CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-912

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation
Clinical Studies

NDA/Serial Number:	NDA 21-912
Drug Name:	Arformoterol Tartrate Inhalation Solution administered via Unit Dose Vial (UDV)
Indication(s):	Arformoterol is proposed to be indicated for the treatment of COPD
Applicant:	Sepracor
Date(s):	Applicant's letter date: December 8, 2005
Review Priority:	Standard
Biometrics Division:	Biometrics Division 2
Statistical Reviewer:	Ted Guo, Ph.D.
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Keywords:	NDA review, clinical studies

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Table of Contents

List of Tables

List of Figures

EXECUTIVE SUMMARY

Brief Overview of Clinical Studies

Arformoterol Tartrate Inhalation Solution, administered via Unit Dose Vial (UDV), is proposed to be indicated for the treatment of COPD.

The applicant describes Arformoterol as a highly selective, potent, and long-acting beta2-adrenoceptor agonist currently under development in the United States for the long-term maintenance treatment of [ ] associated with COPD. [ ] b(4)

The applicant submitted two Phase III pivotal studies, 091-050 and 091-051 to demonstrate that arformoterol delivered via UDV is effective and safe to treat COPD. These studies had identical designs. The primary objective of the studies was to "investigate the effect on FEV1 over 12 weeks of treatment among the following treatment groups: arformoterol 50 μg QD, arformoterol 25 μg BID, arformoterol 15 μg BID, salmeterol metered-dose inhaler (MDI) 42 μg BID, and placebo" (Page 30, 8 Study Objectives, 091-050.pdf).

Studies 091-050 and 091-051 were each a double-blind, double-dummy, randomized, placebo- and active-controlled, multi-center, parallel-group study of adult patients with COPD (Page 30, 9 Investigational Plan, 091-050.pdf).

This reviewer's evaluation of the effectiveness of arformoterol is focused on whether the superiority of arformoterol over placebo is demonstrated, based on the sponsor's data. Since no specific safety endpoints or analyses were identified as warranting formal statistical investigation, the drug's safety was not the focus of this review.

Statistical Issues and Findings

This reviewer reanalyzed the sponsor's data for Studies 091-050 and 091-051 and confirmed the sponsor's statistical findings for the primary efficacy analysis.

Table 1 shows the LS-means of percent changes from study baseline in FEV_1 to the end of dosing interval (i.e., the primary efficacy endpoint) for each treatment group and the differences in LS means between the active treatments and placebo. As shown in Table 2, the values for active treatments are consistently statistically significantly greater than that of placebo ($p<0.001$ for all comparisons in both studies).

As might have been expected, the LS-mean of 50 mcg QD regimen is numerically lower than that of the 25 mcg BID, though the daily doses are the same. The LS-mean of the salmeterol group is numerically similar with that of the arformoterol groups; however, formal non-inferiority testing of these groups was not planned a priori.

Table 1 LS-means of percent change from study baseline in FEV_1 to the end of dosing interval (Studies 091-050 and 091-051)

Treatment	Study 091-050		Study 091-051	
	Ls-means	Diff. from placebo	Ls-means	Diff. from placebo
Placebo	6.7946		6.8481	
15 mcg BID arformoterol	19.3053	-12.5107	17.7605	-10.9124
25 mcg BID arformoterol	20.9000	-14.1054	22.5045	-15.6564
50 mcg QD arformoterol	16.4200	-9.6253	18.4108	-11.5627
42 mcg BID Salmeterol	19.8966	-13.1020	19.0423	-12.1942

Source: kokospirdata8

Table 2 Efficacy findings based on 12-week percent change from baseline to trough FEV_1 (Studies 091-050 and 091-051 compared)

Comparison		091-050	091-051	Findings consistently positive
15 mcg BID arformoterol	Vs. Placebo	<0.0001	<0.0001	Yes
25 mcg BID arformoterol		<0.0001	<0.0001	Yes
50 mcg QD arformoterol		<0.0001	<0.0001	Yes
42 mcg BID Salmeterol		<0.0001	<0.0001	Yes

Source: kokospirdata8

Comments on Labeling

This reviewer evaluated the **Clinical Trials** subsection of the proposed labeling in the **Proposed Labeling Text** section of the NDA submission for accuracy. In general, this reviewer agrees with the sponsor on the efficacy claims for arformoterol.

Conclusions and Recommendations

Efficacy Conclusions:

This reviewer evaluated the sponsor's efficacy analyses of the effect on FEV_1 over 12 weeks of treatment among the following treatment groups: arformoterol 50 μg QD, arformoterol 25 μg BID, arformoterol 15 μg BID, salmeterol metered-dose inhaler (MDI) 42 μg BID, and placebo. All three dose groups of arformoterol and the comparator, salmeterol, were demonstrated to be statistically superior to placebo in terms of the primary efficacy endpoint in both studies.

Recommendations:

Since from a statistical perspective arformoterol has been proven to be efficacious compared with placebo, this reviewer recommends the approval of arformoterol based on the efficacy evaluation of the sponsor's data in Studies 091-050 and 091-051.

INTRODUCTION

Overview

Arformoterol Tartrate Inhalation Solution, administered via Unit Dose Vial (UDV), is proposed to be indicated for the treatment of COPD.

The applicant describes Arformoterol as a highly selective, potent, and long-acting beta2-adrenoceptor agonist currently under development in the United States for the long-term maintenance treatment of [ ] associated with COPD. [ ]

[ ] b(4)

The applicant submitted two Phase III pivotal studies, 091-050 and 091-051 to demonstrate that arformoterol delivered via UDV is effective and safe to treatment COPD. These studies had the same study design. The primary objective, for both studies, "was to investigate the effect on FEV_1 over 12 weeks of treatment among the following treatment groups: arformoterol 50 μg QD, arformoterol 25 μg BID, arformoterol 15 μg BID, salmeterol metered-dose inhaler (MDI) 42 μg BID, and placebo" (Page 30, 8 Study Objectives, 091-050.pdf).

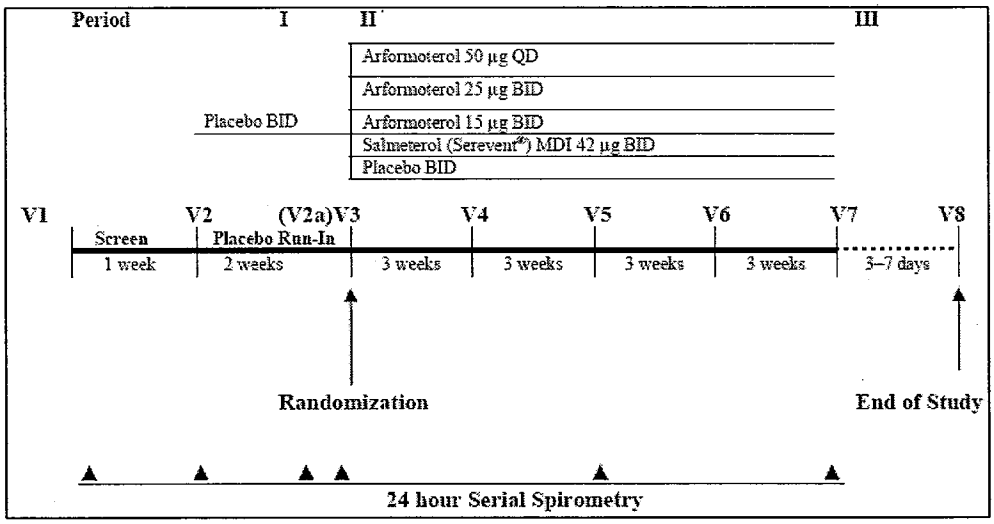
Scope of Statistical Review: Pivotal Efficacy Studies

The sponsor submitted two pivotal studies for efficacy: Studies 091-050 and 091-051. They were each a double-blind, double-dummy, randomized, placebo- and active-controlled, multi-center, parallel-group study of adult patients with COPD (Page 30, 9 Investigational Plan, 091-050.pdf).

The efficacy measurements included serial FEV_1 measurements over time. FEV_1 was collected using serial spirometry at Visit 3 (Week 0), Visit 5 (Week 6), and Visit 7 (Week 12) each over a 24-hour period including the following time points: pre-dosing, immediately post dosing, 15 and 40 minutes post dosing, subsequently, 1, 2, 3, 4, 5, 6, 8, 10, 12, 23, and 24 hours post dosing.

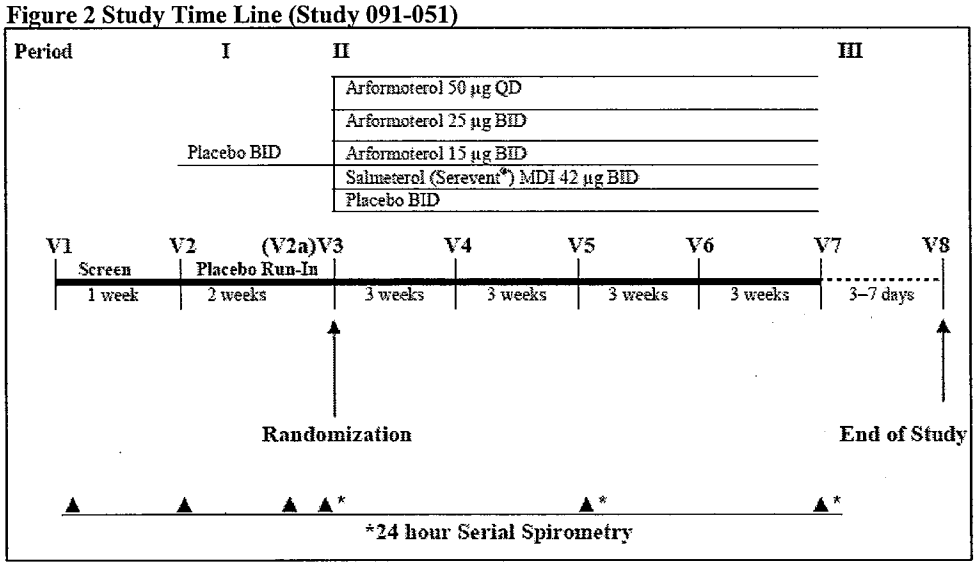
The time lines of the studies are shown in the Figures 1 and 2. The two studies had identical designs.

Figure 1 Study Time Line (Study 091-050)



Source: Page 37, Section 5.1, 091-050.pdf

Figure 2 Study Time Line (Study 091-051)



Source: Page 43, Section 5.1, 091-051.pdf

Because salmeterol is administered via MDI and arformoterol via UDV studies utilized a double-dummy approach in order to maintain the treatment bind, as is indicated in Table 3.

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Table 3 Treatments (Studies 091-050 and 091-051)

TREATMENT ARM	AM TREATMENT		PM TREATMENT	
	UDV	MDI	UDV	MDI
Arformoterol 50 μg QD	Arformoterol 50 μg	placebo	placebo	placebo
Arformoterol 25 μg BID	Arformoterol 25 μg	placebo	Arformoterol 25 μg	placebo
Arformoterol 15 μg BID	Arformoterol 15 μg	placebo	Arformoterol 15 μg	placebo
Salmeterol 42 μg bid	Placebo	Salmeterol 42 μg	placebo	Salmeterol 42 μg
Placebo	Placebo	Placebo	Placebo	Placebo

Certain FEV_1 measurements were pre-specified in the protocol for the primary efficacy evaluation. The trough FEV_1 defined as the FEV_1 at the end of the dosing interval, i.e., 24 hours post dosing for QD regimen and 12 hours post dosing for BID regimen, was chosen in these studies. The pre-dosing FEV_1 before the first study dose was used as the baseline.

The sponsor's primary efficacy analyses were performed based on the percent change in FEV_1 from study baseline FEV_1 to the trough FEV_1, at Week 12 (i.e., the end of the double blind treatment period).

This reviewer's evaluation of the effectiveness of arformoterol is focused on whether the superiority of arformoterol over placebo is demonstrated, based on the sponsor's data. Since no specific safety endpoints or analyses were identified as warranting formal statistical investigation, the drug's safety was not the focus of this review.

Data Source

The sponsor submitted this NDA including the data to the FDA Electronic Document Room (EDR). The submission is recorded in the EDR as indicated in Table 4, below. All the data submitted are in SAS v.5 transport format. The numbers of data files for the pivotal studies are shown in Table 5.

Table 4 Data Source

DOCUMENT 2791353		
Application: N021912	Letter Date: 3-Jan-2006	Stamp Date: 4-Jan-2006
Incoming_Doc_Type: N	Sup_Modification_Type: BZ	In_Doc_Type_Seq_No: 000
Company: SEPRACOR		
Drug: ARFORMOTEROL/TARTRATE		

Source: EDR of FDA

Table 5 Sponsor's Data Location

PATH/LOCATION	NUMBER OF DATA FILES INCLUDED
\\cdsesub1\N21605\N_000\2004-04-30\Clinical Data\091-050\	61
\\cdsesub1\N21605\N_000\2004-04-30\Clinical Data\091-051\	62

STATISTICAL EVALUATION

Evaluation of Efficacy

Study Design and Endpoints

The pivotal studies 091-050 and 091-051 were each a double-blind, double-dummy, randomized, placebo- and active-controlled, multi-center, parallel-group study of adult patients with COPD.

The efficacy measurements included serial FEV_1 measurements over time. FEV_1 was collected using serial spirometry at Visit 3 (Week 0), Visit 5 (Week 6), and Visit 7 (Week 12) each over a 24-hour period including the following time points: pre-dosing, immediately post dosing, 15 and 40 minutes post dosing, 1, 2, 3, 4, 5, 6, 8, 10, 12, 23, and 24 hours post dosing.

Certain FEV_1 measurements were pre-specified in the protocol for the primary efficacy evaluation. The trough FEV_1 defined as the FEV_1 at the end of the dosing interval, i.e., 24 hours post dosing for QD regimen and 12 hours post dosing for BID regimen, was chosen in these studies. The pre-dosing FEV_1 before the first study dose was used as the baseline.

Patient Disposition, Demographic and Baseline Characteristics

This section focuses on descriptions of patient disposition based on status of completion, status of compliance, and reasons for early withdrawal.

Study 091-050

The ITT population was defined in the protocol as including those subjects who were randomized to double-blind treatment, and had taken at least one dose of double-blind study medication. All efficacy analyses (primary, key secondary, and secondary), and safety analyses were performed on the ITT population, according to treatment randomly assigned (page 73, section 9.7.2.1, 091-050.pdf).

Table 6 summarizes the number of randomized patients by ITT status and treatment. The proportions of subjects excluded from the ITT group are low and relatively constant across treatment groups therefore, the study results likely are not substantially biased by these exclusions.

Table 6 Patients' disposition by ITT status and treatment (Study 091-050)

	ITT STATUS				TOTAL	
	NO		YES			
	N	%	N	%	N	%
Placebo UDV BID and Placebo MDI BID	1	0.69	143	99.31	144	100.00
15 mcg BID (R,R)-formoterol and Placebo MDI BID	3	2.08	141	97.92	144	100.00
25 mcg BID (R,R)-formoterol and Placebo MDI BID			143	100.00	143	100.00
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	1	0.68	146	99.32	147	100.00
42 mcg BID Salmeterol MDI and Placebo UDV BID	2	1.37	144	98.63	146	100.00
Total	7	0.97	**717**	99.03	724	100.00

Source: DEMO (all randomized patients)

Table 7 shows tabulations of the ITT patients who were withdrawn from the study early by the reason for early withdrawal. Note that the sponsor grouped the withdrawal reasons into 6 categories. AE was identified as the most common category (about 47%) leading to early withdrawal.

Table 7 Reasons for early withdrawal by treatment and reason of early withdrawal (Study 091-050)

WITHDRAWAL REASON	TREATMENT										TOTAL	
	Placebo UDV BID and Placebo MDI BID		15 mcg BID (R,R)-formoterol and Placebo MDI BID		25 mcg BID (R,R)-formoterol and Placebo MDI BID		50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)		42 mcg BID Salmeterol MDI and Placebo UDV BID			
	N	%	N	%	N	%	N	%	N	%	N	%
AE	14	43.75	8	47.06	17	51.52	9	40.91	13	50.00	61	46.92
Protocol variance	3	9.38	4	23.53	6	18.18	3	13.64	3	11.54	19	14.62
Subject voluntarily withdrew	14	43.75	4	23.53	8	24.24	10	45.45	4	15.38	40	30.77
Lost to follow-up	1	3.13							1	3.85	2	1.54
Does not meet entry criteria			1	5.88	1	3.03			2	7.69	4	3.08
Other					1	3.03			3	11.54	4	3.08
Total	32	100.00	17	100.00	33	100.00	22	100.00	26	100.00	130	100.00

Source: DEMO where ITT='YES' and COMPLETE='NO'

Table 8 shows the overall percentage of the subjects who discontinued early by treatment group.

