6.1 showed the overall change of the mean total score at each visit.

Figure VI.6.1.1 Overall change of the mean total score at each visit



4. The missing value is not treated using the last observation carried forward (LOCF) method for the primary analysis (visit 8 comparison). To confirm the efficacy showed in the modeling results, a LOCF method was used to test the differences between the two treatment arms. Table VI.6.1.2 showed the result using LOCF for the primary analysis.

Table VI.6.1.2 ADHD Rating Scale Total Score (CAARS-Inv:SV) Change from Baseline to Endpoint-Study Period II) LOCF-LYAA

VII.2 Objective

The primary objective of this study was to test the hypothesis that, compared with placebo, administration of atomoxetine at total daily doses of 60 mg to 120 mg for up to 10 weeks would result in a statistically significantly greater reduction in mean Total ADHD Symptom Score on the investigator-administered and scored Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV).

The secondary objectives of the study were:

(1) To compare percentages of responders among atomoxetine-treated and placebo-treated patients who have completed a minimum of 3 visits following randomization. Determination of clinical response was based on the CAARS-Inv:SV and the Clinical Global Impressions-ADHD-Severity CGI-ADHD-S scores.
(2) To compare improvement of neurocognitive function during treatment with atomoxetine to improvement during treatment with placebo using the Stroop Color Word Test.
(3) To compare the safety of atomoxetine with placebo in a population of adult patients who meet DSM-IV criteria for ADHD
(4) To assess changes in health outcomes.

VII.3 Efficacy Variables

The primary efficacy measure is Conners Adult ADHD Rating Scale-Investigator rated: Screening Version (CAARS-INV:SV). The CAARS-INV:SV is a 30-item scale containing 3 subscales: the 9-item inattention subscale and the 9-item hyperactivity/impulsivity subscale, and the 12-item ADHD index. The 18-item total ADHD symptom score (sum of the inattention subscale and the hyperactivity/impulsivity subscale) is considered to be the primary efficacy measure.

VII.4 Sample Size

A total of 256 patients were enrolled and randomized into two studies with 129 patients in TMX arm and 127 in the placebo arm. One hundred ninety (190) patients were to be enrolled into this study. A sample size of 190 patients (95 placebo and 95 atomoxetine) was calculated to provide approximately 82% power for the treatment difference between atomoxetine and placebo. This calculation assumed a detectable effect size of 0.42 on the 18-item CAARS-Inv:SV Total ADHD Symptom Score using a 2-sided, 0.05 level test, and that at most 5% of the enrolled patients would provide no postbaseline information from each study. When enrollment in this study concluded, 241 patients were enrolled in the EM stratum and 256 total patients were enrolled. Thus, the actual study sample size provided 91% power for comparing atomoxetine and placebo under the same assumptions as above.

VII.5 Population and Statistical Analysis

The primary analysis is the intent-to-treat analysis (ITT) which includes all enrolled patients who take at least one dose of study medication at phase II and who have both a baseline and at least one post baseline CAARS-INV:SV total ADHD symptom score.

The primary efficacy analysis is based on the repeated measures mixed effect model in which the change from baseline in CAARS-INV:SV total ADHD symptom scores (at visits 4 to 9) will be the dependent variable. The model included fixed class effect terms for treatment, investigator, visit, CYP2D6 status, and an interaction term of treatment by visit. The model also included a random subject effect and the baseline (visit 3) CAARS-INV:SV total ADHD symptom score as covariates. Four different within patient covariance structures were considered: unstructured, heterogeneous toeplitz, heterogeneous autoregressive of order 1, and heterogeneous compound symmetry. The covariance structure which provide the largest Akaike's information criteria score was used for the primary analysis. The primary efficacy comparison was performed at Visit 9 using a contrast from the repeated measures mixed effect model. If more than 1 item is missing in a subscale, the subscale (or the total) score was considered as missing. For a single missing item, the mean score was used to impute the missing item and then to compute the subscale or total scores.

All statistical tests will be two-sided at the 0.05 level.

