Conclusions

Based on the survival data analysis and the tests for dose-tumor positive linear trend, this reviewer concludes:

- There was no statistically significant positive or negative dose-mortality trend.
- There was a statistically significant dose-tumor positive linear for hepatocellular carcinoma (code 365) in liver (code 144) in male mice with p=0.0012.
- There was a statistically significant dose-tumor positive linear for leiomyosarcoma (code 444) in uterus (code 257) in female mice with p=0.019.
- There was a statistically significant dose-tumor positive linear for leiomyoma (code 442) and leiomyosarcoma (code 444) **combined** in uterus (code 257) in female mice with p=0.0006.
- There was a statistically significant dose-tumor positive linear for leiomyoma (code 442) and leiomyosarcoma (code 444) **combined** in uterus (code 257), vagina (code 254) and fallopian tube (code 268) **combined** in female mice with p=0.012.

In summary, Foradil may be carcinogenic affecting livers in male mice and reproductive system in female mice.

Filename: [redacted]

Discussions

This reviewer compared his analyses and the sponsor's findings. The results of the comparisons are given in the following tables. The symbol, "†" represents the significant findings concluded by the sponsor; the symbol "††" indicates significant findings in the reviewer's conclusions.

Note that there are differences in p-values between the sponsor's and this reviewer's results. Even for similar p-values, the criteria for significance may also be different. The differences in p-values might be explained by different computational considerations implemented by different computer programs. The sponsor used the MULTTEST procedure in SAS and this reviewer employed StatXact as the software tool.

Female Rats

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Ovary (265)	Benign granulosa (399)	Sponsor	1	5	6	6	8	0.03657†
		Reviewer	1	5	6	6	8	0.10910

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Fallopian tube (268)	Leiomyoma (442)	Sponsor	0	0	1	1	3	0.02993†
		Reviewer	0	0	1	1	3	0.02900

Male Mice

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Liver (144)	Hepatocellular carcinoma (365)	Sponsor	10	12	19	18	26	0.00328†
		Reviewer	10	12	19	18	26	0.00120††

††: The spontaneous tumor rate was about 15%. The p-value, 0.0012 is compared against 0.005, the Agency's cutoff p-value.

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Liver (144)	Hepatoma or carcinoma (combined)	Sponsor	28	31	40	40	41	0.01505†
		Reviewer	28	31	40	40	41	0.02060

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Subcutaneous tissue (16)	Lipoma (436)	Sponsor	1	2	5	5	5	0.03531†
		Reviewer	1	2	5	5	5	0.1051

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Female Mice

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Liver (144)	Benign hepatoma (363)	Sponsor	9	8	16	17	12	0.04090†
		Reviewer	9	8	16	17	12	0.17100

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Liver (144)	Hepatocellular carcinoma (365)	Sponsor	2	5	3	11	7	0.00419†
		Reviewer	2	5	3	11	7	0.01420

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Liver (144)	Hepatoma or carcinoma (combined)	Sponsor	11	13	19	26	19	0.00103†
		Reviewer	11	13	19	26	19	0.0165

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Uterus (257)	Leiomyoma (442)	Sponsor	4	10	13	14	16	0.00208†
		Reviewer	4	10	13	14	16	0.00990

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Uterus (257)	Leiomyosarcoma (444)	Sponsor	0	3	2	3	5	0.01804†
		Reviewer	0	3	2	3	5	0.01900††

††: The spontaneous tumor rate was 0 (i.e., <1%). The p-value, 0.019 is compared against 0.025, the Agency's cutoff p-value.

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Uterus (257)	Leiomyoma and Leiomyosarcoma (combined)	Sponsor	4	13	15	17	21	0.00010†
		Reviewer	4	13	15	17	21	0.00060††

††: The spontaneous tumor rate was about 6%. The p-value, 0.0006 is compared against 0.005, the Agency's cutoff p-value.

Organ	Tumor		#Animals with Tumor					P-value
			ctrl	low	med	high	highest	
Fallopian tube (268) + vagina (254) + uterus (257)	Leiomyoma (442) + leiomyosarcoma (444)	Sponsor	—	—	—	—	—	—
		Reviewer	4	16	16	17	22	0.0012††

††: The spontaneous tumor rate was about 6%. The p-value, 0.0012 is compared against 0.005, the Agency's cutoff p-value.