Table 8 Patients' disposition by completing status and treatment (Study 091-050)

	Completed Study?				Total	
	NO		YES			
	N	%	N	%	N	%
Placebo UDV BID and Placebo MDI BID	32	22.38	111	77.62	143	100.00
15 mcg BID (R,R)-formoterol and Placebo MDI BID	17	12.06	124	87.94	141	100.00
25 mcg BID (R,R)-formoterol and Placebo MDI BID	33	23.08	110	76.92	143	100.00
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	22	15.07	124	84.93	146	100.00
42 mcg BID Salmeterol MDI and Placebo UDV BID	26	18.06	118	81.94	144	100.00
Total	130	18.13	587	81.87	717	100.00

Source: DEMO where ITT='YES'

The overall percentage of subjects who discontinued early was approximately 18% of the total patients. The same percentages across the treatment groups appear to be balanced.

Tables 9 through 11 summarize the patients' demographic characteristics by race, sex, and age, respectively.

Table 9 Number of patients by treatment and race (Study 091-050)

	RACE								TOTAL	
	ASIAN		BLACK		CAUCASIAN		HISPANIC			
	N	%	N	%	N	%	N	%	N	%
Placebo UDV BID and Placebo MDI BID	1	0.70	4	2.80	137	95.80	1	0.70	143	100.00
15 mcg BID (R,R)-formoterol and Placebo MDI BID	1	0.71	6	4.26	132	93.62	2	1.42	141	100.00
25 mcg BID (R,R)-formoterol and Placebo MDI BID			5	3.50	138	96.50			143	100.00
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	1	0.68	3	2.05	140	95.89	2	1.37	146	100.00
42 mcg BID Salmeterol MDI and Placebo UDV BID			7	4.86	133	92.36	4	2.78	144	100.00
Total	3	0.42	25	3.49	680	94.84	9	1.26	717	100.00

Source: DEMO, where ITT='YES'

The proportions of subjects of each race were fairly balanced across treatment groups with nearly all (approximately 95%) of the patients being Caucasian.

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Table 10 Number of patients by treatment and sex (Study 091-050)

	SEX				TOTAL	
	FEMALE		MALE			
	N	%	N	%	N	%
Treatment Placebo UDV BID and Placebo MDI BID	52	36.36	91	63.64	143	100.00
15 mcg BID (R,R)-formoterol and Placebo MDI BID	69	48.94	72	51.06	141	100.00
25 mcg BID (R,R)-formoterol and Placebo MDI BID	62	43.36	81	56.64	143	100.00
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	61	41.78	85	58.22	146	100.00
42 mcg BID Salmeterol MDI and Placebo UDV BID	57	39.58	87	60.42	144	100.00
Total	301	41.98	416	58.02	717	100.00

Source: DEMO, where ITT='YES'

The proportions of subjects of each gender were fairly balanced across treatment groups with approximately 40% of the patients being female and 60% being male.

Table 11 Patient-age distributions (Study 091-050)

TREATMENT	#PATIENTS	MEAN	STD	MIN	MAX	RANGE	LOWER QUARTILE	MEDIAN	UPPER QUARTILE
Placebo UDV BID and Placebo MDI BID	143	63.11	8.40	40.00	83.00	43.00	58.50	64.00	69.00
15 mcg BID (R,R)-formoterol and Placebo MDI BID	141	62.04	9.08	34.00	78.00	44.00	56.00	62.50	70.00
25 mcg BID (R,R)-formoterol and Placebo MDI BID	143	63.52	9.16	40.00	84.00	44.00	57.00	63.00	71.00
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	146	62.38	9.37	35.00	82.00	47.00	56.00	64.00	70.00
42 mcg BID Salmeterol MDI and Placebo UDV BID	144	63.42	8.81	37.00	82.00	45.00	58.00	63.50	70.00
Overall	717	62.89	8.97	34.00	84.00	50.00	57.00	63.00	70.00

Source: DEMO, where ITT='YES'

The means (and standard deviations) of the age of subjects in each treatment group were fairly similar with the overall mean age of subjects in the study being approximately 63 years (and standard deviation of approximately 9 years).

Table 12 summarizes the patients' baseline FEV_1 by treatment group.

Table 12 Baseline mean and std. FEV_1 (Study 091-050)

TREATMENT	#PATIENTS	MEAN	STD
Placebo UDV BID and Placebo MDI BID	143	1.20	0.48
15 mcg BID (R,R)-formoterol and Placebo MDI BID	140	1.15	0.47
25 mcg BID (R,R)-formoterol and Placebo MDI BID	143	1.13	0.51
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	144	1.22	0.42
42 mcg BID Salmeterol MDI and Placebo UDV BID	142	1.22	0.46

Source: DEMO and KOKOSPIRDATA_BASELINE, where baseline FEV_1 values are non-missing

The baseline average FEV_1 appeared to be balanced across treatment groups.

Study 091-051

The ITT population was defined in the protocol as including those subjects who were randomized to double-blind treatment, and had taken at least one dose of double-blind study medication. All efficacy analyses (primary, key secondary, and secondary), and safety analyses were performed on the ITT population, according to treatment randomly assigned (page 75, section 9.7.2.1, 091-051.pdf).

Table 13 summarizes the number of randomized patients by ITT status and treatment. The proportions of subjects excluded from the ITT group are low and relatively constant across treatment groups therefore, the study results likely are not substantially biased by these exclusions.

Table 13 Patients' disposition by ITT status and treatment (Study 091-051)

	ITT STATUS				TOTAL	
	NO		YES			
	N	%	N	%	N	%
Placebo UDV BID and Placebo MDI BID			150	100.00	150	100.00
15 mcg BID (R,R)-formoterol and Placebo MDI BID	1	0.68	147	99.32	148	100.00
25 mcg BID (R,R)-formoterol and Placebo MDI BID			149	100.00	149	100.00
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)			147	100.00	147	100.00
42 mcg BID Salmeterol MDI and Placebo UDV BID	1	0.68	146	99.32	147	100.00
Total	2	0.27	739	99.73	741	100.00

Source: DEMO (all randomized patients)

Table 14 shows tabulations of the ITT patients who were withdrawn from the study early by the reasons for early withdrawal. Note that the sponsor grouped withdrawal reasons

into 6 categories. AE was identified as the most common category (about 49%) leading to early withdrawal.

Table 14 Reasons for early withdrawal by treatment and reason of early withdrawal (Study 091-051)

WITHDRAWAL REASON	TREATMENT										TOTAL	
	Placebo UDV BID and Placebo MDI BID		15 mcg BID (R,R)-formoterol and Placebo MDI BID		25 mcg BID (R,R)-formoterol and Placebo MDI BID		50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)		42 mcg BID Salmeterol MDI and Placebo UDV BID			
	N	%	N	%	N	%	N	%	N	%	N	%
AE	13	40.63	15	40.54	19	54.29	16	61.54	9	50.00	72	48.65
Protocol variance	3	9.38	5	13.51	3	8.57	2	7.69			13	8.78
Subject voluntarily withdrew	10	31.25	11	29.73	5	14.29	5	19.23	3	16.67	34	22.97
Lost to follow-up	1	3.13	1	2.70	2	5.71			1	5.56	5	3.38
Does not meet entry criteria			2	5.41	1	2.86			1	5.56	4	2.70
Other	5	15.63	3	8.11	5	14.29	3	11.54	4	22.22	20	13.51
Total	32	100.00	37	100.00	35	100.00	26	100.00	18	100.00	148	100.00

Source: DEMO where ITT='YES' and COMPLETE='NO'. There are 144 distinct reasons for dropout.

Table 15 shows the overall percentages of the subjects who discontinued early by treatment group.

Table 15 Patients' disposition by completing status and treatment (Study 091-051)

	COMPLETED STUDY?				TOTAL	
	NO		YES			
Treatment	N	%	N	%	N	%
Placebo UDV BID and Placebo MDI BID	32	21.33	118	78.67	150	100.00
15 mcg BID (R,R)-formoterol and Placebo MDI BID	37	25.17	110	74.83	147	100.00
25 mcg BID (R,R)-formoterol and Placebo MDI BID	35	23.49	114	76.51	149	100.00
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	26	17.69	121	82.31	147	100.00
42 mcg BID Salmeterol MDI and Placebo UDV BID	18	12.33	128	87.67	146	100.00
Total	148	20.03	591	79.97	739	100.00

Source: DEMO where ITT='YES'

The overall percentage of subjects who discontinued early was approximately 20% of the total patients. The percentages of discontinued patients in the following treatment groups appear to be lower than those in the other groups: Arformoterol 50 mcg QD and Placebo. This imbalance should be kept in mind in the interpretation of the by-treatment-group efficacy comparisons.

Tables 16 through 18 summarize the patients' demographic characteristics by race, sex, and age, respectively.

Table 16 Number of patients by treatment and race (Study 091-051)

	RACE										TOTAL	
	ASIAN		BLACK		CAUCASIAN		HISPANIC		OTHER			
Treatment	N	%	N	%	N	%	N	%	N	%	N	%
Placebo UDV BID and Placebo MDI BID	1	0.67	2	1.33	146	97.33			1	0.67	150	100.00
15 mcg BID (R,R)-formoterol and Placebo MDI BID			8	5.44	138	93.88	1	0.68			147	100.00
25 mcg BID (R,R)-formoterol and Placebo MDI BID	2	1.34	4	2.68	142	95.30			1	0.67	149	100.00
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	1	0.68	6	4.08	139	94.56			1	0.68	147	100.00
42 mcg BID Salmeterol MDI and Placebo UDV BID	3	2.05	4	2.74	138	94.52			1	0.68	146	100.00
Total	7	0.95	24	3.25	703	95.13	1	0.14	4	0.54	739	100.00

Source: DEMO, where ITT='YES'

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The proportions of subjects of each race were fairly balanced across treatment groups with nearly all (approximately 95%) of the patients being Caucasian.

Table 17 Number of patients by treatment and sex (Study 091-051)

	SEX				TOTAL	
	FEMALE		MALE			
Treatment	N	%	N	%	N	%
Placebo UDV BID and Placebo MDI BID	64	42.67	86	57.33	150	100.00
15 mcg BID (R,R)-formoterol and Placebo MDI BID	53	36.05	94	63.95	147	100.00
25 mcg BID (R,R)-formoterol and Placebo MDI BID	55	36.91	94	63.09	149	100.00
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	60	40.82	87	59.18	147	100.00
42 mcg BID Salmeterol MDI and Placebo UDV BID	63	43.15	83	56.85	146	100.00
Total	295	39.92	444	60.08	739	100.00

Source: DEMO, where ITT='YES'

The proportions of subjects of each gender were fairly balanced across treatment groups with approximately 40% of the patients being female and 60% being male.

Table 18 Patient-age distributions (Study 091-051)

TREATMENT	#PATIENTS	MEAN	STD	MIN	MAX	RANGE	LOWER QUARTILE	MEDIAN	UPPER QUARTILE
Placebo UDV BID and Placebo MDI BID	150	63.30	9.40	41.00	89.00	48.00	57.00	64.00	69.00
15 mcg BID (R,R)-formoterol and Placebo MDI BID	147	63.24	8.69	43.00	80.00	37.00	57.00	64.00	70.00
25 mcg BID (R,R)-formoterol and Placebo MDI BID	149	63.69	9.45	40.00	82.00	42.00	57.00	64.00	70.00
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	147	62.07	9.72	38.00	84.00	46.00	55.00	62.00	69.00
42 mcg BID Salmeterol MDI and Placebo UDV BID	146	62.27	8.72	42.00	82.00	40.00	57.00	63.00	68.00
Overall	739	62.92	9.20	38.00	89.00	51.00	56.00	64.00	69.00

Source: DEMO, where ITT='YES'

The means (and standard deviations) of the age of subjects in each treatment group were fairly similar with the overall mean age of subjects in the study being approximately 63 years (and standard deviation of approximately 9 years).

Table 19 summarizes the patients' baseline FEV_1 by treatment group.

Table 19 Baseline mean and std. FEV_1 (Study 091-051)

TREATMENT	#PATIENTS	MEAN	STD
Placebo UDV BID and Placebo MDI BID	149	1.21	0.45
15 mcg BID (R,R)-formoterol and Placebo MDI BID	143	1.21	0.51
25 mcg BID (R,R)-formoterol and Placebo MDI BID	145	1.19	0.48
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	142	1.16	0.41
42 mcg BID Salmeterol MDI and Placebo UDV BID	144	1.21	0.48

Source: DEMO and KOKOSPIRDATA_BASELINE, where baseline FEV_1 values are non-missing

The baseline average FEV_1 appeared to be balanced across treatment groups.

Statistical Methodologies

Studies 091-050 and 091-051

Detailed descriptions of the statistical method specified in the protocol and applied by the sponsor for the primary efficacy analysis are directly quoted from the application:

> "The analysis of the primary efficacy endpoint was performed on the ITT population and utilized SAS/PROC MIXED with restricted maximum likelihood estimation to fit a repeated measures linear model with fixed effects for treatment, time (Visits 3, 5, and 7 [Weeks 0, 6, and 12]), treatment-by-time interaction, and site type, with baseline FEV_1 as a covariate, and treatment-by-baseline-FEV_1 interaction. An unstructured, first-order autoregressive or compound symmetric within-subject covariance matrix, whichever provided the best fit to the data according to Akaike's Information Criterion, was employed. For tests of fixed effects, the Kenward and Roger correction for denominator degrees of freedom, standard errors, and test statistics, were utilized. Employing a Bonferroni adjustment, the primary analysis consisted of a comparison of the percent change from study baseline at 24 hours postdose for the 50 µg QD dose of arformoterol versus placebo (tested at the 0.0250 level), and two comparisons of the percent change from study baseline at 12 hours post second dose for each BID dose of arformoterol versus placebo (tested at the 0.0125 level) (page 75, section 9.7. 2.7 Analysis of Efficacy, 091-050.pdf)." The identical method was applied for Study 090-051 and can be found on page 77, section 9.7. 2.7 Analysis of Efficacy, 091-051.pdf.

In order to verify the sponsor's statistical findings, this reviewer used repeated measures analysis of the primary efficacy variable (percent change from study baseline in FEV_1 to the end of the dosing interval) assuming an unstructured variance-covariance matrix for the model. This analysis used all available ITT-patient data. The statistical model included effects of treatment, center, visit as time factor, and baseline FEV_1 as a covariate. To adjust for multiplicity, Bonferroni approach was used.

Statistical Analyses

The main focus of this reviewer's statistical analysis is first to confirm the sponsor's analyses and second to assess the robustness of the conclusions of the sponsor's analyses utilizing a simpler statistical approach. In the following text when quoting the sponsor's analyses, treatment codes, 1 through 5, represent arformoterol 15, 25 mcg BID, 50 mcg QD, and salmeterol 42 mcg BID, respectively.

Study 091-050

Verification of Sponsor's Statistical Analysis

The following tables were generated from a reviewer's analysis utilizing mainly the following SAS data sets from the submission: `base_f.sas7bdat` and `kokospir.sas7bdat`. The sponsor's SAS program `mixed.sas` was edited by this reviewer in order to reproduce the statistical analysis results. As originally written, this program excluded certain ITT patients from the analysis. The sponsor included patients under the following restrictions:

```
where &var ne . and visit in ('VIS03','VIS05','VIS07')
and interval = '24' and ko_6ipal ne 1;
```

This set of restriction means that only those who had non-missing percent change from baseline in FEV_1, had 24-hour post dose data and did not have any ipratropium use within 6 hours after taking the test drug were included in the analysis. Under such restriction, the actual number of patients included in the statistical analysis was 695 rather than 717 total ITT patients.

The results of this analysis are contained in Tables 20 through 22.

In Table 20, the sponsor's variable for the treatment arms is TRTSRT_F, valued 1 through 5, representing placebo, arf 15, 25, and 50 μg QD; and salmeterol 42 μg BID, respectively. Variable, vis, stands for visit, basevar for baseline FEV_1, and prcstrat for random stratum site type. The variable definitions were specified by the sponsor in define.pdf.