VII.6. Sponsor's Results and Statistical Reviewer's Findings/Comments

VII.6.1. Patient Deposition

Of the 256 enrolled patients, 66.4% were male; 94.5% were Caucasian, 51.3% had no prior stimulant exposure, and 6.8% were determined to be poor metabolizers (PMs). The mean age for these patients was 42.1 years (range of 18.6 to 76.7).

Baseline demographic and other characteristics were examined, these including age, gender, race, height, weight, family history of ADHD, prior stimulant exposure. No statistically significant differences were found in the comparison of the two treatment arms (at the level of 0.05).

VII.6.2. Primary Endpoint

The primary efficacy endpoint was the Total ADHD Symptom Score on the investigator-administered and scored Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV). The analysis of the primary efficacy variable included all randomized patients who had a baseline and at least 1 postbaseline measurement. Of the 256 patients randomized to either atomoxetine or placebo, 248 met the criteria to be included in the primary efficacy analysis. 8 patients who were enrolled, but did not have postbaseline efficacy measurements.

The primary analysis of the primary efficacy measure assessed treatment difference between atomoxetine and placebo using a repeated measures mixed model on the CAARS-Inv:SV

Total ADHD Symptom scores across all postbaseline visits during Study Period II. The model used contained fixed class effect terms for treatment, investigational site, visit, cytochrome P450 2D6, and an interaction term between treatment and visit. The model also included baseline (Visit 3) CAARS-Inv:SV Total ADHD Symptom Score as a covariate. A random patient effect was used to determine the within patient covariance structure for the model. The primary efficacy analysis was the comparison of atomoxetine and placebo at Visit 8. The result of the analysis is showed on Table VII.6.1.1.

Figure VII.6.1.1 Overall change of the mean total score at each visit

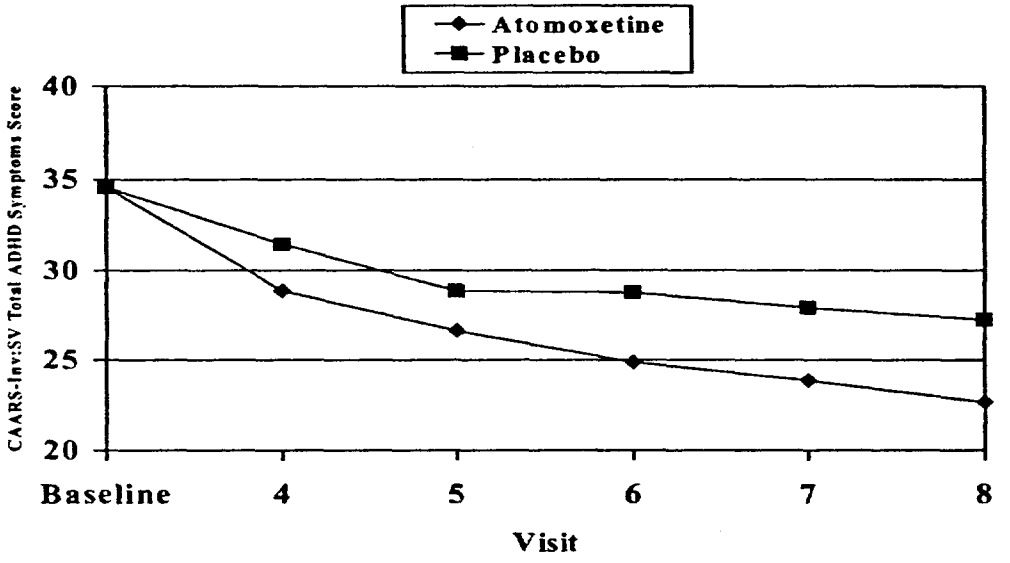


Table VII.6.1.1. CAARS-INV:SV Total Score Repeated Measures Least Squares Means Study Period II – LYAO