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Signoff Page

Statistical Reviewer: Ji-Yang (Ted) Guo /S/

Concur: Karl K. Lin, Ph.D. /S/ 6/4/98

CC:
Archival NDA 20-831
HFD-570/Division file
HFD-570/TZoetis
HFD-570/PJani
HFD-715/Division file
HFD-715/KLin
HFD-715/TGuo
HFD-700/CAnello
TG/April 25, 1998.

Filename:

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date	APR 2 6 2000
NDA #	20-831
Applicant	Novartis
Name of Drug	Foradil™ (formoterol fumarate) Capsules for Inhalation
Indication	Prevention and maintenance treatment of bronchoconstriction for patients, including patients aged 5-12 years, [redacted] asthma
Document Reviewed	☐ Vol. 1 Sponsor's cover letter dated 11/23/1999: Complete Response to Approvable Letter ☐ Vol. 13-19, 36-42 (Clinical Trial Report) ☐ Data submitted: Formoterol Protocol 49 Interim Efficacy Analysis Data sets (12/1/98) PR49-1.trp(zip)
Statistical Reviewer	Ted J. Guo, Ph.D., Div II/OEB, HFD-715
Medical Input	Raymond Anthracite, MD., Division of Pulmonary Drug Products (ODE II, HFD-570)
Key Words	FEV1, AUC

Summary

The sponsor submitted Study 049 in response to the Agency's approvable letter dated 6/26/1998. Study 049 was a placebo-controlled trial of 518 patients aged 5-12 years with mild to moderate asthma. Based on the evaluation of this study with emphasis on effectiveness, this reviewer concludes:

- Foradil at 12 and 24 μg is superior to the placebo.
- Based on this reviewer's analysis, it appears that Foradil at 24 μg is more effective than Foradil at 12 μg.

In summary, this reviewer concurs with the sponsor's overall statistical conclusions.

File name: [redacted]

Table of Contents

File name: [redacted]

List of Tables

List of Figures

File name: ———————

Introduction

In the 6/26/1998 approvable letter to the sponsor (Novartis), the Agency (ref. **Section B Pre-clinical and Clinical Issues, Comment 1)** stated that, "An additional placebo-controlled study in this age group [children 6-12 years of age] that adequately characterizes the optimal dose for this population is required. (Pages 6-7, vol. 1)"

In response to the Agency's approvable letter, the sponsor conducted a study (Protocol 049) on pediatric patients for efficacy and safety. The efficacy part of the study lasted for three months and was submitted to the Agency on 10/19/1998, while the safety monitoring continued for 12 months. The blind was broken for the statistical analysis. In *Response 1* of the *Resubmission Summary Document* dated 11/23/1999, the sponsor indicated that the efficacy study was the "interim clinical report for protocol 049, as conducted under IND ———

Protocol 049 was a placebo-controlled trial of 518 patients aged 5-12 years, with mild to moderate asthma. These patients were treated with Foradil at 12 and 24 μ g b.i.d. The proposed dose for children is 12 μg, b.i.d.

This review focuses on the effectiveness of Foradil in this pediatric patient population.

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Sponsor's Analysis

Overview of Study 049

Study 049 was submitted to the Agency in response to the Agency's Comment #1 of the action letter dated 6/26/98. In the letter, the Agency required adequate efficacy and safety studies for patients aged 6-12 years with asthma, in order for the sponsor to claim the pediatric use of Foradil.

The Study 049 is a 12-month double-blind placebo-controlled study including three treatment arms. The aim of the study was to confirm the efficacy, safety, and tolerability claims of Foradil, which is delivered through inhalation, BID. The study population consisted of asthma patients aged 5-12 years. The study began with its first enrollment dated Dec. 13, 1996 and was completed on Dec. 8, 1998.

The efficacy analyses were based on the study's first three months of data. The safety evaluation was based on the results of the entire 12-month study.

Description of Study Plan

Table 1 highlights the characteristics of this study.

Table 1. Characteristics of Study 049

Study	General Feature	Specific Characteristics
Protocol 049 (Treating mild to moderate asthma) (pp. 13-15, vol. 18.6)	3-month efficacy study	Efficacy study began with a 2-week baseline period. Safety monitoring continued for 12-months of treatment.
	Randomized	3 groups: Foradil 12 μg, Foradil 24 μg, and the Placebo control, administered with single-dose inhalation, b.i.d. (at 6:00-9:00 A.M. and 6:00-9:00 P.M.)
	Double-blind	
	Parallel-group	
	Multi-center	
	Primary efficacy variable: AUC of FEV1	AUC of FEV1 over 12 hours at Visit 5 (end of the third month of treatment). When the rescue medication (salbutamol) was used, the 6-hour washout period prior to the visit to the trial facility applied.