Appears This Way
On Original

All active treatments in Table 22 are shown to be superior to placebo. The differences among the active treatments are insignificant. The primary efficacy comparisons (i.e., comparisons of each dose of arformoterol to placebo) are shown in the shaded region.

Reviewer's Statistical Analysis

The following analysis uses all available ITT patient records. A simple statistical model is used by this reviewer to access the robustness of the conclusions of the more complicated (and therefore more assumption driven) analysis specified in the protocol. This repeated measures model includes effects of treatment, visit, and baseline FEV_1 as a covariate with the response variable being the percent change from baseline to the end of the dosing interval in FEV_1 over the 12 week treatment period and assuming an unstructured variance-covariance matrix. A total of 706 patients were included in the following analysis.

The results of this analysis are contained in Tables 23 through 25 and Figure 3.

Table 23 Test of effects in the model (Study 091-050)

TYPE 3 TESTS OF FIXED EFFECTS				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	4	642	13.19	<0.0001
CENTER	59	648	1.30	0.0719
VISIT	2	595	36.95	<0.0001
KO_BLFEV	1	651	70.68	<0.0001

Source: kokospirdata8

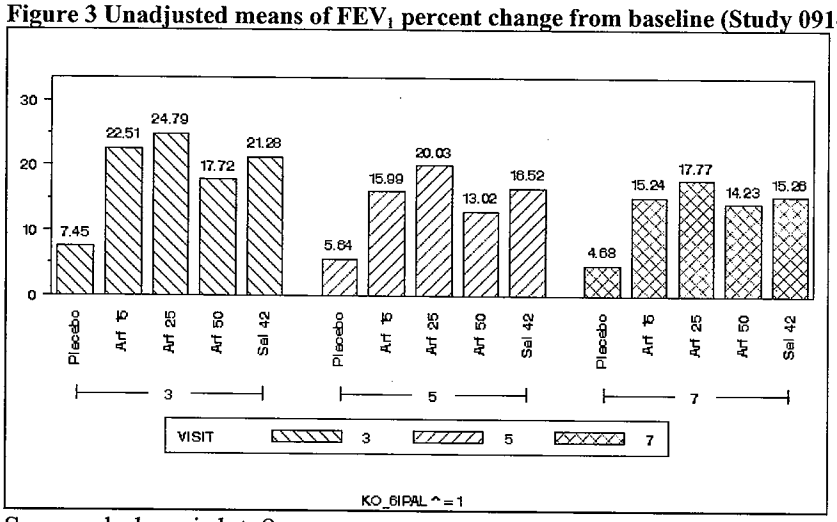
As shown in Table 23, this analysis shows that the center effect is not significant but treatment and baseline remain important predictors of outcome.

Table 24 LS-means of FEV_1 percent change from baseline (Study 091-050)

TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > |T|
Placebo UDV BID and Placebo MDI BID	6.7946	1.6798	664	4.04	<0.0001
15 mcg BID (R,R)-formoterol and Placebo MDI BID	19.3053	1.6604	643	11.63	<0.0001
25 mcg BID (R,R)-formoterol and Placebo MDI BID	20.9000	1.6406	664	12.74	<0.0001
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	16.4200	1.6454	647	9.98	<0.0001
42 mcg BID Salmeterol MDI and Placebo UDV BID	19.8966	1.6702	654	11.91	<0.0001

Source: kokospirdata8

Figure 3 Unadjusted means of FEV_1 percent change from baseline (Study 091-050)



Source: kokospirdata8

Table 25 Differences in LS-means of FEV_1 percent change from baseline (Study 091-050)

TREATMENT	TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > |T|
Placebo UDV BID and Placebo MDI BID	15 mcg BID (R,R)-formoterol and Placebo MDI BID	-12.5107	2.2314	644	-5.61	<0.0001
Placebo UDV BID and Placebo MDI BID	25 mcg BID (R,R)-formoterol and Placebo MDI BID	-14.1054	2.2412	650	-6.29	<0.0001
Placebo UDV BID and Placebo MDI BID	50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	-9.6253	2.2095	644	-4.36	<0.0001
Placebo UDV BID and Placebo MDI BID	42 mcg BID Salmeterol MDI and Placebo UDV BID	-13.1020	2.2323	642	-5.87	<0.0001
15 mcg BID (R,R)-formoterol and Placebo MDI BID	25 mcg BID (R,R)-formoterol and Placebo MDI BID	-1.5947	2.2097	643	-0.72	0.4707
15 mcg BID (R,R)-formoterol and Placebo MDI BID	50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	2.8854	2.1863	635	1.32	0.1874
15 mcg BID (R,R)-formoterol and Placebo MDI BID	42 mcg BID Salmeterol MDI and Placebo UDV BID	-0.5913	2.2290	637	-0.27	0.7909
25 mcg BID (R,R)-formoterol and Placebo MDI BID	50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	4.4800	2.2052	643	2.03	0.0426
25 mcg BID (R,R)-formoterol and Placebo MDI BID	42 mcg BID Salmeterol MDI and Placebo UDV BID	1.0034	2.2187	646	0.45	0.6512
50 mcg QD (R,R)-formoterol and Placebo	42 mcg BID Salmeterol MDI and Placebo UDV	-3.4766	2.2023	640	-1.58	0.1149

TREATMENT	TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > |T|
MDI (AM) / Placebo UDV and Placebo MDI (PM)	BID					

Source: kokospirdata8

All active treatments in Table 25 are shown to be superior to placebo. The primary efficacy comparisons (i.e., comparisons of each dose of arformoterol to placebo) are shown in the shaded region. The differences among the active treatments are insignificant. Here this reviewer applied a slightly different but less assumption dependent model to fit the data. The results prove to be consistent with the sponsor's findings.

Study 091-051

Verification of Sponsor's Statistical Analysis

The following tables were generated from a reviewer's analysis utilizing mainly the following SAS data sets from the submission: `base_f.sas7bdat` and `kokospir.sas7bdat`. The sponsor's SAS program mixed.sas was edited to produce the primary statistical analysis. As originally written, this program excluded certain ITT patients from the analysis. The sponsor included patients under the following restrictions:

```
where &var ne . and visit in ('VIS03','VIS05','VIS07') and
interval = '24' and ko_6ipal ne 1;
```

This means that only those who had non-missing percent change from baseline in FEV_1 and had 24-hour post dose data and ipratropium use must not be within 6 hours after taking the test drug were included in the analysis. Under such restriction, the actual number of patients included in the primary analysis was 710 rather than 739 total ITT patients.

The results of this analysis are contained in Tables 26 through 28.

In Table 26, the sponsor's variable for the treatment arms is TRTSRT_F, valued 1 through 5, representing placebo, arf 15, 25, and 50 μg QD; and salmeterol 42 μg BID, respectively. Variable, vis, stands for visit, basevar for baseline FEV_1, and prcstrat for random stratum site type. The variable definitions were specified by the sponsor in define.pdf.

All active treatments in Table 28 are shown to be superior to placebo. The differences among the active treatments are insignificant, except for the difference between the 15 and 25 μg arformoterol groups (P=0.01). The primary efficacy comparisons (i.e., comparisons of each dose of arformoterol to placebo) are shown in the shaded region.

Reviewer's Statistical Analysis

The following analysis uses all available ITT patient records. A simple statistical model is used by this reviewer to access the robustness of the conclusions of the more complicated (and therefore more assumption driven) analysis specified in the protocol. This repeated measures model includes effects of treatment, visit, and baseline FEV_1 as the covariate with the response variable being the percent change from baseline to the end of the dosing interval in FEV_1 over the 12 weeks treatment period and assuming an unstructured variance-covariance matrix. A total of 710 patients were included in the following analysis.

The results of this analysis are contained in Tables 29 through 31 and Figure 4.

Table 29 Test of effects in the model (Study 091-051)

TYPE 3 TESTS OF FIXED EFFECTS				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	4	642	14.71	<0.0001
CENTER	63	651	1.58	0.0040
VISIT	2	612	22.87	<0.0001
KO_BLFEV	1	646	86.47	<0.0001

Source: kokospirdata8

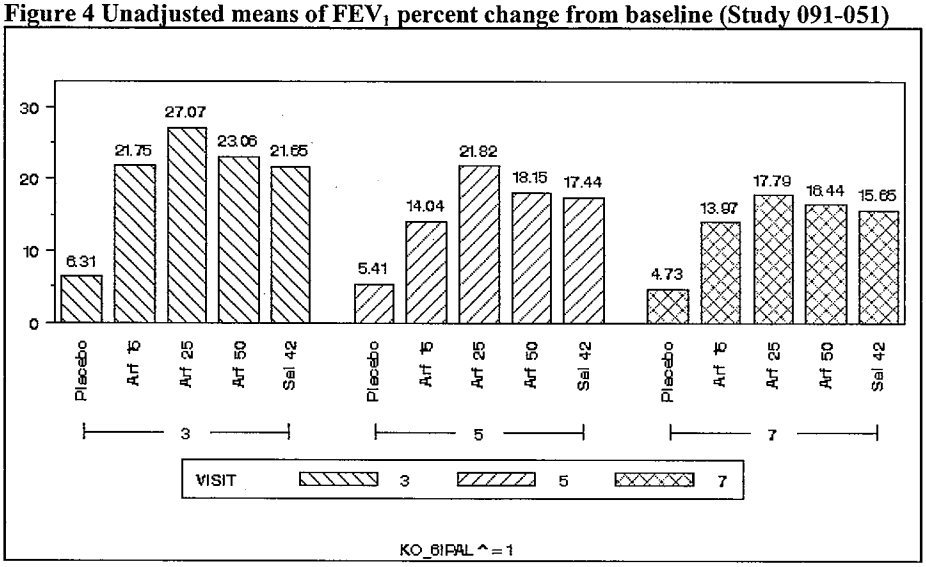
As shown in Table 29, this analysis shows that the center effect is not significant but treatment and baseline remain important predictors of outcome.

Table 30 LS-means in FEV_1 percent change from baseline (Study 091-051)

TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > |T|
Placebo UDV BID and Placebo MDI BID	6.8481	1.7025	666	4.02	<0.0001
15 mcg BID (R,R)-formoterol and Placebo MDI BID	17.7605	1.7274	679	10.28	<0.0001
25 mcg BID (R,R)-formoterol and Placebo MDI BID	22.5045	1.6387	661	13.73	<0.0001
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	18.4108	1.7232	657	10.68	<0.0001
42 mcg BID Salmeterol MDI and Placebo UDV BID	19.0423	1.7431	653	10.92	<0.0001

Source: kokospirdata8

Figure 4 Unadjusted means of FEV_1 percent change from baseline (Study 091-051)



Source: kokospirdata8

Table 31 Differences in FEV_1 percent change from baseline (Study 091-051)

TREATMENT	TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > |T|
Placebo UDV BID and Placebo MDI BID	15 mcg BID (R,R)-formoterol and Placebo MDI BID	-10.9124	2.2388	649	-4.87	<0.0001
Placebo UDV BID and Placebo MDI BID	25 mcg BID (R,R)-formoterol and Placebo MDI BID	-15.6564	2.1767	638	-7.19	<0.0001
Placebo UDV BID and Placebo MDI BID	50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	-11.5627	2.2233	644	-5.20	<0.0001
Placebo UDV BID and Placebo MDI BID	42 mcg BID Salmeterol MDI and Placebo UDV BID	-12.1942	2.1855	640	-5.58	<0.0001
15 mcg BID (R,R)-formoterol and Placebo MDI BID	25 mcg BID (R,R)-formoterol and Placebo MDI BID	-4.7440	2.2191	643	-2.14	0.0329
15 mcg BID (R,R)-formoterol and Placebo MDI BID	50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	-0.6503	2.2357	648	-0.29	0.7712
15 mcg BID (R,R)-formoterol and Placebo MDI BID	42 mcg BID Salmeterol MDI and Placebo UDV BID	-1.2818	2.2497	644	-0.57	0.5691
25 mcg BID (R,R)-formoterol and Placebo MDI BID	50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	4.0937	2.2095	637	1.85	0.0644
25 mcg BID (R,R)-formoterol and Placebo MDI BID	42 mcg BID Salmeterol MDI and Placebo UDV BID	3.4622	2.1964	634	1.58	0.1154

TREATMENT	TREATMENT	ESTIMATE	STANDARD ERROR	DF	T VALUE	PR > |T|
50 mcg QD (R,R)-formoterol and Placebo MDI (AM) / Placebo UDV and Placebo MDI (PM)	42 mcg BID Salmeterol MDI and Placebo UDV BID	-0.6314	2.2116	640	-0.29	0.7753

Source: kokospirdata8

All active treatments in 31 are shown to be superior to placebo. The primary efficacy comparisons (i.e., comparisons of each dose of arformoterol to placebo) are shown in the shaded region. The differences among the active treatments are insignificant, except for the difference between the 15 and 25 μg groups (P=0.03). Here this reviewer applied a slightly different but less assumption dependent model to fit the data. The results prove to be consistent with the sponsor's findings.

Results and Conclusions

Table 32 shows the LS-means of percent changes from study baseline in FEV_1 to the end of dosing interval (i.e., the primary efficacy endpoint) for each treatment group and the differences in LS means between the active treatments and placebo. As shown in Table 33, the values for active treatments are consistently statistically significantly greater than that of placebo ($p<0.0001$ for all comparisons in both studies).

As might have been expected, the LS-mean of 50 mcg QD regimen is numerically lower than that of the 25 mcg BID, though the daily doses are the same. The LS-mean of the salmeterol group is numerically similar with that of the arformoterol groups; however, formal non-inferiority testing of these groups was not planned a priori.

Table 32 LS-means of percent change from study baseline in FEV_1 to the end of dosing interval (Studies 091-050 and 091-051)

Treatment	Study 091-050		Study 091-051	
	Ls-means	Diff. from placebo	Ls-means	Diff. from placebo
Placebo	6.7946		6.8481	
15 mcg BID arformoterol	19.3053	-12.5107	17.7605	-10.9124
25 mcg BID arformoterol	20.9000	-14.1054	22.5045	-15.6564
50 mcg QD arformoterol	16.4200	-9.6253	18.4108	-11.5627
42 mcg BID Salmeterol	19.8966	-13.1020	19.0423	-12.1942

Source: kokospirdata8

Table 33 Efficacy findings based on 12-week percent change from baseline to trough FEV_1 (Studies 091-050 and 091-051 compared)

Comparison		091-050	091-051	Findings consistently positive
15 mcg BID arformoterol	Vs. Placebo	<0.0001	<0.0001	Yes
25 mcg BID arformoterol		<0.0001	<0.0001	Yes
50 mcg QD arformoterol		<0.0001	<0.0001	Yes
42 mcg BID Salmeterol		<0.0001	<0.0001	Yes

Source: kokospirdata8

Having evaluated the sponsor's efficacy analyses of the effect on FEV_1 over 12 weeks of treatment among the following treatment groups: arformoterol 50 μg QD, arformoterol 25 μg BID, arformoterol 15 μg BID, salmeterol metered-dose inhaler (MDI) 42 μg BID, and placebo; this reviewer concludes that the statistical superiority of arformoterol compared to placebo in terms of percent change in FEV_1 from baseline to the end of the dosing interval over 12 weeks of treatment has been established.

SUMMARY AND CONCLUSIONS

Statistical Issues and Collective Evidence

Table 34 shows the LS-means of percent change from study baseline in FEV_1 to the end of dosing interval (i.e., the primary efficacy endpoint) for each treatment group and the differences in LS means between the active treatments and placebo for both studies.

Table 34 LS-means of percent change from study baseline in FEV_1 to the end of dosing interval (Studies 091-050 and 091-051)

Treatment	Study 091-050		Study 091-051	
	Ls-means	Diff. from placebo	Ls-means	Diff. from placebo
Placebo	6.7946		6.8481	
15 mcg BID arformoterol	19.3053	-12.5107	17.7605	-10.9124
25 mcg BID arformoterol	20.9000	-14.1054	22.5045	-15.6564
50 mcg QD arformoterol	16.4200	-9.6253	18.4108	-11.5627
42 mcg BID Salmeterol	19.8966	-13.1020	19.0423	-12.1942

Source: kokospirdata8

As shown in Table 35, the values for active treatments are consistently statistically significantly greater than that of placebo ($p<0.0001$ for all comparisons in both studies).

As might have been expected, the LS-mean of 50 mcg QD regimen is numerically lower than that of the 25 mcg BID, though the daily doses are the same. The LS-mean of the salmeterol group is numerically similar with that of the arformoterol groups; however, formal non-inferiority testing of these groups was not planned a priori.