Visit	TMX Mean	TMX SE	Placebo Mean	Placebo SE	Change Mean	Change SE	p-value TMX v.s. placebo
4	28.81	1.17	31.43	1.14	-2.62	0.95	.006
5	26.61	1.24	28.80	1.22	-2.19	1.12	.052
6	24.87	1.29	28.74	1.27	-3.87	1.23	.002
7	23.88	1.34	27.89	1.31	-4.01	1.32	.003
8	22.63	1.37	27.23	1.33	-4.60	1.37	<.001

Reviewer Comment:

1. In Table VII.6.1.1, p-values are from tests for a treatment difference in least squares means at the given visit.
2. Results are based on a mixed model with a term for visit, (treated as a class variable) baseline, treatment and treatment by visit interaction using an unstructured covariance matrix to model.
3. The analysis at Visit 8 is the primary analysis. Both groups showed an overall improvement (decrease) from baseline total score at each visit. Mean reductions for atomoxetine were statistically significantly larger compared with placebo($p<0.001$). The FigureVII.6.6.1 showed the overall change of the mean total score at each visit.
4. The missing value is not treated using the last observation carried forward (LOCF) method for the primary analysis (visit 8 comparison). To confirm the efficacy showed in the modeling results, a LOCF method was used to test the differences between the two treatment arms. Table VII.6.1.2 showed the result using LOCF for the primary analysis.

Table VII.6.1.2 ADHD Rating Scale Total Score (CAARS-Inv:SV) Change from Baseline to Endpoint-Study Period II) LOCF-LYAO

		Baseline		Endpoint		Change		p-value
								TMX v.s. placebo
Treatment	n	Mean	SD	Mean	SD	Mean	SD	
TMX	124	34.9	6.9	24.4	11.21	-10.5	10.9	0.002
PLACEBO	124	34.2	7.5	27.5	11.40	-6.7	9.3	

V.7. Sponsor's Conclusion and Reviewer's Conclusion/Comments

Based upon the primary efficacy endpoint using LOCF method, Atomoxetine treatment resulted in a statistically significantly greater mean reduction in CAARS-Inv: SV Total ADHD Symptom score than placebo. The mean changes for the atomoxetine and placebo treatment groups were –10.5 and –6.7 (p=.002).

VIII. Statistical Evaluation of Collective Evidence

Atomoxetine hydrochloride (Atomoxetine) is being proposed to be used for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children, adolescents, and adults. The sponsor submitted 7 controlled trials to support the claim of the efficacy and safety of the treatment. This section summarized the NDA efficacy submission by using the following two tables.

Table VIII. 1 Summary of Acute, randomized, double-blind placebo-controlled child studies