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A total of 601 patients were screened for this trial and 518 were randomized. The patients represented 5 countries and 40 centers. By the end of Visit 5, 467 (90%) patients completed this interim-phase of the trial. Table 2 summarizes the patient accountability. The percentages of completed patients (90.15%) indicate a reasonably good follow-up rate. It appeared to be little difference between treatment groups in the follow-up rate.

Table 2. Patient Counts (Study 049)

	Randomized	Pct	Completed	Pct
Foradil 24 *mcg*	171	33.01	158	92.40
Foradil 12 *mcg*	171	33.01	153	89.47
Placebo	176	33.98	156	88.64
Total	518	100.00	467	90.15

More details can be found in the sponsor's report (pp. 43, vol. 18.6).

Sponsor's Statistical Methods

The sponsor's statistical analysis was based on the ITT patients. These patients comprised all randomized patients with at least one dose of trial medication. The Analysis of Covariance (ANCOVA) was applied to all ITT patients. The statistical model employed is summarized in the following points:

- The AUC of FEV1 over 12 hours at Visit 5 (end of 3rd month of active treatment) was analyzed as the primary outcome variable. The AUC of FEV1 was standardized for the time span of FEV1 measurements.
- Treatment, patients' sex, country, and center nested within country were included as effects of interest.
- The pre-treatment AUC at Visit 2 was included in the statistical model as a covariate.

The sponsor compared

- Foradil at 24 µg, b.i.d. vs. placebo
- Foradil at 12 µg, b.i.d. vs. placebo
- Foradil at 24 µg, b.i.d. vs. Foradil at 12 µg b.i.d.

Each of the comparisons was based on the two-sided test of significance at the 5% level.

The sponsor noted that the treatment-by-center interaction was not investigated. If a patient discontinued the trial, the last available observation was carried forward to the end of the study for analysis. Details of the statistical methods can be found in the sponsor's report (page 38, vol. 18.6).

Outcome variable, the number of asthma exacerbations since the previous visit, was analyzed as a secondary efficacy variable (pp. 29, vol. 18.6). The sponsor's analysis of this variable was for exploratory purposes. The sponsor concluded that, "treatment group differences in the number of asthma exacerbations were only small and did not reach statistical significance. (Page 63, vol. 13.)"

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Sponsor's Statistical Results

The sponsor's efficacy results are summarized in the following Table 3. More details can be found in the sponsor's report.

Table 3. Efficacy Results based on AUC at Visit 5 (Study 049)

Analysis of ITT Patients	Estimate of AUC (L)	95% CL of AUC (L)	P-value
Foradil 24 vs. Placebo	0.18	0.12 – 0.24	<0.0001
Foradil 12 vs. Placebo	0.15	0.09 – 0.21	<0.0001
Foradil 24 vs. Foradil 12	0.03	-0.03 – +0.09	0.3441

Source: Table 11.1-1, pp. 56, vol. 18.6

Sponsor's Conclusions

The sponsor concluded (pp. 76, vol. 18.6),

> "In children aged 5-12 years who required asthma anti-inflammatory treatment and daily bronchodilator treatment, formoterol doses of 12 µg b.i.d. and 24 µg b.i.d. were superior to the placebo with respect to lung function measurements and symptom control over a three month period.
>
> No difference in efficacy nor the occurrence of adverse events was shown between the 12 µg b.i.d. and 24 µg b.i.d. doses of formoterol."

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Reviewer's Evaluation of Study 049

This reviewer's evaluation is based on the sponsor's data dated 12/10/98 and submission dated 7/2/99. Table 4 shows the number of patients included in this study.

Table 4. Number of Patients

Foradil 12 µg	171
Foradil 24 µg	171
Placebo	176
Total	518

Table 5 describes patient accountability for the ITT patients. A total of 467 (90%) out of 518 patients completed the study. The rate of completion appears to be reasonably high.