Table 35 Efficacy findings based on 12-week percent change from baseline to trough FEV_1 (Studies 091-050 and 091-051 compared)

Comparison		091-050	091-051	Findings consistently positive
15 mcg BID arformoterol	Vs. Placebo	<0.0001	<0.0001	Yes
25 mcg BID arformoterol		<0.0001	<0.0001	Yes
50 mcg QD arformoterol		<0.0001	<0.0001	Yes
42 mcg BID Salmeterol		<0.0001	<0.0001	Yes

Source: kokospirdata8

Comments on Labeling

This reviewer evaluated the **Clinical Trials** subsection of the proposed labeling in **Proposed Labeling Text** section of the NDA submission for accuracy. In general, this reviewer agrees with the sponsor on the efficacy claims for arformoterol.

Conclusions and Recommendations

Efficacy Conclusions:

This reviewer evaluated the sponsor's efficacy analyses of the effect on FEV_1 over 12 weeks of treatment among the following treatment groups: arformoterol 50 μg QD, arformoterol 25 μg BID, arformoterol 15 μg BID, salmeterol metered-dose inhaler (MDI) 42 μg BID, and placebo. All three dose groups of arformoterol and the comparator, salmeterol, were demonstrated to be statistically superior to placebo in terms of the primary efficacy endpoint in both studies.

Recommendations:

Since from a statistical perspective, arformoterol has been proven to be efficacious compared with placebo, this reviewer recommends the approval of arformoterol based on the efficacy evaluation of the sponsor's data in Studies 091-050 and 091-051.

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

/s/

Ted Guo
8/11/2006 11:31:04 AM
BIOMETRICS
Stats review

Ruth Davi
8/11/2006 11:35:27 AM
BIOMETRICS

About this addendum

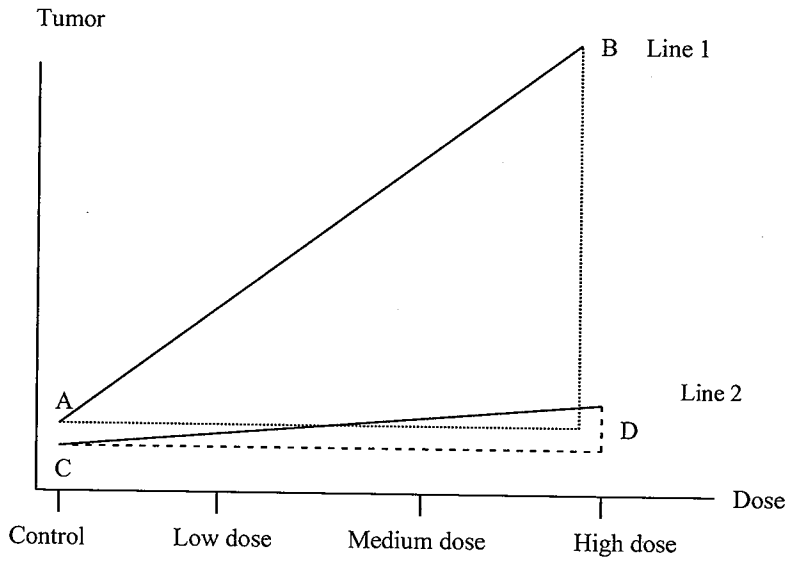
Included in this addendum are analyses consisting of pairwise comparisons between selected groups upon demands from the pharmtox reviewer. This reviewer considers these analyses to be exploratory on-demand analyses. Caution: Incorrect interpretation of the findings in this report could result in misleading conclusions.

The rationale for these additional statistical analyses is understood by this reviewer to be the following: If a statistically significant dose-tumor linear trend has been discovered for a particular tumor type, then we want to find out the minimal toxic dose that is responsible for causing the tumor using the method of pairwise comparison.

This reviewer would argue that the discovery a statistically significant dose-tumor linear trend may not automatically lead to the discovery of a statistically significant pairwise comparison.

Here is simple illustration to explain why this could be the case.

Figure 1 Illustration of dose-tumor linear trend



In this graph, both lines, AB and CD, show significant dose-tumor linear trends, because the dose-tumor relationship is seen to form a straightly line. The pairwise comparison between, say, the high and control is represented by the vertical distance between the incidence rates at points A and B (or at points C and D). It is clearly shown that Line 1 represents a significant pairwise difference between the high and control group, while Line 2 does not, even though both lines represent a significant dose-tumor linear trend.

With this simple illustration in mind, this reviewer can further show this is the case through the following analyses.

Additional Analyses

Dr. Ching-Long Sun and Dr. Timothy Robison requested that pairwise comparisons be made for the tumor types showing significant dose-response relationships (trends). This report serves as an addendum to the statistical review of carcinogenicity dated 5/24/06.

Table 1, below, shows the tumor types with significant findings. This table also can be found in the executive summary of the statistical review.

Table 1 Statistical findings on dose-tumor linear trend based on decision rules of the Office of Biostatistics at CDER

Analysis consideration	Sex	Dose (mg/kg/day)	Organ	Tumor	P-value
Analysis by protocol: Organs and tumors analyzed as reported	Male	Ctrl_2, 40, 100, 200	Soft tissue (THO)	malignant liposarcoma	0.0237
	Female	Ctrl_2, 40, 200		None	
Exploratory analysis: Selected organs or tumors combined (The combining is denoted by the symbol +)	Male	Ctrl_1, Ctrl_2, 40, 100, 200, 400		None	
		Ctrl_1, Ctrl_2, 40, 100, 200	Soft Tissue (THO)	Malignant liposarcoma	0.0085
	Female	Ctrl_1, Ctrl_2, 40, 100, 200, 400	Skin	Fibroma +Fibrosarcoma	0.0219
		Ctrl_1, Ctrl_2, 40, 100, 200	Thyroid glands	Adenoma, c-cell +Adenoma, c-cell, multiple + Carcinoma, c-cell	0.001

The following tables report results from pairwise comparisons for each of the significant findings in the trend test.

Pairwise comparisons for significant finding in male rats:

Ctrl_2, 40, 100, 200	Soft tissue (THO)	malignant liposarcoma	P=0.0237

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR2 0 MG	200 MG	P-VALUE (EXACT METHOD)
SH	SOFT TISSUE-THO	HP026004	#M LIPOSARCOMA	0	2	0.2179

Source data: R4M21912

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR2 0 MG	100 MG	P-VALUE (EXACT METHOD)
SH	SOFT TISSUE-THO	HP026004	#M LIPOSARCOMA	0	1	0.4815

Source data: R4M21912

Pairwise comparisons for significant finding in male rats:

Ctrl_1, Ctrl_2, 40, 100, 200	Soft Tissue (THO)	Malignant liposarcoma	P=0.0085

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1 0 MG	CTR2 0 MG	200 MG	P-VALUE (EXACT METHOD)
SH	SOFT TISSUE-THO	HP072001	#M LIPOSARCOMA	0	0	2	0.0959

Source data: R8M21912

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1 0 MG	CTR2 0 MG	100 MG	P-VALUE (EXACT METHOD)
SH	SOFT TISSUE-THO	HP072001	#M LIPOSARCOMA	0	0	1	0.3238

Source data: R8M21912

Pairwise comparisons for significant finding in male rats:

Ctrl_1, Ctrl_2, 40, 100, 200, 400	Skin	Fibroma + Fibrosarcoma	P=0.0219

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1 0 MG	CTR2 0 MG	400 MG	P-VALUE (EXACT METHOD)
SK	SKIN	HP046003	Fibroma +Fibrosarcoma	0	1	3	0.0730

Source data: R8F21912

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1 0 MG	CTR2 0 MG	200 MG	P-VALUE (EXACT METHOD)
SK	SKIN	HP046003	Fibroma +Fibrosarcoma	0	1	1	0.5578

Source data: R8F21912

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1 0 MG	CTR2 0 MG	100 MG	P-VALUE (EXACT METHOD)
SK	SKIN	HP046003	Fibroma +Fibrosarcoma	0	1	1	0.5321

Source data: R8F21912

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1 0 MG	CTR2 0 MG	40MG	P-VALUE (EXACT METHOD)
SK	SKIN	HP046003	Fibroma +Fibrosarcoma	0	1	1	0.5210

Source data: R8F21912

Pairwise comparisons for significant finding in male rats:

Ctrl_1, Ctrl_2, 40, 100, 200	Thyroid glands	Adenoma, c-cell +Adenoma, c-cell, multiple + Carcinoma, c-cell	P=0.001

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1 0 MG	CTR2 0 MG	200 MG	P-VALUE (EXACT METHOD)
TG	THYROID GLANDS	HP053001	Adenoma, c-cell +Adenoma, c-cell, multiple + Carcinoma, c-cell	2	4	11	0.0054

Source data: R8F21912

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1 0 MG	CTR2 0 MG	100 MG	P-VALUE (EXACT METHOD)
TG	THYROID GLANDS	HP053001	Adenoma, c-cell +Adenoma, c-cell, multiple + Carcinoma, c-cell	2	4	9	0.0147

Source data: R8F21912

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1 0 MG	CTR2 0 MG	40 MG	P-VALUE (EXACT METHOD)
TG	THYROID GLANDS	HP053001	Adenoma, c-cell +Adenoma, c-cell, multiple + Carcinoma, c-cell	2	4	3	0.6041

Source data: R8F21912

Pairwise comparisons in incidences between the control group(s) and each of the treated groups selected by the reviewing pharmacologists for the trend tests are tested at 0.05 and 0.01, respectively, for rare and common tumors. Results (based on the exact p-values) of

the above pairwise comparisons show that there is no significant positive difference between the control group(s) and each of the selected treated groups for the tumors tested except the combination of c-cell adenoma + c-cell adenoma (multiple) + c-cell carcinoma of thyroid glands in male rats. The numbers of tumor bearing animals are 6 and 11 for the combined control and the 200 mg/kg groups, respectively. The exact p-value of the pairwise comparison is 0.0054.

The above non-significant results of pairwise comparison tests for the tumor types showing significant trends in incidences can be used to explain the inappropriateness to use the pairwise comparison tests after trend tests to locate the lowest toxic dose. Except the combination of c-cell adenoma + c-cell adenoma (multiple) + c-cell carcinoma of thyroid glands in male rats, the pairwise comparisons between the control group(s) and each of the selected treated groups are not significant in all the tumor types showing significant positive trends. With the intended use of pairwise comparisons to locate the lowest toxic dose, the pairwise comparisons tell us that none of the doses used in the trend test is the lowest toxic dose. It seems it is a contradiction between the results of the trend tests and of the comparison tests. Actually, it is not a contradiction. It is rather an issue involving the false positive error and false negative error in statistical hypothesis testing. There could be two possibilities for the contradictory results (i.e., significant trend but no significant pairwise comparisons). The first one is that the significant trend may be a false positive due to performing multiple tests without proper control of the overall false positive rate. The second one is that all the non-significant pairwise comparison tests are false negative due to the lack of power to detect true pairwise differences.

Statisticians in CDER have conducted research and developed methods for adjustment for the effect multiple tests to control the overall false positive rate. Based on the methods (testing trends in incidences in common tumors and rare tumors at 0.01 and 0.05 levels of significance, respectively), we are about 90% certain that the significant trends are true effect and not false positive. However, in pairwise comparison tests only a fraction of the available data is use, the power of detecting a true effect is greatly reduce. If the power in a pairwise comparison test is only 50%, then a non-significant difference can give us only 50% assurance that there is really no drug effect. There is a 50% chance that there is a drug effect but there are no enough data to detect the true effect. It will be difficult to justify in making a regulatory decision based only on 50% certainty about a truth.

This reviewer shares concern about the intended use of pairwise comparison test results detailed in Dr. Karl Lin's e-mail included in the Appendix.

Reviewer's Viewpoint

This reviewer relinquishes the responsibility for the interpretation of the findings from the pairwise comparisons in this report for the lack of adequate statistical rationale.

Appendix

Analysis data sets used by this reviewer

The following table shows the analysis data sets used by this reviewer. This table also can be found in the executive summary of the statistical review on page 12.

Table 2 Reviewer's analysis datasets used

DATA SETS IN FOLDER: C:\DATA\CARCIN	#VARS	#RECORDS	DATE MODIFIED	DATA SET LABEL
R1M21912	18	1026	04MAY2006 09:26:30	DTHSACST NOT FIXED male rat
R1F21912	18	1187	04MAY2006 09:25:54	DTHSACST NOT FIXED female rat
R3M21912	18	1025	04MAY2006 11:35:03	DTHSACST **NOT FIXED** male rat - combo - based on **R1M21912**
R3F21912	18	1180	04MAY2006 11:35:30	DTHSACST **NOT FIXED** female rat - combo - based on **R1F21912**
R2M21912	18	1026	04MAY2006 09:27:45	DTHSACST FIXED male rat data - based on **R1M21912**
R2F21912	18	1187	04MAY2006 09:27:22	DTHSACST FIXED female rat data - based on **R1F21912**
R4M21912	18	731	04MAY2006 09:29:12	DTHSACST FIXED male rat data **excl** 0 400 mg/kg/day groups - based on **R2M21912**
R4F21912	18	579	04MAY2006 09:28:45	DTHSACST FIXED female rat data **excl** 0 100 400 mg/kg/day groups - based on **R2F21912**
R6M21912	18	730	04MAY2006 10:58:07	DTHSACST FIXED - **excl** 0 400 mg/kg/day groups - **combo** - based on **R2M21912**
R6F21912	18	575	04MAY2006 10:58:32	DTHSACST FIXED - **excl** excl 0 100 400 mg/kg/day groups - **combo** - based on **R2F21912**
R8M21912	18	1025	04MAY2006 13:03:23	DTHSACST FIXED male rat - **combo - all groups incld.** - based on **R2M21912**
R8F21912	18	1180	04MAY2006 13:03:39	DTHSACST FIXED female rat - **combo - all groups incld.** - based on **R2F21912**

Appears This Way
On Original

Dr. Karl Lin's 5/24/06 e-mail

From: Lin, Karl K
Sent: Wednesday, May 24, 2006 4:27 PM
To: Sun, Ching-Long J; Robison, Timothy W
Cc: Guo, Ted
Subject: Pairwise Comparisons of Seprator Tumor Data (NDA 21-912)

Drs. Sun and Robison:

I have just talked with Ted about your request for performing pairwise comparisons between the control group and each of the treated groups for those tumor types showing significant dose-response relationships (trends). Ted has kindly agreed to perform the additional analyses. I have suggested to Ted that after he completes the additional analyses, he write an addendum to his report to be included in DFS.

Ted also has the strong concern about incorrect interpretations of the pairwise comparison results. In a complicated experiment like a carcinogenicity study, results of statistical tests are not quite straight forward as people usually think. A statistical test in a complicated experiment does not simply end with conclusion of significant or not significant. In a complicated design with multiple endpoints, a significant result can be false positive, and a negative result can be false negative. Therefore, it is important to control the overall false positive rate by adjust for the effect of multiple tests (by using a smaller level of significance); to control the false negative rate by making sure that there are enough data to detect a true effect. Only with those proper controls of the two types of error, one can be sure that a statistically significant result is a true effect, and that a non-statistically significant results is a true non-effect.

We proposed the use of 0.025 and 0.005 levels of significance for trend test in incidences of a rare and a common tumor, respectively, so that there would be an overall false positive rate about 10% in a standard two-species-and-two-sex study. So in this respect, we have some control over how large the overall positive rate is.

However, with the standard design with 50, 60, or 70 animals per group, the evaluation of false negative rate is complicated. In addition to the group size, the probability of getting a false negative finding depends also on the spontaneous rate of the tumor tested, magnitudes of drug effect (both toxic and carcinogenic effects), how early the tumor appears during the study, etc. One thing is known, i.e., the power of a test of trend or group difference of a rare tumor is low. Under such a situation, it will be dangerous to conclude that a negative statistical test result implies no drug effect. It is very likely that there is a drug effect, but there are not enough data to detect the true effect.

Since a two-group pairwise comparison uses only half of the available (assuming there are four treatment groups), it will be less powerful (capable) in detecting a true effect. That is why we have a concern about the way you intend to use results of pairwise comparison tests to define a toxic dose. If the pairwise comparison of C-H is statistically significant but that of C-M is not, your conclusion that the toxic dose is H and higher may not be correct because the nonsignificant result of the C-M comparison may be a false negative result. The toxic dose may be M and above.

Thank you for the opportunity to discuss the statistical issues that most nonstatistician scientists are not aware of.