Study	Study Design	Analyzed Population /age	treatment	Primary Efficacy Endpoint
HFBD 7 sites; US 11/19/98-2/17/00	Double-blind, randomized, placebo-controlled trial that compared outcomes in children with ADHD after approximately **9 weeks** of acute therapy with either atomoxetine or placebo Randomization was stratified by whether or not patients were previously on stimulant therapy for Atomoxetine and placebo group. **Only stimulant naïve children were randomized to methylphinidate group.** **No poor metabolizer (CYP2D6)**	Atomoxetine : n=64 Placebo : n=61 Age 7-12.9 (mean :9.7) M:119; F:28 Comments : original protocol allowed trt group down titrated to 0 dose Interim analysis using Triangular method.	Atomoxetine BID Placebo BID	Change from baseline of ADHDRS-IV-parent : **Inv =trt+site (pooled)+previous-stimulant use** Total score : p<0.001 Changes: -15.6 (SD: 13.7) -5.5 (SD: 11.6)
HFBK 10 sites; US 2/17/99-10/21/99	Double-blind, randomized, placebo-controlled trial that compared outcomes in children with ADHD after approximately **9 weeks** of acute therapy with either atomoxetine or placebo Randomization was stratified by whether or not patients were previously on stimulant therapy for Atomoxetine and placebo group. **Only stimulant naïve children were randomized to methylphinidate group.** **No poor metabolizer (CYP2D6)**	Atomoxetine : n= 63 Placebo : n=60 Age 7-12 (mean: 9.9) M:117;F=27 Comments : Interim analysis using Triangular method.	Atomoxetine BID Placebo BID	Change from baseline of ADHDRS-IV-parent : Inv =trt+site (pooled)+previous-stimulant use Total score : p<0.001 Changes: -14.4 (SD: 13.0) -5.9 (SD: 13.0)
LYAC 13 sites; US 4/00-12/00	4-arm, fixed-dose study comparing the efficacy of atomoxetine 0.5 mg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day with placebo in children and adolescents. **8-week** acute treatment period. Stratified by CYP2D6 status & for EM patient : also stratified by prior stimulant use	Atomoxetine 0.5 mg.kg/day : n=43 1.2 mg.kg/day : n=84 1.8 mg.kg/day : n=82 placebo : n=83 M:212; F:85; Age 8-18 (11.2)	0.5 mg.kg/day BID 1.2 mg.kg/day BID 1.8 mg.kg/day BID Placebo BID	Change from baseline of ADHDRS-IV-parent : Inv = trt + baseline+ site +CYP2D6 status (ANCOVA : include only hi and med dose groups per sponsor : 6/22/00); use Dunnett's test for 2 primary comparison -9.9(SD:14.6) -13.6(SD:14.0) p<0.001 (compare w/plc) -13.5(SD:14.5) p<0.001 (compare w/plc) -5.8(10.9)
LYAT 9 sites; US 2/6/01-5/18/01	6-week acute randomized,double-blind, placebo-controlled, parallel study After V6, patients may participate in a long-term study (e.g. LYAI)	Atomoxetine : n=85 Placebo : n=85 M:=119; F:52 Age 6-16 (10.3)	Titrated to safety and efficaccy; QD dosing max1.5 mg/kg/day Placebo QD	Repeated ANOVA ADHDRS-IV-parent:Inv (V3-V6)=fixed effect : site+trt+visit+visit*trt+baseline random subject effect P<0.001

Table VIII. 2 Summary of Acute, Randomized, Double-blind placebo-controlled Adult Studies

Study	Study Design	Population /age	Treatment	Primary Efficacy Endpoint
LYAA 17 sites; US & Canada 07/28/98-8/1/01	A 10-week, Double-blind, randomized, placebo-controlled trial. **Stratified by CYP2D6 status**	Atomoxetine : n= 141 Placebo : n= 139 Age 18-67.5 (Mean: 40.3) M:178; F:102	Titrated Atomoxetine BID Placebo BID	Repeated ANOVA CAARS-INV:SV (V4-V8)=fixed effect : site+trt+visit+visit*trt+baseline+CYP2D6 status random subject effect Total score : p=0.004 at week 8 (trt vs. pls) Mixed Model Analysis LOCF: p=0.006 at week 8 (trt vs. pls)
LYAO 14 sites; US 8//00-04/01	A 10-week, Double-blind, randomized, placebo-controlled trial. **Stratified by CYP2D6 status**	Atomoxetine : n= 129 Placebo : n=127 Age 18-76 (42.1) M:170;F=86	Titrated Atomoxetine BID Placebo BID	Repeated ANOVA CAARS-INV:SV (V4-V8)=fixed effect : site+trt+visit+visit*trt+baseline+CYP2D6 status random subject effect Total score : p<0.001 at week 8 LOCF: p=0.002 at week 8 (trt vs. pls)

Based upon the above summary, in this reviewer's opinion the study results appear to support efficacy claim made by the sponsor for Atomoxetine hydrochloride (Atomoxetine).

APPEARS THIS WAY
ON ORIGINAL

Ning Li
Statistical Reviewer

Date:

Concur: Dr. Kin
Team Leader

Dr. Chi
Division Director, DBI

Cc:

HFD-120/Anna Marie Homonnay
HFD-120/Roberta Glass
HFD-120/Tom Laughren
HFD-120/Russell Katz
HFD-710/Ning Li
HFD-710/Kun Jin
HFD-710/George Chi
HFD-700/C. Annello

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/s/

Ning Li
6/14/02 04:02:34 PM
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Kun Jin
6/14/02 04:08:07 PM
BIOMETRICS

George Chi
6/17/02 09:23:25 AM
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