Table 5. Accountability of ITT Patients in the US Centers

	Treat						Total
	FORAD12		FORAD24		PLACEBO		
	N	PCT	N	PCT	N	PCT	N
pdtermq=1 if prematurely withdrawn							
.	153	32.76	158	33.83	156	33.4	467
1	18	35.29	13	25.49	20	39.22	51
Total	171	33.01	171	33.01	176	33.98	518

(Sponsor's variable, PDTERMQ is an indicator for status of withdraw)

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Table 6 gives the mean values of FEV1 at baseline among the treatment groups. The baseline is defined as the pre-treatment FEV1 values at Visit 2. The overall difference in FEV1 appears to be small among the treatment groups (p=0.3211). Note that such difference remains small (p=0.518) while examining the completers.

Table 6. Baseline FEV1

		MEAN	STD	MAX
FORAD12	171	1.6287	0.4822	
FORAD24	171	1.7078	0.5142	
PLACEBO	176	1.6544	0.4885	

1.1384	2	0.3211

A graphic representation of baseline FEV1 values is depicted in Figure 1 as box-plots.

Figure 1 shows the distributions of the baseline FEV1 values among the treatments. The bottom and top edges of the boxes mark the 25th and 75th percentiles of the sample; the medians are connected by a line; and the maximums, minimums, and means are labeled.

Figure 1. Baseline FEV1

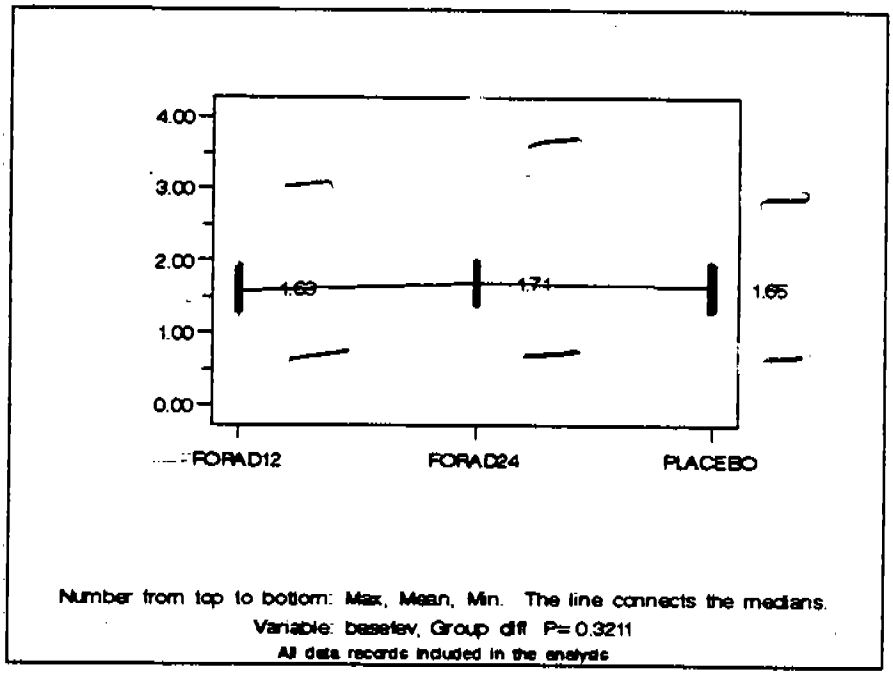

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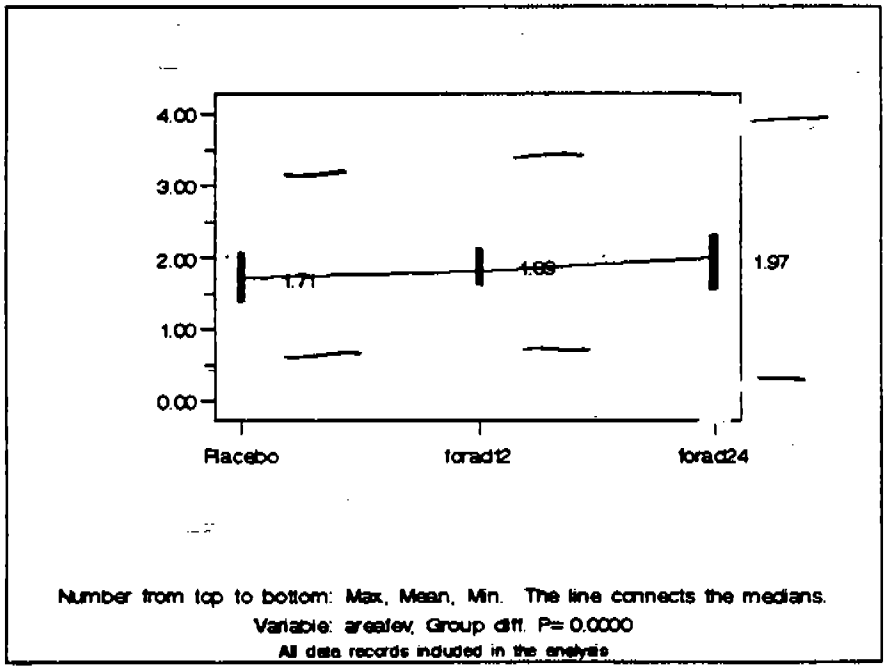
Table 7 shows selected statistics for the AUC values of FEV1 at Visit 2 among the treatment groups. The overall difference in AUC is statistically significant. In addition, the means of AUC increase with dose.