Karl

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

/s/

Ted Guo
6/2/2006 10:22:28 AM
BIOMETRICS
Addendum to Carcin review for NDA 21-912

Karl Lin
6/2/2006 11:05:50 AM
BIOMETRICS
Concur with review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation
Carcinogenicity Study

BLA/Serial Number:	NDA 21-912
Drug Name:	Arformoterol Inhalation Solution
Indication(s):	Treatment of Subjects with Chronic Obstructive Pulmonary Disease
Applicant:	Sepracor Inc.
Date(s):	January 3, 2006
Review Priority:	Standard
Biometrics Division:	Biometrics Division 2
Statistical Reviewer:	Ted Guo, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D., Biometrics Division 2
Medical Division:	Division of Pulmonary and Allergy Drug Products (ODE II)
Pharmacologist:	Timothy W. Robison, Ph.D., Pharmacology (ODE II)
Project Manager:	Ladan Jafari (ODE II)

Keywords: NDA review, carcinogenicity
Last modified: 5/24/2006

Table of Contents

List of Tables

List of Figures

EXECUTIVE SUMMARY

The evaluation of carcinogenic potential of Arformoterol in male and female rat was performed based on a subset analysis. This subset analysis was recommended by the Agency's ECAC and in consultation with the pharmtox reviewer, Dr. Timothy W. Robison.

The subset analysis includes the following three considerations:

1. For male and female rats, the first control (Ctrl 1) and the 400 mg/kg/day groups were excluded from the analysis. In addition, the 100 mg/kg/day group was excluded from the analysis for the females.
2. Death/sacrifice in the Agency-required variable, DTHSACST, was adjusted using information in the sponsor's optional variable, ASACST (actual death/sacrifice status), because of erroneous coding for DTHSACST.
3. Upon request from Dr. Timothy W. Robison, selected tumors and organs were combined for additional tumor analyses.

Under the considerations, above, this reviewer's statistical analyses produced the following results.

Table 1 Statistical findings on dose-tumor linear trend based on decision rules of the Office of Biostatistics at CDER

Analysis consideration	Sex	Dose (mg/kg/day)	Organ	Tumor	P-value
Analysis by protocol: Organs and tumors analyzed as reported	Male	Ctrl_2, 40, 100, 200	Soft tissue (THO)	malignant liposarcoma	0.0237
	Female	Ctrl_2, 40, 200		None	
Exploratory analysis: Selected organs or tumors combined (The combining is denoted by the symbol +)	Male	Ctrl_1, Ctrl_2, 40, 100, 200, 400		None	
		Ctrl_1, Ctrl_2, 40, 100, 200	Soft Tissue (THO)	Malignant liposarcoma	0.0085
	Female	Ctrl_1, Ctrl_2, 40, 100, 200, 400	Skin	Fibroma +Fibrosarcoma	0.0219
		Ctrl_1, Ctrl_2, 40, 100, 200	Thyroid glands	Adenoma, c-cell +Adenoma, c-cell, multiple + Carcinoma, c-cell	0.001

Based on the protocol-speficied statistical analysis, this reviewer concludes that Arformoterol is carcinogenic in male rats causing malignant liposarcoma in soft tissue (THO) with a p-value 0.0237. The other analyses were done upon the request of the pharmtox reviewer.

INTRODUCTION

Background

In the May 12, 2005 facsimile to Sepracor, Inc. of the FDA 5/10/2005 Executive CAC (ECAC) meeting minutes, the committee concluded the following:

"The sponsor sacrificed all surviving males in control group 1 and the 400 ìg/kg/day during weeks 91-92. All surviving females in control group 1 and the 400 ìg/kg/day group were sacrificed during weeks 90-91, and all remaining females in the 100 ìg/kg/day group were sacrificed during week 92. The remaining females in control group 2 and the 40 and 200 ìg/kg/day groups were sacrificed during weeks 100-101. The males in control group 2 and the 40, 100, and 200 ìg/kg/day groups were sacrificed during week 104."

The committee recommended that the sponsor complete histopathological evaluations of organs and tissues in all dose groups in order for the Agency to reevaluate the adequacy of the rat study.

Objective

The sponsor submitted its rat data with updated histopathological information, supposedly having followed the Agency's recommendations. The objective of this review is to evaluate the Sepracor's carcinogenicity studies on rats in order to determine the carcinogenic potential of Arformoterol Inhalation Solution when it was given to male and female rats.

This reviewer's statistical analysis was based on the sponsor's updated data files named 312051FH.xpt and 312051MH.xpt as SAS v.5 transport files. Both data files are located at FDA Electronic Document Room in folder: \\Cdsesub1\n21912\N_000\2006-04-27 > pharmtox > datasets > 090-828. The document, **DEFINE.PDF** specifying variable definitions was used in this review.

Review method – Special Consideration for Early Termination

Note that early terminal sacrifices conducted more than two (2) months earlier than the scheduled terminal sacrifice, could bias the findings. In consultation with the pharmtox reviewer, Dr. Timothy W. Robison for the review of the rat data, for the **male rats**, the first control group (labeled Ctrl 1 in the text) and the highest dose group (400 mg/kg/day) need to be excluded from the statistical analysis because of early terminal sacrifice in these two groups. For the same reason, for the **female rats**, first control group (Ctrl 1), the 100 and 400 mg/kg/day groups also need to be excluded from the statistical analysis. The regular terminal sacrifice was scheduled around 101 weeks.

To analyze the data correctly, this reviewer incorporated the actual death/sacrifice status in variable ASACST to adjust for the erroneous DTHSACST.

Reviewer's Statistical Analyses

For statistical evaluation, this reviewer converted the rat data files, 312051FH.xpt and 312051MH.xpt, to SAS data sets.

Analysis of Death/ Sacrifice Status

File name: C:\Inetpub\wwwroot\N21912\report\carcin\Ted Guo carcin review NDA21912.doc

The following analyses assess the extent to which the variable DTHSACST (death/sacrifice status, the variable required by the Agency) and ASACST (actual death/sacrifice status, as optional variable) differ. These analyses would give the reviewer an idea how much adjustment to DTHSACST is needed using ASACST.

Analysis of Death/Sacrifice in Male Rats

The following table shows the number of animals by death/terminal sacrifice status and actual sacrifice status in male rats.

Table 2 Analysis of death/sacrifice status in male rats

DTHSACST (DEATH/TERMINAL SACRIFICE STATUS)	ASACST (ACTUAL DEATH/SACRIFICE STATUS)			TOTAL
	Natural death or moribund sacrifice (1)	Scheduled terminal sacrifice (2)	Early terminal sacrifice (3)	
	N	N	N	N
Natural death or moribund sacrifice (1)	172	0	0	172
Terminal sacrifice (2)	44	92	52	188
Total	216	92	52	360

Source: carcin analysis 1.sas based on 312051MH.xpt

The above table shows that, across dose groups and among 188 terminally sacrificed animals, there were 92 scheduled terminal sacrifices, 52 early terminal sacrifices, and 44 with contradicting status between DTHSACST and ASACST. The 44 animals' death/sacrifice status in DTHSACST has to be adjusted while doing the analysis.

The following analysis further breaks down the above table by dose group. It shows that some animals in the 1st control group and the 400 mg/kg/day group were early sacrificed and there were no scheduled terminal sacrifices; in the other groups, natural death and moribund sacrifice appeared under terminal sacrifice category, indicating the contradicting coding.

Table 3 Analysis of death/sacrifice status by dose group in male rats

DODSEGP	DTHSACST				TOTAL
	NATURAL DEATH OR MORIBUND SACRIFICE (1)	TERMINAL SACRIFICE (2)			
	ASACST	ASACST			
	NATURAL DEATH OR MORIBUND SACRIFICE (1)	NATURAL DEATH OR MORIBUND SACRIFICE (1)	SCHEDULED TERMINAL SACRIFICE (2)	EARLY TERMINAL SACRIFICE (3)	
	N	N	N	N	N
Ctrl 1	27	0	0	33	60
Ctrl 2	23	13	24	0	60
40 mg/kg/day	26	10	24	0	60
100 mg/kg/day	26	11	23	0	60
200 mg/kg/day	30	9	21	0	60
400 mg/kg/day	40	1	0	19	60

DODSEGP	DTHSACST				TOTAL
	NATURAL DEATH OR MORIBUND SACRIFICE (1)	TERMINAL SACRIFICE (2)			
	ASACST	ASACST			
	NATURAL DEATH OR MORIBUND SACRIFICE (1)	NATURAL DEATH OR MORIBUND SACRIFICE (1)	SCHEDULED TERMINAL SACRIFICE (2)	EARLY TERMINAL SACRIFICE (3)	
	N	N	N	N	N
Total	172	44	92	52	360

Source: carcin analysis 1.sas based on 312051MH.xpt

Table 4 Minimum and maximum weeks of death and sacrifice in male rats

DOSE GROUP	DEATH OR SACRIFICE STATUS	ACTUAL DEATH OR SACRIFICE STATUS	#ANIMALS	MIN WEEK	MAX WEEK
Ctrl 1	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	27	32	92
Ctrl 1	Terminal sacrifice (2)	Early terminal sacrifice (3)	33	92	92
Ctrl 2	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	23	25	90
Ctrl 2	Terminal sacrifice (2)	Natural death or moribund sacrifice (1)	13	92	105
Ctrl 2	Terminal sacrifice (2)	Scheduled terminal sacrifice (2)	24	104	105
40 mg/kg/day	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	26	39	91
40 mg/kg/day	Terminal sacrifice (2)	Natural death or moribund sacrifice (1)	10	94	104
40 mg/kg/day	Terminal sacrifice (2)	Scheduled terminal sacrifice (2)	24	104	105
100 mg/kg/day	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	26	9	89
100 mg/kg/day	Terminal sacrifice (2)	Natural death or moribund sacrifice (1)	11	92	104
100 mg/kg/day	Terminal sacrifice (2)	Scheduled terminal sacrifice (2)	23	104	105
200 mg/kg/day	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	30	15	91
200 mg/kg/day	Terminal sacrifice (2)	Natural death or moribund sacrifice (1)	9	92	104
200 mg/kg/day	Terminal sacrifice (2)	Scheduled terminal sacrifice (2)	21	104	105
400 mg/kg/day	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	40	23	92
400 mg/kg/day	Terminal sacrifice (2)	Natural death or moribund sacrifice (1)	1	92	92
400 mg/kg/day	Terminal sacrifice (2)	Early terminal sacrifice (3)	19	92	92

Source: carcin analysis 1.sas based on 312051MH.xpt

It is important to note that except for the 1st control group and the 400 mg/kg/day dose group, there were no early terminal sacrifices. Those identified contradictorily as both terminal sacrifice and natural death or moribund sacrifices were terminated as early as 92 weeks of the study, the same week as the early terminal sacrifice week. It appears that the actual terminal sacrifice weeks across the groups were way ahead of the scheduled terminal sacrifice weeks.

Table 5 Analysis of time to death in male rats

	DEATH OR SACRIFICE STATUS							
	Natural death or moribund sacrifice (1)				Terminal sacrifice (2)			
	#Animals	Min week	Max week	Weeks between min and max weeks	#Animals	Min week	Max week	Weeks between min and max weeks
Dose group Ctrl 1	27	32	92	60	33	92	92	0
Ctrl 2	23	25	90	65	37	92	105	13
40 mg/kg/day	26	39	91	52	34	94	105	11
100 mg/kg/day	26	9	89	80	34	92	105	13
200 mg/kg/day	30	15	91	76	30	92	105	13
400 mg/kg/day	40	23	92	69	20	92	92	0

Source: carcin analysis 1.sas based on 312051MH.xpt

The above table shows that the terminal sacrifice started as early as Week 92 in all groups except for the 40 mg/kg/day group for which the terminal sacrifice started from Week 94.

Analysis of Death/Sacrifice in Female Rats

The following table shows the number of animals by death/terminal sacrifice status and actual sacrifice status in female rats.

Table 6 Analysis of death/sacrifice status in female rats

DTHSACST (DEATH/TERMINAL SACRIFICE STATUS)	ASACST (ACTUAL DEATH/SACRIFICE STATUS)				TOTAL
	NATURAL DEATH OR MORIBUND SACRIFICE (1)	SCHEDULED TERMINAL SACRIFICE (2)	EARLY TERMINAL SACRIFICE (3)	ACCIDENTAL DEATH (4)	
	N	N	N	N	N
Natural death or moribund sacrifice (1)	178	0	0	0	178
Terminal sacrifice (2)	36	65	79	0	180
Accidental Death (4)	0	0	0	2	2
Total	214	65	79	2	360

Source: carcin analysis 1.sas based on 312051FH.xpt

The above table shows that, across dose groups and among 180 terminally sacrificed animals, there were 65 scheduled terminal sacrifices, 79 early terminal sacrifices, and 36 with contradicting status. The 36 animals' death/sacrifice status in DTHSACST has to be adjusted while doing the analysis.

The following table further breaks down the above table by dose group. It shows that some animals in the 1st control group, the 100 and 400 mg/kg/day group were early sacrificed and there were no scheduled terminal sacrifices; in the other groups, natural death appeared under the terminal sacrifice category, indicating the contradicting coding.

Table 7 Analysis of death/sacrifice status by dose group in female rats

DODSEGP	DTHSACST			TOTAL
	Natural death or moribund sacrifice (1)	Terminal sacrifice (2)	Accidental Death (4)	

	ASACST	ASACST			ASACST	
	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	Scheduled terminal sacrifice (2)	Early terminal sacrifice (3)	Accidental Death (4)	
	N	N	N	N	N	N
Ctrl 1	27	0	0	32	1	60
Ctrl 2	27	9	24	0	0	60
40 mg/kg/day	27	16	17	0	0	60
100 mg/kg/day	38	2	0	20	0	60
200 mg/kg/day	27	9	24	0	0	60
400 mg/kg/day	32	0	0	27	1	60
Total	178	36	65	79	2	360

Source: carcin analysis 1.sas based on 312051FH.xpt

Table 8 Minimum and maximum weeks of death and sacrifice in female rats

DOSE GROUP	DEATH OR SACRIFICE STATUS	ACTUAL DEATH OR SACRIFICE STATUS	#ANIMALS	MIN WEEK	MAX WEEK
Ctrl 1	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	27	30	90
Ctrl 1	Terminal sacrifice (2)	Early terminal sacrifice (3)	32	91	91
Ctrl 1	Accidental Death (4)	Accidental Death (4)	1	25	25
Ctrl 2	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	27	51	88
Ctrl 2	Terminal sacrifice (2)	Natural death or moribund sacrifice (1)	9	93	98
Ctrl 2	Terminal sacrifice (2)	Scheduled terminal sacrifice (2)	24	101	102
40 mg/kg/day	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	27	7	90
40 mg/kg/day	Terminal sacrifice (2)	Natural death or moribund sacrifice (1)	16	91	101
40 mg/kg/day	Terminal sacrifice (2)	Scheduled terminal sacrifice (2)	17	101	102
100 mg/kg/day	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	38	18	90
100 mg/kg/day	Terminal sacrifice (2)	Natural death or moribund sacrifice (1)	2	91	91
100 mg/kg/day	Terminal sacrifice (2)	Early terminal sacrifice (3)	20	92	92
200 mg/kg/day	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	27	26	90
200 mg/kg/day	Terminal sacrifice (2)	Natural death or moribund sacrifice (1)	9	93	100
200 mg/kg/day	Terminal sacrifice (2)	Scheduled terminal sacrifice (2)	24	101	102
400 mg/kg/day	Natural death or moribund sacrifice (1)	Natural death or moribund sacrifice (1)	32	26	90
400 mg/kg/day	Terminal sacrifice (2)	Early terminal sacrifice (3)	27	91	91
400 mg/kg/day	Accidental Death (4)	Accidental Death (4)	1	58	58

Source: carcin analysis 1.sas based on 312051FH.xpt

It is important to note that except for the 1st control group, the 100 and 400 mg/kg/day dose group, there were no early terminal sacrifices. Those identified contradictorily as both terminal sacrifice and natural death or moribund sacrifices were terminated as early as 91 weeks of the study, the same week as the early terminal sacrifice week. It appears that the actual terminal sacrifice weeks across the groups were way ahead of the scheduled terminal sacrifice weeks.

Table 9 Analysis of time to death in female rats

	DEATH OR SACRIFICE STATUS											
	NATURAL DEATH OR MORIBUND SACRIFICE (1)				TERMINAL SACRIFICE (2)				ACCIDENTAL DEATH (4)			
	#ANIMALS	MIN WEEK	MAX WEEK	WEEKS BETWEEN MIN AND MAX WEEKS	#ANIMALS	MIN WEEK	MAX WEEK	WEEKS BETWEEN MIN AND MAX WEEKS	#ANIMALS	MIN WEEK	MAX WEEK	WEEKS BETWEEN MIN AND MAX WEEKS
Dose group Ctrl 1	27	30	90	60	32	91	91	0	1	25	25	0
Ctrl 2	27	51	88	37	33	93	102	9	0	0	0	0
40 mg/kg/day	27	7	90	83	33	91	102	11	0	0	0	0
100 mg/kg/day	38	18	90	72	22	91	92	1	0	0	0	0
200 mg/kg/day	27	26	90	64	33	93	102	9	0	0	0	0
400 mg/kg/day	32	26	90	64	27	91	91	0	1	58	58	0

Source: carcin analysis 1.sas based on 312051FH.xpt

The above table shows that the terminal sacrifice started as early as Week 91 in all groups except for the control 2 and 200 mg/kg/day group for which the terminal sacrifice started from Week 93.

Reviewer's Analysis Data Sets

The following table shows the analysis data sets used by this reviewer.

Table 10 Reviewer's analysis datasets used

DATA SETS IN FOLDER: C:\DATA\CARCIN	#VARS	#RECORDS	DATE MODIFIED	DATA SET LABEL
R1M21912	18	1026	04MAY2006 09:26:30	DTHSACST NOT FIXED male rat
R1F21912	18	1187	04MAY2006 09:25:54	DTHSACST NOT FIXED female rat
R3M21912	18	1025	04MAY2006 11:35:03	DTHSACST **NOT FIXED** male rat - combo - based on **R1M21912**
R3F21912	18	1180	04MAY2006 11:35:30	DTHSACST **NOT FIXED** female rat - combo - based on **R1F21912**
R2M21912	18	1026	04MAY2006 09:27:45	DTHSACST FIXED male rat data - based on **R1M21912**
R2F21912	18	1187	04MAY2006 09:27:22	DTHSACST FIXED female rat data - based on **R1F21912**
R4M21912	18	731	04MAY2006 09:29:12	DTHSACST FIXED male rat data excl 0 400 mg/kg/day groups - based on **R2M21912**
R4F21912	18	579	04MAY2006 09:28:45	DTHSACST FIXED female rat data excl 0 100 400 mg/kg/day groups - based on **R2F21912**
R6M21912	18	730	04MAY2006 10:58:07	DTHSACST FIXED - excl 0 400 mg/kg/day groups - **combo** - based on **R2M21912**
R6F21912	18	575	04MAY2006 10:58:32	DTHSACST FIXED - excl excl 0 100 400 mg/kg/day groups - **combo** - based on **R2F21912**
R8M21912	18	1025	04MAY2006 13:03:23	DTHSACST FIXED male rat - **combo** - all groups incld. - based on **R2M21912**
R8F21912	18	1180	04MAY2006 13:03:39	DTHSACST FIXED female rat - **combo** - all groups incld. - based on **R2F21912**

Analysis of Tumor data

As a sensitive analysis of carcinogenicity study, this reviewer incorporated the actual death/sacrifice status in variable ASACST to adjust for the erroneous DTHSACST. This reviewer also performed an analysis using unadjusted DTHSACST. The results were compared in making the final judgment on the carcinogenicity of the drug.

Actual death/sacrifice status adjusted tumor-data analysis

Analysis of Male Rats

Mortality Analysis

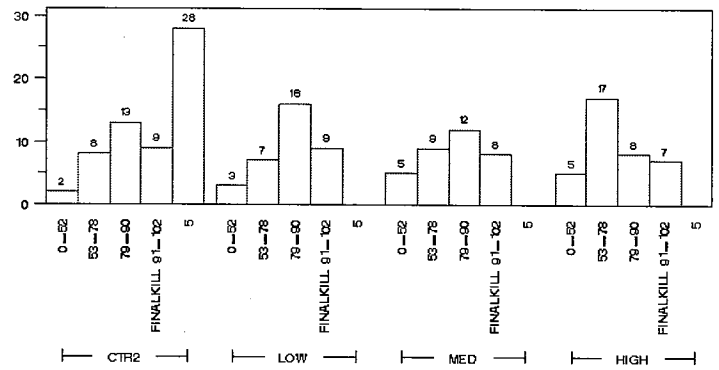
The mortality analysis starts with the display of the animal-mortality statistics by treatment and time interval. The main purpose for these analyses is to discover any statistically significant dose-mortality trend that justifies the age-adjusted test of positive dose-tumor linear trend.

Table 11 Analysis of Mortality Data for Male Rats by Treatment and Time

ANALYSIS OF MORTALITY		NO. RISK	NO. DIED	NO. ALIVE	PCT SURVIVAL	PCT MORTALITY
CTR2 (0)	0-52	60	2	58	96.7	3.3
	53-78	58	8	50	83.3	16.7
	79-91	50	13	37	61.7	38.3
	92-103	37	9	28	46.7	53.3
	FINALKILL104-105	28	28	0	0.0	100.0
LOW (40)	0-52	60	3	57	95.0	5.0
	53-78	57	7	50	83.3	16.7
	79-91	50	16	34	56.7	43.3
	92-103	34	9	25	41.7	58.3
	FINALKILL104-105	25	25	0		
MED (100)	0-52	60	5	55	91.7	8.3
	53-78	55	9	46	76.7	23.3
	79-91	46	12	34	56.7	43.3
	92-103	34	8	26	43.3	56.7
	FINALKILL104-105	26	26	0		
HIGH (200)	0-52	60	5	55	91.7	8.3
	53-78	55	17	38	63.3	36.7
	79-91	38	8	30	50.0	50.0
	92-103	30	7	23	38.3	61.7
	FINALKILL104-105	23	23	0		

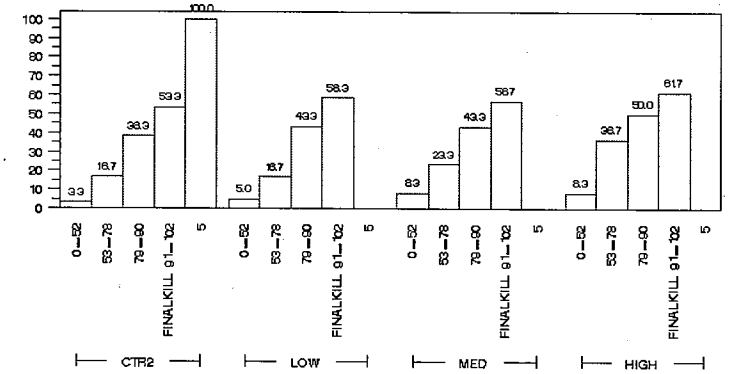
Source data: Analysis data (SAS v. 9.1) R4M21912

Figure 1 Number of Male Rats Died During Study by Time



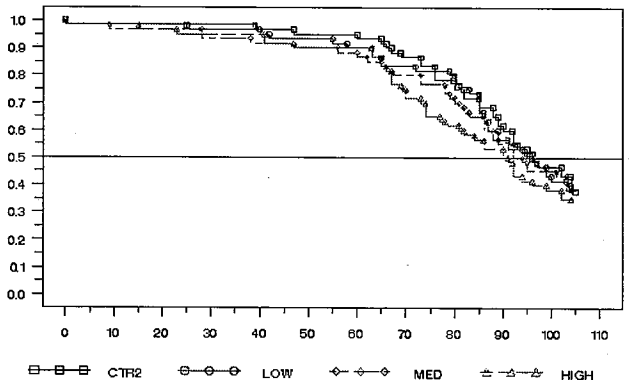
Source data: Analysis data (SAS v. 9.1) R4M21912

Figure 2 Cumulative Pct. of Death in Male Rats



Source data: Analysis data (SAS v. 9.1) R4M21912

Figure 3 Kaplan-Meier Survival Functions for Male Rats



Source data: Analysis data (SAS v. 9.1) R4M21912

The analysis of dose-mortality trend is done using a computer program described in the article "Trend and Homogeneity Analyses of Proportions and Life Table Data," Version 2.1, by Donald G. Thomas, National Cancer Institute. A significant dose-tumor trend gives rise to a statistical justification for the age-adjusted test of positive dose-tumor linear trend.

Table 12 Analysis of Dose-Mortality Trend for Male Rats

Time-Adjusted Trend Test	METHOD			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Depart from Trend	0.1021	0.9502	0.0305	0.9849
Dose-Mortality Trend	1.5286	0.2163	2.4743	0.1157
Homogeneity	1.6306	0.6525	2.5048	0.4744

Source data: Analysis data (SAS v. 9.1) R4M21912

Reviewer's Comment on Mortality Analysis:
The dose-mortality trend was found not to be statistically significant.

Trend Analysis

The test for positive dose-tumor linear trend is the ultimate objective of the evaluation of the carcinogenicity-study. We are looking for such trend because, in most situations, the carcinogenic potential of the test drug is unclear. Tumor incidences among the treatment groups appear random in many cases, while these incidences might be a result of the drug effect that needs to be detected and reported. Occasionally, pairwise comparisons are employed, but only under certain condition of the data and are decided on case by case bases. As a cautionary note, blindly imposing pairwise comparisons can only undermine the importance of the trend test, inflate the type-1 error, and produce untrustworthy results. The significance of the test is decided based on a decision rule adopted by the Office of Biostatistics. The details of the decision rule can be found in the Appendix of this review.

Table 13 Tumor findings in male rats

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTRL2	40MG	100MG	200MG
AC	ADRENAL CORTEX	HP027003	#B ADENOMA	1	3	0	0
AC	ADRENAL CORTEX	HP085008	#M CARCINOMA	0	1	1	0
AM	ADRENAL MEDULLA	HP086002	#B PHEOCHROMOCYTOMA, BENIGN	7	3	6	6
AM	ADRENAL MEDULLA	HP086005	#M PHEOCHROMOCYTOMA, MALIGNANT	0	0	0	1
AO	AORTA	HP003005	#M PARAGANGLIOMA, MALIGNANT	0	0	1	0
AO	AORTA	HP026004	#M LIPOSARCOMA	0	0	1	0
BR	BRAIN	HP007001	#B OLIGODENDROGLIOMA, BENIGN	0	0	0	1
BR	BRAIN	HP007003	#M ASTROCYTOMA, MALIGNANT	2	1	1	2
DU	DUODENUM	HP085008	#M CARCINOMA	1	0	0	0
GI	GINGIVA	HP095001	#M CARCINOMA, SQUAMOUS CELL	0	1	0	0
HE	HEART	HP017012	#B SCHWANNOMA, BENIGN	0	0	1	0
JE	JEJUNUM	HP019002	#M LEIOMYOSARCOMA	1	0	1	0
LD	LYMPH NODE, MAND	HP028002	#M CARCINOMA; UNKNOWN	1	0	0	0

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTRL2	40MG	100MG	200MG
LI	LIVER	HP021012	#M CARCINOMA, HEPATOCELLULAR	0	0	1	0
LS	LYMPH NODE, MED	HP026004	#M LIPOSARCOMA	0	1	0	0
LU	LUNGS	HP026004	#M LIPOSARCOMA	0	1	0	0
LU	LUNGS	HP026021	#M CARCINOMA, HEPATOCELLULAR; UNKNOWN	0	0	0	1
MG	MAMMARY GLAND	HP027002	#B FIBROADENOMA	0	1	0	0
MG	MAMMARY GLAND	HP027003	#B ADENOMA	0	0	1	0
MG	MAMMARY GLAND	HP027004	#M ADENOCARCINOMA	0	1	1	0
MG	MAMMARY GLAND	HP027005	#B FIBROMA	1	1	3	0
PA	PANCREAS	HP034006	#B ADENOMA, ISLET CELL	3	0	1	0
PA	PANCREAS	HP034008	#B ADENOMA, ISLET CELL, MULTIPLE	1	1	0	0
PA	PANCREAS	HP034014	#B ADENOMA, ACINAR CELL	0	0	1	0
PI	PITUITARY	HP040001	#B ADENOMA, PARS DISTALIS	34	30	33	29
PI	PITUITARY	HP040006	#M CARCINOMA, PARS DISTALIS	0	0	0	1
PR	PROSTATE	HP017012	#B SCHWANNOMA, BENIGN	0	0	0	1
PT	PARATHYROID	HP027003	#B ADENOMA	0	1	0	0
PW	PAW(S)	HP079002	#B PAPILLOMA	0	1	0	0
SH	SOFT TISSUE-THO	HP003005	#M PARAGANGLIOMA, MALIGNANT	0	0	1	0
SH	SOFT TISSUE-THO	HP026004	#M LIPOSARCOMA	0	0	1	2
SK	SKIN	HP027005	#B FIBROMA	1	2	0	0
SK	SKIN	HP046003	#M FIBROSARCOMA	0	1	2	0
SK	SKIN	HP046004	#M SCHWANNOMA, MALIGNANT	0	0	1	1
SK	SKIN	HP046007	#B KERATOACANTHOMA, BENIGN	5	8	2	4
SK	SKIN	HP046014	#M MYXOSARCOMA	1	0	0	0
SK	SKIN	HP046017	#M OSTEOSARCOMA; UNKNOWN	1	0	0	0
SK	SKIN	HP046019	#B LIPOMA	1	1	2	1
SY	SYSTEMIC TUMORS	HP094001	#M LYMPHOMA, MALIGNANT	2	1	1	0
SY	SYSTEMIC TUMORS	HP094002	#M SARCOMA, HISTIOCYTIC	3	0	2	0
SY	SYSTEMIC TUMORS	HP094003	#M FIBROUS HISTIOCYTOMA, MALIGNANT	0	0	1	0
TA	TAIL	HP077004	#M NEUROFIBROSARCOMA	0	0	0	1
TE	TESTES	HP051003	#B ADENOMA, INTERSTITIAL CELL	1	1	1	2
TG	THYROID GLANDS	HP053001	#B ADENOMA, C-CELL	12	4	7	8
TG	THYROID GLANDS	HP053003	#M CARCINOMA, FOLLICULAR CELL	1	0	1	0
TG	THYROID GLANDS	HP053007	#M CARCINOMA, C-CELL	1	0	1	1
TG	THYROID GLANDS	HP053008	#B ADENOMA, C-CELL, MULTIPLE	0	0	0	1
TH	THYMUS GLAND	HP052005	#M THYMOMA, MALIGNANT	0	1	0	0
ZG	ZYMBAL'S GLAND	HP085008	#M CARCINOMA	2	0	0	1

Source data: Analysis data (SAS v. 9.1) R4M21912

In the following table, we only report trend-test results with p-value less than 0.05, which may not imply a statistical significance. Throughout this report, this icon indicates a statistically significant trend: (!)

Table 14 Report on Test for Positive Linear Dose-Tumor Trends in Male Rats

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR 2	LO W	ME D	HIG H	P-VALUE (EXACT METHOD)	P-VALUE (ASYMPTOTIC METHOD)
BR	BRAIN	HP00700 1	#B OLIGODENDROGLIOMA , BENIGN	0	0	0	1	0.2086	0.0467
LU	LUNGS	HP02602 1	#M CARCINOMA, HEPATOCELLULAR;	0	0	0	1	0.2151	0.0488
SH	SOFT TISSUE - THO	HP02600 4	#M LIPOSARCOMA	0	0	1	2	0.0523	0.0237 (!)
TA	TAIL	HP07700 4	#M NEUROFIBROSARCOM A	0	0	0	1	0.2121	0.0474

Source data: Analysis data (SAS v. 9.1) R4M21912

Table 15 Interpretation for trend-test results based on p-values (male rat)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	OVERALL TUMOR TYPE	TUMOR RATE AS PCT. IN CONTROL GROUP	SUGGESTED INTERPRETATION FOR TREND-TEST
SH	SOFT TISSUE- THO	HP02600 4	#M LIPOSARCOMA	Both fatal and incidental	0.00	Use asymptotic p-value. Use p-value cutoff point of 0.025.

Source data: Analysis data (SAS v. 9.1) R4M21912

Table 16 Statistically Significant Positive Linear Dose-Tumor Trend Found In Male Rats

Organ Name	Tumor Name	P-Value
SOFT TISSUE- THO	#M LIPOSARCOMA	0.0237 < 0.025 cutoff

Source data: Analysis data (SAS v. 9.1) R4M21912

Reviewer's Statistical Findings from the Trend-Test:
The dose-tumor linear trend in male rats was statistically significant for malignant LIPOSARCOMA in soft tissue with p-value 0.0237.