Table 7. AUC of FEV1 at Visit 2

	N	MEAN	SD	MIN	MAX
Placebo	176	1.7145	0.5137		
forad12	171	1.8912	0.5217		
forad24	171	1.9722	0.5688		
[illegible]	[illegible]	[illegible]			
10.546	2	0			

Figure 2 shows the distributions of AUC values of FEV1 at Visit 2 among the treatments. The bottom and top edges of the boxes mark the 25th and 75th percentiles of the sample; the medians are connected by a line; and the maximums, minimums, and means are labeled.

Figure 2. AUC of FEV1 at Visit 2



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To visualize spirometric differences in FEV1 AUC values over time Figure 3 and Figure 4 depict hourly FEV1 measurements at Visits 2 and 5. According to the protocol amendments dated 7/26/97, "The primary variable should be the area under the 12 hour FEV1 curve after three months treatment (Visit 5) (pp. 33, vol. 13)." Clearly, Foradil at 12 and 24 μg demonstrate superiority to the placebo. The figures in both tables show that the FEV1 lines of Foradil 24, 12 and placebo (upper, middle and lower lines) are clearly separated and remain separated for 12 hours of measurements.

Figure 3. Hourly FEV1 at Visit 2

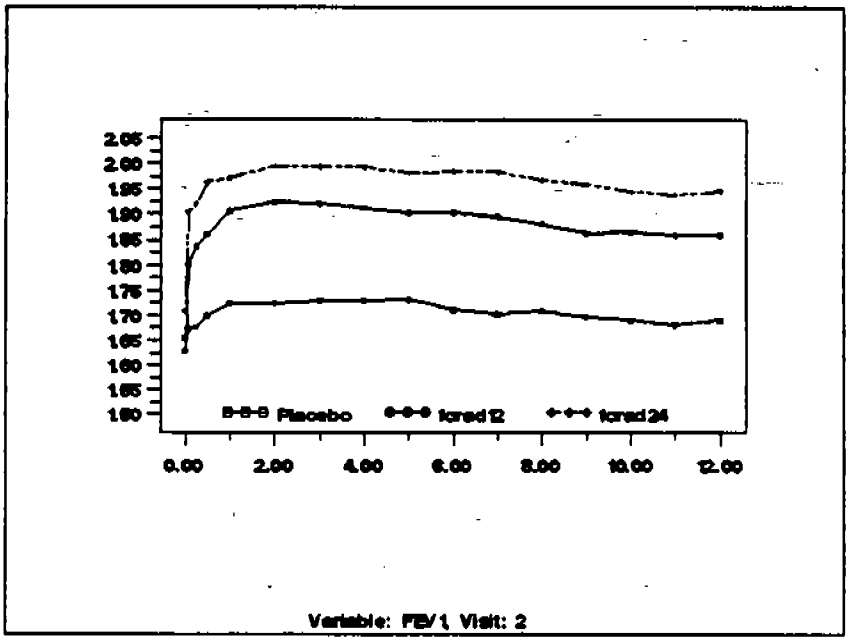
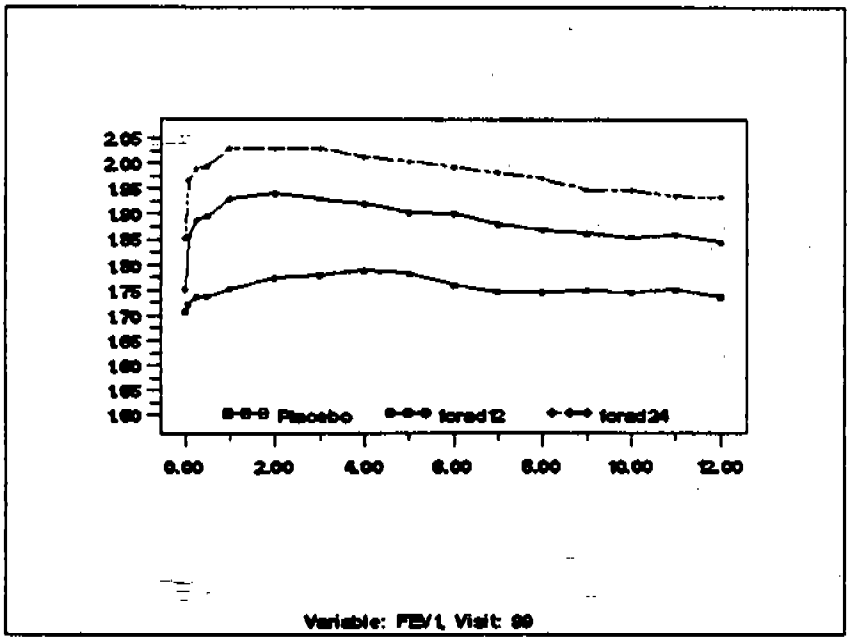