Analysis of Female Rats

Mortality Analysis

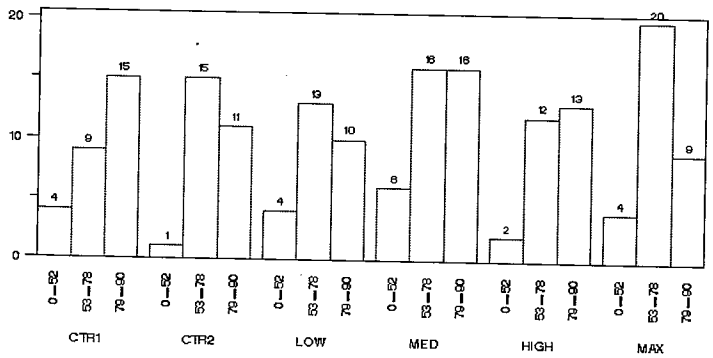
The mortality analysis starts with the display of the animal-mortality statistics by treatment and time interval. The main purpose for these analyses is to discover any statistically significant dose-mortality trend that justifies the age-adjusted test of positive dose-tumor linear trend.

Table 17 Analysis of Mortality Data for Female Rats by Treatment and Time

ANALYSIS OF MORTALITY		NO. RISK	NO. DIED	NO. ALIVE	PCT SURVIVAL	PCT MORTALITY
CTR2 (0)	0-52	60	1	59	98.3	1.7
	53-78	59	15	44	73.3	26.7
	79-91	44	11	33	55.0	45.0
	92-100	33	9	24	40.0	60.0
	FINALKILL101-102	24	24	0		
LOW (40)	0-52	60	4	56	93.3	6.7
	53-78	56	13	43	71.7	28.3
	79-91	43	13	30	50.0	50.0
	92-100	30	11	19	31.7	68.3
	FINALKILL101-102	19	19	0		
HIGH (200)	0-52	60	2	58	96.7	3.3
	53-78	58	12	46	76.7	23.3
	79-91	46	13	33	55.0	45.0
	92-100	33	9	24	40.0	60.0
	FINALKILL101-102	24	24	0		

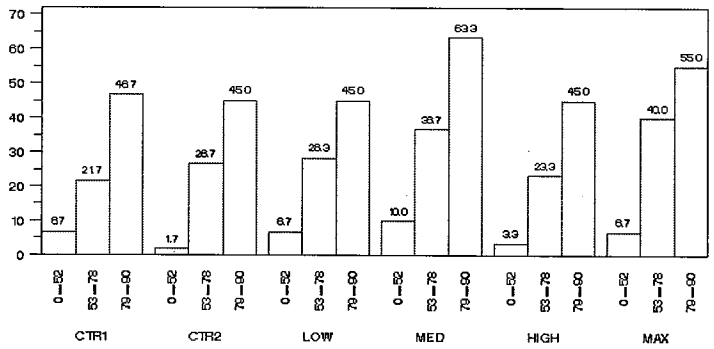
Source data: Analysis data (SAS v. 9.1) R4F21912

Figure 4 Number of Female Rats Died During Study by Time



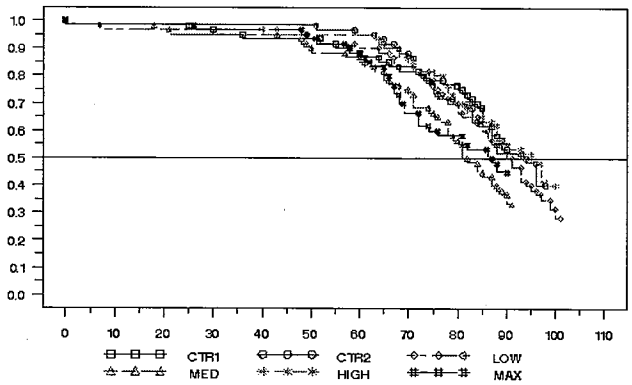
Source data: Analysis data (SAS v. 9.1) R4F21912

Figure 5 Cumulative Pct. of Death in Female Rats



Source data: Analysis data (SAS v. 9.1) R4F21912

Figure 6 Kaplan-Meier Survival Functions for Female Rats



Source data: Analysis data (SAS v. 9.1) R4F21912

The analysis of dose-mortality trend is done using a computer program described in the article "Trend and Homogeneity Analyses of Proportions and Life Table Data," Version 2.1, by Donald G. Thomas, National Cancer Institute. A significant dose-tumor trend gives rise to a statistical justification for the age-adjusted test of positive dose-tumor linear trend.

Table 18 Analysis of Dose-Mortality Trend for Female Rats

Time-Adjusted Trend Test	METHOD			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Depart from Trend	0.9182	0.3379	0.6042	0.4370
Dose-Mortality Trend	0.1889	0.6639	0.2210	0.6383
Homogeneity	1.1071	0.5749	0.8252	0.6619

Source data: Analysis data (SAS v. 9.1) R4F21912

Reviewer's Comment on Mortality Analysis:
The dose-mortality trend was found not to be statistically significant.

Trend Analysis

The test for positive dose-tumor linear trend is the ultimate objective of the evaluation of the carcinogenicity-study. We are looking for such trend because, in most situations, the carcinogenic potential of the test drug is unclear. Tumor incidences among the treatment groups appear random in many cases, while these incidences might be a result of the drug effect that needs to be detected and reported. Occasionally, pairwise comparisons are employed, but only under certain condition of the data and are decided on case by case bases. As a cautionary note, blindly imposing pairwise comparisons can only undermine the importance of the trend test, inflate the type-1 error, and produce untrustworthy results. The significance of the test is decided based on a decision rule adopted by the Office of Biostatistics. The details of the decision rule can be found in the Appendix of this review.

Table 19 Tumor findings in female rats

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTRL2	40MG	200MG
AC	ADRENAL CORTEX	HP027005	#B ADENOMA	2	1	2
AM	ADRENAL MEDULLA	HP085002	#B PHEOCHROMOCYTOMA, BENIGN	2	2	1
AM	ADRENAL MEDULLA	HP085005	#B PHEOCHROMOCYTOMA, COMPLEX, BENIGN	0	0	1
AM	ADRENAL MEDULLA	HP085006	#M PHEOCHROMOCYTOMA, MALIGNANT	0	0	1
BR	BRAIN	HP007010	#M SARCOMA, MENINGEAL	0	1	0
CL	CLITORAL GLAND	HP060009	#M CARCINOMA	2	0	0
CX	CERVIX	HP063009	#B LEIOMYOMA	0	1	0
LE	LAC. GLAND, EXOR	HP027005	#B ADENOMA	0	1	0
LI	LIVER	HP021012	#M CARCINOMA, HEPATOCELLULAR	0	1	0
LU	LUNGS	HP081001	#M LIPOSARCOMA	0	0	1
MG	MAMMARY GLAND	HP027002	#B FIBROADENOMA	12	16	11
MG	MAMMARY GLAND	HP027003	#B FIBROADENOMA, MULTIPLE	8	5	4
MG	MAMMARY GLAND	HP027005	#B ADENOMA	1	5	2
MG	MAMMARY GLAND	HP027006	#M ADENOCARCINOMA, MULTIPLE	6	4	3
MG	MAMMARY GLAND	HP027007	#M ADENOCARCINOMA	7	15	14
MG	MAMMARY GLAND	HP027011	#B ADENOLIPOMA	1	0	0
OV	OVARIES	HP033005	#B SERTOLI CELL TUMOR, BENIGN	1	0	0
OV	OVARIES	HP033006	#B GRANULOSA CELL TUMOR, BENIGN	0	0	1
OV	OVARIES	HP033009	#B ADENOMA, SEX CORD STROMAL, MULTIPLE	0	0	1
PA	PANCREAS	HP034006	#B ADENOMA, ISLET CELL	1	0	1
PI	PITUITARY	HP040001	#B ADENOMA, PARS DISTALIS	57	56	54
PT	PARATHYROID	HP027005	#B ADENOMA	0	1	1
PT	PARATHYROID	HP035005	#B ADENOMA, MULTIPLE	0	1	0
SA	SOFT TISSUE-ABD	HP061003	#M SCHWANNOMA, MALIGNANT	0	1	0
SA	SOFT TISSUE-ABD	HP081001	#M LIPOSARCOMA	0	0	1
SH	SOFT TISSUE-THO	HP081001	#M LIPOSARCOMA	2	2	0
SK	SKIN	HP045006	#M FIBROSARCOMA	0	1	0
SK	SKIN	HP046007	#B KERATOACANTHOMA, BENIGN	1	0	1
SK	SKIN	HP046011	#B FIBROMA	1	0	1
SK	SKIN	HP046014	#M MYXOSARCOMA	0	1	0

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTRL2	40MG	200MG
SK	SKIN	HP046015	#M CARCINOMA, SQUAMOUS CELL	0	1	1
SK	SKIN	HP046022	#M CARCINOMA, UNDIFFERENTIATED	0	1	0
SK	SKIN	HP081001	#M LIPOSARCOMA	0	1	0
SM	SKELETAL MUSCLE	HP045006	#M FIBROSARCOMA	0	0	1
SY	SYSTEMIC TUMORS	HP090001	#M LYMPHOMA, MALIGNANT	1	0	2
SY	SYSTEMIC TUMORS	HP090002	#M SARCOMA, HISTIOCYTIC	1	1	0
SY	SYSTEMIC TUMORS	HP090003	#B HEMANGIOMA	0	0	1
TG	THYROID GLANDS	HP053001	#B ADENOMA, C-CELL	3	2	9
TG	THYROID GLANDS	HP053006	#B ADENOMA, C-CELL, MULTIPLE	1	1	1
TG	THYROID GLANDS	HP053007	#B ADENOMA, FOLLICULAR CELL	1	1	0
TG	THYROID GLANDS	HP053008	#M CARCINOMA, C-CELL	0	0	2
UT	UTERUS	HP027005	#B ADENOMA	0	1	0
UT	UTERUS	HP060003	#B POLYP, ENDOMETRIAL STROMAL	3	1	3
UT	UTERUS	HP060009	#M CARCINOMA	1	0	0
UT	UTERUS	HP061003	#M SCHWANNOMA, MALIGNANT	1	0	0
VA	VAGINA	HP061003	#M SCHWANNOMA, MALIGNANT	1	0	0

Source data: Analysis data (SAS v. 9.1) R4F21912

We only report trend-test results with p-value less than 0.05, which may not imply a statistical significance.

Table 20 Report on Test for Positive Linear Dose-Tumor Trends in Female Rats

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR2	LOW	HIGH	P-VALUE (EXACT METHOD)	P-VALUE (ASYMPTOTIC METHOD)
TG	THYROID GLANDS	HP053001	#B ADENOMA, C-CELL	3	2	9	0.0137	0.0088
TG	THYROID GLANDS	HP053008	#M CARCINOMA, C-CELL	0	0	2	0.0887	0.0178

Source data: Analysis data (SAS v. 9.1) R4F21912

Table 21 Interpretation for trend-test results based on p-values (female rat)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	OVERALL TUMOR TYPE	TUMOR RATE AS PCT. IN CONTROL GROUP	SUGGESTED INTERPRETATION FOR TREND-TEST
TG	THYROID GLANDS	HP053001	#B ADENOMA, C-CELL	Incidental	5.00	Use exact p-value. Use p-value cutoff point of 0.005.
TG	THYROID GLANDS	HP053008	#M CARCINOMA, C-CELL	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.

Source data: Analysis data (SAS v. 9.1) R4F21912

Table 22 Determine significance of positive linear dose-tumor trend for the tumor in female rats

Organ Name	Tumor Name	P-Value
THYROID GLANDS	#B ADENOMA, C-CELL	0.0137>0.005 cutoff
THYROID GLANDS	#M CARCINOMA, C-CELL	0.0887>0.025 cutoff

Source data: Analysis data (SAS v. 9.1) R4F21912

Reviewer's Statistical Findings from the Trend-Test:
The dose-tumor linear trend in female rats was not statistically significant in any of the reported tumors.

Actual death/sacrifice status adjusted tumor-data analysis based on combined organ and/or tumor types

The following analyses were based on combined organ and/or tumor types. Selected organ and/or tumor types were combined before the trend test was done. This work was completed in consultation with the pharmtox reviewer, Dr. Tim Robison.

The following table shows how combining organs and tumors are done.

Table 23 Combining organs and tumors for male-rat data

INTENDED COMBINING OF TUMORS BASED ON STUDY REPORT	INTENDED COMBINING OF TUMORS BASED ON DATA FILE	ORGAN/TISSUE
Thyroid gland C cell adenoma (single and multiple) + carcinoma	#B ADENOMA, C-CELL + #B ADENOMA, C-CELL, MULTIPLE + #M CARCINOMA, C-CELL	THYROID GLANDS
Soft tissue-Thorax liposarcoma + liposarcoma, multiple	#M LIPOSARCOMA	SOFT TISSUE- THO
Testes interstitial cell adenoma	#B ADENOMA, INTERSTITIAL CELL	TESTES

Table 24 Combining organs and tumors for female-rat data

INTENDED COMBINING OF TUMORS BASED ON STUDY REPORT	INTENDED COMBINING OF TUMORS BASED ON DATA FILE	ORGAN/TISSUE
Thyroid gland C cell adenoma (single and multiple) + carcinoma	#B ADENOMA, C-CELL + #B ADENOMA, C-CELL, MULTIPLE + #M CARCINOMA, C-CELL	THYROID GLANDS
Skin fibroma + fibrosarcoma	#B FIBROMA + #M FIBROSARCOMA	SKIN
Mammary gland adenoma (single and multiple) + adenocarcinoma (single and multiple)	#B ADENOMA + #B Adenoma, multiple* + #M ADENOCARCINOMA + #M ADENOCARCINOMA, MULTIPLE	MAMMARY GLAND
Soft tissue-Thorax liposarcoma + liposarcoma, multiple	#M LIPOSARCOMA + #M Liposarcoma, multiple*	SOFT TISSUE- THO
Uterus + Cervix Endometrial stromal polyp	#B POLYP, ENDOMETRIAL STROMAL	UTERUS + Cervix*

*: The tumor/organ type appears might not appear in data when certain groups are excluded.

Analysis of Male Rats

Analysis including Ctrl 2, 40, 100, 200 mg/kg/day dose group

Table 25 Report on Trend Test for Positive Linear Dose-Tumor Trends in Male Rats Combining Selected Organs or Tumors in male rats

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR2	LOW (40)	MED (100)	HIGH (200)	P-VALUE (EXACT METHOD)	P-VALUE (ASYMPTOTIC METHOD)
BR	BRAIN	HP007001	#B OLIGODENDROGLIOMA, BENIGN	0	0	0	1	0.2086	0.0467
LU	LUNGS	HP026021	#M CARCINOMA, HEPATOCELLULAR;	0	0	0	1	0.2151	0.0488
SH	SOFT TISSUE-THO	HP026004	#M LIPOSARCOMA	0	0	1	2	0.0523	0.0237 (!)
TA	TAIL	HP077004	#M NEUROFIBROSARCOMA	0	0	0	1	0.2121	0.0474

Source data: Analysis data (SAS v. 9.1) R6M21912

Reviewer's Statistical Findings from the Trend-Test:
The dose-tumor linear trend in male rats was statistically significant for malignant LIPOSARCOMA in soft tissue with p-value 0.0237. No significant findings for the other listed tumors.

Analysis including all dose groups including 400 mg/kg/day group

Table 26 Report on Trend Test for Positive Linear Dose-Tumor Trends in Male Rats Combining Selected Organs or Tumors in male rats (400 mg/kg/day group included)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1	CTR2	LOW	MED	HIGH	MAX	P-VALUE (EXACT METHOD)	P-VALUE (ASYMPTOTIC METHOD)
PI	PITUITARY	HP040001	#B ADENOMA, PARS DISTALIS	22	34	30	33	29	29	0.0229	0.0210
PR	PROSTATE	HP042006	#M CARCINOMA, TRANSITIONAL CEL	0	0	0	0	0	1	0.1633	0.0244
TH	THYMUS GLAND	HP072001	#M LIPOSARCOMA	0	0	0	0	0	1	0.1429	0.0169

Source data: Analysis data (SAS v. 9.1) R8M21912

Table 27 Interpretation for trend-test results based on p-values (male rat)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	OVERALL TUMOR TYPE	TUMOR RATE AS PCT. IN CONTROL GROUP	SUGGESTED INTERPRETATION FOR TREND-TEST
PI	PITUITARY	HP040001	#B ADENOMA, PARS DISTALIS	Both fatal and incidental	46.67	Use asymptotic p-value. Use p-value cutoff point of 0.005.
PR	PROSTATE	HP042006	#M CARCINOMA, TRANSITIONAL CEL	Fatal	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
TH	THYMUS GLAND	HP072001	#M LIPOSARCOMA	Fatal	0.00	Use exact p-value. Use p-value cutoff point of 0.025.

Source data: Analysis data (SAS v. 9.1) R8M21912

Reviewer's Statistical Findings from the Trend-Test:
No significant findings for the listed tumors.

Analysis including all dose groups excluding 400 mg/kg/day group

Table 28 Report on Trend Test for Positive Linear Dose-Tumor Trends in Male Rats Combining Selected Organs or Tumors in male rats (400 mg/kg/day group excluded)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1	CTR2	LOW	MED	HIGH	P-VALUE (EXACT METHOD)	P-VALUE (ASYMPTOTIC METHOD)
AM	ADRENAL MEDULLA	HP086005	#M PHEOCHROMOCYTOMA, MALIGNANT	0	0	0	0	1	0.1786	0.0321
LU	LUNGS	HP026021	#M CARCINOMA, HEPATOCELLULAR;	0	0	0	0	1	0.1737	0.0303
PR	PROSTATE	HP042012	#B SCHWANNOMA, BENIGN	0	0	0	0	1	0.1775	0.0320
SH	SOFT TISSUE-THO	HP072001	#M LIPOSARCOMA	0	0	0	1	2	0.0262	0.0085 (!)
TA	TAIL	HP077004	#M NEUROFIBROSARCOMA	0	0	0	0	1	0.1775	0.0320

Source data: Analysis data (SAS v. 9.1) R8M21912

Table 29 Interpretation for trend-test results based on p-values (male rat)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	OVERALL TUMOR TYPE	TUMOR RATE AS PCT. IN CONTROL GROUP	SUGGESTED INTERPRETATION FOR TREND-TEST
AM	ADRENAL MEDULLA	HP086005	#M PHEOCHROMOCYTOMA, MALIGNANT	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
LU	LUNGS	HP026021	#M CARCINOMA, HEPATOCELLULAR;	Fatal	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
PR	PROSTATE	HP042012	#B SCHWANNOMA, BENIGN	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
SH	SOFT TISSUE-THO	HP072001	#M LIPOSARCOMA	Both fatal and incidental	0.00	Use asymptotic p-value. Use p-value cutoff point of 0.025.
TA	TAIL	HP077004	#M NEUROFIBROSARCOMA	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.

Source data: Analysis data (SAS v. 9.1) R8M21912

Reviewer's Statistical Findings from the Trend-Test:
The dose-tumor linear trend in male rats was statistically significant for malignant LIPOSARCOMA in soft tissue with p-value 0.0085. No significant findings for the other listed tumors.

Analysis of Female Rats

Analysis including Ctrl 2, 40, 200 mg/kg/day dose group

Table 30 Report on Trend Test for Positive Linear Dose-Tumor Trends in Female Rats Combining Selected Organs or Tumors in female rats

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR2	LOW	HIGH	P-VALUE (EXACT METHOD)	P-VALUE (ASYMPTOTIC METHOD)
TG	THYROID GLANDS	HP053001	#B ADENOMA, C-CELL + #B ADENOMA, C-CELL, MULTIPLE + #M CARCINOMA, C-CELL	4	3	11	0.0097	0.0067

Source data: Analysis data (SAS v. 9.1) R6F21912

Table 31 Interpretation for trend-test results based on p-values (female rat)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	OVERALL TUMOR TYPE	TUMOR RATE AS PCT. IN CONTROL GROUP	SUGGESTED INTERPRETATION FOR TREND-TEST
TG	THYROID GLANDS	HP053001	#B ADENOMA, C-CELL + #B ADENOMA, C-CELL, MULTIPLE + #M CARCINOMA, C-CELL	Incidental	6.67	Use exact p-value. Use p-value cutoff point of 0.005

Source data: Analysis data (SAS v. 9.1) R6F21912

Reviewer's Statistical Findings from the Trend-Test:
No significant findings for the listed tumors.

Analysis including all dose groups including 400 mg/kg/day group

Table 32 Report on Trend Test for Positive Linear Dose-Tumor Trends in Female Rats Combining Selected Organs or Tumors in female rats (400 mg/kg/day group included)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1	CTR2	LOW	MED	HIGH	MAX	P-VALUE (EXACT METHOD)	P-VALUE (ASYMPTOTIC METHOD)
CX	CERVIX+UTERUS	HP060003	#B POLYP, ENDOMETRIAL STROMAL	2	3	1	4	3	6	0.0274	0.0213
CX	CERVIX	HP063013	#B GRANULAR CELL TUMOR, BENIGN	0	0	0	0	0	1	0.1500	0.0208
KI	KIDNEYS	HP081005	#B LIPOMA	0	0	0	0	0	1	0.1500	0.0208
LU	LUNGS	HP026024	#M CARCINOMA; UNKNOWN	0	0	0	0	0	1	0.1500	0.0208
NE	NERVE,SCIATIC	HP029004	#M SARCOMA, UNDIFFERENTIATED	0	0	0	0	0	1	0.1216	0.0125
OV	OVARIES	HP033008	#B ADENOMA, SEX CORD STROMAL	0	0	0	0	0	1	0.1500	0.0208
PI	PITUITARY	HP040001	#B ADENOMA, PARS DISTALIS	49	57	56	54	54	56	0.0385	0.0360

PW	PAW(S)	HP046014	#M MYXOSARCOMA	0	0	0	0	0	1	0.1469	0.0200
SA	SOFT TISSUE-ABD	HP081005	#B LIPOMA	0	0	0	0	0	1	0.1508	0.0212
SH	SOFT TISSUE-THO	HP081001	#M LIPOSARCOMA+ #M Liposarcoma, multiple	0	2	2	6	0	5	0.0558	0.0456
SK	SKIN	HP046003	#B FIBROMA + #M FIBROSARCOMA	0	1	1	1	1	3	0.0334	0.0219 (!)
SK	SKIN	HP046012	#B PILOMATRICOMA	0	0	0	0	0	1	0.1508	0.0211
SL	STOMACH, GLD	HP087010	#M LEIOMYOSARCOMA	0	0	0	0	0	1	0.1500	0.0208
TG	THYROID GLANDS	HP053001	#B ADENOMA, C-CELL + #B ADENOMA, C-CELL, MULTIPLE + #M CARCINOMA, C-CELL	2	4	3	9	11	5	0.0527	0.0473

Source data: Analysis data (SAS v. 9.1) R8F21912

Table 33 Interpretation for trend-test results based on p-values (female rat)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	OVERALL TUMOR TYPE	TUMOR RATE AS PCT. IN CONTROL GROUP	SUGGESTED INTERPRETATION FOR TREND-TEST
CX	UTERUS + CERVIX	HP060003	#B POLYP, ENDOMETRIAL STROMAL	Incidental	4.17	Use exact p-value. Use p-value cutoff point of 0.005.
CX	CERVIX	HP063013	#B GRANULAR CELL TUMOR, BENIGN	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
KI	KIDNEYS	HP081005	#B LIPOMA	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
LU	LUNGS	HP026024	#M CARCINOMA; UNKNOWN	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
NE	NERVE,SCIATIC	HP029004	#M SARCOMA, UNDIFFERENTIATED	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
OV	OVARIES	HP033008	#B ADENOMA, SEX CORD STROMAL	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
PI	PITUITARY	HP040001	#B ADENOMA, PARS DISTALIS	Both fatal and incidental	88.33	Use asymptotic p-value. Use p-value cutoff point of 0.005.
PW	PAW(S)	HP046014	#M MYXOSARCOMA	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
SA	SOFT TISSUE-ABD	HP081005	#B LIPOMA	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
SH	SOFT TISSUE-THO	HP081001	#M LIPOSARCOMA + #M Liposarcoma, multiple	Both fatal and incidental	1.67	Use asymptotic p-value. Use p-value cutoff point of 0.005.
SK	SKIN	HP046003	#B FIBROMA + #M FIBROSARCOMA	Both fatal and incidental	0.83	Use asymptotic p-value. Use p-value cutoff point of 0.025.
SK	SKIN	HP046012	#B PILOMATRICOMA	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
SL	STOMACH, GLD	HP087010	#M LEIOMYOSARCOMA	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
TG	THYROID GLANDS	HP053001	#B ADENOMA, C-CELL + #B ADENOMA, C-CELL, MULTIPLE + #M CARCINOMA, C-CELL	Incidental	5.00	Use exact p-value. Use p-value cutoff point of 0.005.

Source data: Analysis data (SAS v. 9.1) R8F21912

Reviewer's Statistical Findings from the Trend-Test:

The dose-tumor linear trend in male rats was statistically significant for FIBROMA+FIBROSARCOMA in SKIN with p-value 0.0219. No significant findings for the other listed tumors.

Analysis including all dose groups excluding 400 mg/kg/day group

Table 34 Report on Trend Test for Positive Linear Dose-Tumor Trends in Female Rats Combining Selected Organs or Tumors in female rats (400 mg/kg/day group excluded)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	CTR1	CTR2	LOW	MED	HIGH	P-VALUE (EXACT METHOD)	P-VALUE (ASYMPTOTIC METHOD)
AM	ADRENAL MEDULLA	HP085005	#B PHEOCHROMOCYTOMA, COMPLEX,	0	0	0	0	1	0.1875	0.0393
AM	ADRENAL MEDULLA	HP085006	#M PHEOCHROMOCYTOMA, MALIGNANT	0	0	0	0	1	0.2192	0.0450
LU	LUNGS	HP081001	#M LIPOSARCOMA	0	0	0	0	1	0.2157	0.0430
OV	OVARIES	HP033006	#B GRANULOSA CELL TUMOR, BENIG	0	0	0	0	1	0.2157	0.0430
SA	SOFT TISSUE-ABD	HP081001	#M LIPOSARCOMA	0	0	0	0	1	0.2222	0.0464
SM	SKELETAL MUSCLE	HP046003	#M FIBROSARCOMA	0	0	0	0	1	0.2027	0.0418
SY	SYSTEMIC TUMORS	HP090003	#B HEMANGIOMA	0	0	0	0	1	0.2157	0.0430
TG	THYROID GLANDS	HP053001	#B ADENOMA, C-CELL + #B ADENOMA, C-CELL, MULTIPLE + #M CARCINOMA, C-CELL	2	4	3	9	11	0.0010 (!)	0.0006

Source data: Analysis data (SAS v. 9.1) R8F21912

Table 35 Interpretation for trend-test results based on p-values (female rat)

ORGAN CODE	ORGAN NAME	TUMOR CODE	TUMOR NAME	OVERALL TUMOR TYPE	TUMOR RATE AS PCT. IN CONTROL GROUP	SUGGESTED INTERPRETATION FOR TREND-TEST
AM	ADRENAL MEDULLA	HP085005	#B PHEOCHROMOCYTOMA, COMPLEX,	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
AM	ADRENAL MEDULLA	HP085006	#M PHEOCHROMOCYTOMA, MALIGNANT	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
LU	LUNGS	HP081001	#M LIPOSARCOMA	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
OV	OVARIES	HP033006	#B GRANULOSA CELL TUMOR, BENIG	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
SA	SOFT TISSUE-ABD	HP081001	#M LIPOSARCOMA	Fatal	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
SM	SKELETAL MUSCLE	HP046003	#M FIBROSARCOMA	Fatal	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
SY	SYSTEMIC TUMORS	HP090003	#B HEMANGIOMA	Incidental	0.00	Use exact p-value. Use p-value cutoff point of 0.025.
TG	THYROID GLANDS	HP053001	#B ADENOMA, C-CELL + #B ADENOMA, C-CELL, MULTIPLE + #M CARCINOMA, C-CELL	Incidental	5.00	Use exact p-value. Use p-value cutoff point of 0.005.

Source data: Analysis data (SAS v. 9.1) R8F21912

Reviewer's Statistical Findings from the Trend-Test:
The dose-tumor linear trend in male rats was statistically significant for THYROID GLANDS

in ADENOMA, C-CELL + ADENOMA, C-CELL, MULTIPLE + M CARCINOMA, C-CELL with p-value 0.001. No significant findings for the other listed tumors.

Conclusion

Table 36 Statistical findings on dose-tumor linear trend based on decision rules of the Office of Biostatistics at CDER

Analysis consideration	Sex	Dose (mg/kg/day)	Organ	Tumor	P-value
Analysis by protocol: Organs and tumors analyzed as reported	Male	Ctrl_2, 40, 100, 200	Soft tissue (THO)	malignant liposarcoma	0.0237
	Female	Ctrl_2, 40, 200		None	
Exploratory analysis: Selected organs or tumors combined (The combining is denoted by the symbol +)	Male	Ctrl_1, Ctrl_2, 40, 100, 200, 400		None	
		Ctrl_1, Ctrl_2, 40, 100, 200	Soft Tissue (THO)	Malignant liposarcoma	0.0085
	Female	Ctrl_1, Ctrl_2, 40, 100, 200, 400	Skin	Fibroma +Fibrosarcoma	0.0219
		Ctrl_1, Ctrl_2, 40, 100, 200	Thyroid glands	Adenoma, c-cell +Adenoma, c-cell, multiple + Carcinoma, c-cell	0.001

Based on the protocol-speficied statistical analysis, this reviewer concludes that Arformoterol is carcinogenic in male rats causing malignant liposarcoma in soft tissue (THO) with a p-value 0.0237. The other analyses were done upon the request of the pharmtox reviewer.

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/s/

Ted Guo
5/24/2006 01:53:05 PM
BIOMETRICS
NDA 21-912 - Statistical Carcinogenicity Review

Karl Lin
5/24/2006 02:07:40 PM
BIOMETRICS
Concur with review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL FILING REVIEW

CLINICAL STUDIES

NDA/Serial Number:	NDA 21-912
Drug Name:	Arformoterol Tartrate Inhalation Solution administered via Unit Dose Vial (UDV)
Indication(s):	Arformoterol is proposed to be indicated for the treatment of COPD
Applicant:	Sepracor
Date(s):	Applicant's letter date: December 8, 2005
Review Priority:	Standard
Biometrics Division:	Biometrics Division 2
Statistical Reviewer:	Ted Guo, Ph.D. (HFD-715)
Concurring Reviewers:	Ruthanna Davi, M.S., Team Leader, Biometrics Division 2
Medical Division:	Division of Pulmonary and Allergy Drug Products (ODE II, HFD-570)
Clinical Team:	Anthony G. Durmowicz, M.D., Medical Officers (ODE II, HFD-570)
Project Manager:	Ladan Jafari (ODE II, HFD-570)
Keywords:	NDA review, clinical studies

Arformoterol Tartrate Inhalation Solution, administered via Unit Dose Vial (UDV), is proposed to be indicated for the treatment of COPD.

The applicant describes Arformoterol as a highly selective, potent, and long-acting beta2-adrenoceptor agonist currently under development in the United States for the long-term maintenance treatment of [redacted] associated with COPD. [redacted] b(4)

The applicant submitted two Phase III pivotal studies, 091-050 and 091-051 to demonstrate that arformoterol delivered via UDV is effective and safe to treat COPD. These studies had the same design. The primary objective for the studies was to "investigate the effect on FEV_1 over 12 weeks of treatment among the following treatment groups: arformoterol 50 μg QD, arformoterol 25 μg BID, arformoterol 15 μg BID, salmeterol metered-dose inhaler (MDI) 42 μg BID, and placebo (Page 30, 8 Study Objectives, 091-050.pdf)."

This reviewer's filing review is based on the criteria listed in the following table.

Criteria	Reviewer's Observation
Index sufficient to locate necessary reports, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Protocol amendments are not available. Only revised protocol is available.
Safety and efficacy for gender, racial, and geriatric subgroups investigated	Not available
Data sets in EDR conform to applicable guidance	Yes

The submission is filable from a statistical perspective. Protocol amendments and subgroup analyses by gender, race, and age may be requested from the sponsor at later stage in the review.

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/s/

Ted Guo
2/21/2006 02:45:44 PM
BIOMETRICS
Filing review

Ruth Davi
2/22/2006 08:05:15 AM
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