Figure 4. Hourly FEV1 at the Visit 5



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This reviewer's statistical analysis[1] of AUC for Visit 2 is displayed in Table 8, Table 9, and Table 10. This reviewer concludes:

- Foradil at 12 and 24 μg is superior to the placebo.
- Foradil at 24 μg is more effective than Foradil at 12 μg.
- Foradil demonstrates its significant effectiveness on Visits 2 and 5 compared with the placebo.

Table 8. Estimates of AUC Means at Visit 2

Placebo	1.691202	1.724412	1.757621
forad12	1.888049	1.922864	1.957679
forad24	1.897078	1.931880	1.966682

(AREAFEV: AUC of FEV1)

Table 9. Comparisons of AUC between Foradil and Placebo at Visit 2

Dunnett's T tests TREAT Comparison				
forad24 - Placebo	0.20922	0.25763	0.30605	***
forad12 - Placebo	0.12825	0.17667	0.22509	***

Comparisons significant at the 0.05 level are indicated by '***'.

Table 10. Group Comparisons of AUC at Visit 2

Tukey's Studentized Rang TREAT Comparison				
forad24 - forad12	0.02931	0.08096	0.13262	***
forad24 - Placebo	0.20635	0.25763	0.30892	***
forad12 - forad24	-0.13262	-0.08096	-0.02931	***
forad12 - Placebo	0.12538	0.17667	0.22796	***
Placebo - forad24	-0.30892	-0.25763	-0.20635	***
Placebo - forad12	-0.22796	-0.17667	-0.12538	***

Comparisons significant at the 0.05 level are indicated by '***'.

[1] Reviewer's model: *AUC=treatment+center+baselineFEV*, compared to the sponsor's model: *AUC=treatment+country+center(country)+sex+baselineFEV*

File name: [redacted]

Statistical reanalysis of AUC for Visit 5 are demonstrated in Table 11, Table 12, and Table 13. Foradil demonstrates its superiority for Visits 2 and 5 compared with the placebo.

Table 11. Estimates of AUC Means at Visit 5

Placebo	1.724903	1.769318	1.813732
forad12	1.873218	1.919780	1.966342
forad24	1.903866	1.950410	1.996955

(AREAFEV: AUC of FEV1)

Table 12. Comparisons of AUC between Foradil and Placebo at Visit 5

Dunnett's T tests TREAT Comparison				
forad24 - Placebo	0.15881	0.22356	0.28832	***
forad12 - Placebo	0.06777	0.13253	0.19728	***

Comparisons significant at the 0.05 level are indicated by '***'.

Table 13. Group Comparisons of AUC at Visit 5

Tukey's Studentized Range (HSD) TREAT Comparison				
forad24 - forad12	0.02195	0.09104	0.16013	***
forad24 - Placebo	0.15497	0.22356	0.29216	***
forad12 - forad24	-0.16013	-0.09104	-0.02195	***
forad12 - Placebo	0.06393	0.13253	0.20112	***
Placebo - forad24	-0.29216	-0.22356	-0.15497	***
Placebo - forad12	-0.20112	-0.13253	-0.06393	***

Comparisons significant at the 0.05 level are indicated by '***'.

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Comments

This reviewer verified the sponsor's statistical analysis and concluded that the analysis presented in Table 9-1 was accurate. The sponsor's confidence intervals for group differences were based on unadjusted (for multiple comparisons) analysis of covariance with the following linear model:

AUC=treatment+country+center(country)+sex+baselineFEV

The reviewer applied a multiple-comparison-adjusted approach with the following model:

AUC=treatment+center+baselineFEV

The only difference in conclusion between the above approaches is that Foradil 24 μg and Foradil 12 μg differ significantly in the reviewer's analysis while such difference is not statistically significant resulting from the sponsor's analysis.

This reviewer recognizes other analyses for secondary efficacy results by the sponsor. The data were examined but not reanalyzed in this review.

This reviewer reanalyzed the data by excluding the estimated missing data (10% of the total). Such analysis does not change the statistical conclusions resulting from the full-data analysis.

Table 14 shows the number patients withdraw by treatment group. Over all treatments, thirteen patients withdrew due to adverse experience, comprising 25.5% of all the dropouts. Patients of non-compliance consisted of 19.6% among the dropouts. However, the overall percentage of dropout is only about 10%.

Table 14. Patients Withdrawn from Study

Reason for Early Termination	Treatment						Total	
	Form 12æ		Form 24æ		Placebo			
	N	PCT	N	PCT	N	PCT	N	PCT
Administrative problems	0	0	0	0	1	5	1	2
Adverse experience	4	22.2	6	46.2	3	15	13	25.5
Lost to follow-up	1	5.6	0	0	2	10	3	5.9
Non-compliance	4	22.2	1	7.7	5	25	10	19.6
Protocol criteria not met	3	16.7	1	7.7	1	5	5	9.8
Unsatisfactory therapeutic effect	2	11.1	1	7.7	3	15	6	11.8
Withdrawal of consent	3	16.7	3	23.1	3	15	9	17.6
NOT_SPECIFIED	1	5.6	1	7.7	2	10	4	7.8
Total	18	100	13	100	20	100	51	100

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Conclusions

Based on the evaluation of Study 49 with emphasis on the effectiveness of Foradil, this reviewer concludes:

- Foradil at 12 and 24 µg is superior to the placebo.
- Based on this reviewer's analysis, it appears that Foradil at 24 µg is more effective than Foradil at 12 µg.

In conclusion, this reviewer concurs with the sponsor's overall statistical conclusions.

File name: [redacted]

Signoff Page

Reviewer:	**Ted Guo, Ph.D.** /S/ - 4/26/00
Concur:	Steve Wilson, Ph.D. /S/
CC:	
Archival NDA 20-831	
HFD-570/Division file	
HFD-570/ RAnthracite	
HFD-570/PJani	
HFD-715/Division file	
HFD-715/SWilson	
HFD-715/Tguo	
HFD-700/Canello	
TG/April 25, 2000/	

File name: _____

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date	MAY 29 1998
NDA #	20-831
Applicant	Novartis
Name of Drug	Foradil™ (formoterol fumarate) Capsules for Inhalation
Indication	Prevention and maintenance treatment of bronchoconstriction in patients with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma; and for the prevention of exercise-induced bronchospasm

Document Reviewed	• Sponsor's cover letter dated June 24, 1997
	• Clinical studies:
	  • Vol. 1.95 (Study 40 protocol)
	  • Vol. 1.91 (Study 40 Clinical Trial Report 12/31/96)
	  • Vol. 1.182 (Study 41 protocol)
	  • Vol. 1.178 (Study 41 Clinical Trial Report 12/5/96)
	  • Vol. 1.137 (Study 45 Phase II Trial for EIB)
	  • Vol. 1.319 (Study 46 Phase II Trial for EIB)
	  • Vol. 1.1a (File documentation for SAS data sets)
	  • CD (SAS Data sets submitted on 6/27/1997)

Statistical Reviewer	Ji-Yang (Ted) Guo, Ph.D., Div II/OEB, HFD-715
Medical Input	Raymond Anthracite, MD., Division of Pulmonary Drug Products (ODE II, HFD-570)

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Table of Contents

Filename: [redacted]

List of Tables

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