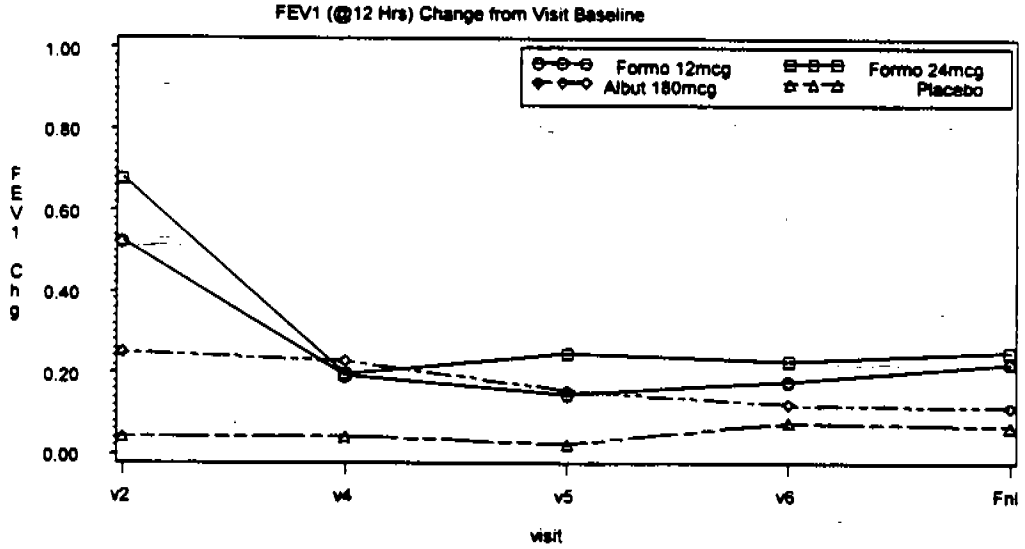
Changes in 12th Hour FEV1 from Visit Baseline

Table 29 and Figure 37 describe the changes in 12th hour FEV1 from the visit baseline, which is the pretreatment observation at the visit. The 12th hour FEV1 changes are smaller than those of the 3rd hour FEV1 changes. However, the trends remain the same.

Table 29. Changes in 12th hour FEV1 from visit baseline (Study 41)

	Chg Fev1 12 hrs from visit baseline									
	v2		v4		v5		v6		Fnl	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
TRT										
Formo 12mcg	0.52	0.41	0.19	0.40	0.15	0.41	0.18	0.39	0.22	0.41
Formo 24mcg	0.68	0.50	0.20	0.44	0.25	0.45	0.23	0.40	0.25	0.43
Albut 180mcg	0.25	0.44	0.23	0.39	0.16	0.43	0.12	0.46	0.11	0.47
Placebo	0.04	0.43	0.04	0.40	0.02	0.42	0.08	0.40	0.07	0.38

Figure 37. Changes in 12th Hour FEV1 from visit baseline (Study 41)



Source: Subt41
WMF: FEV1Chg12H41

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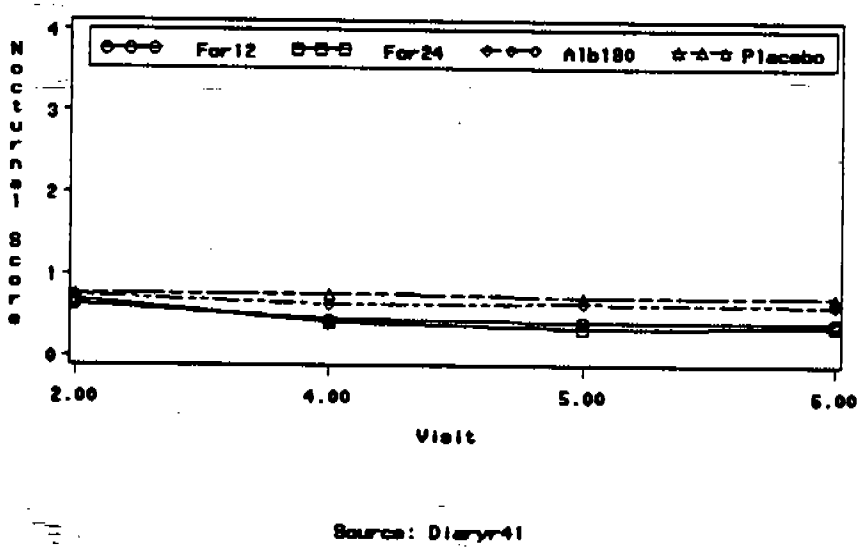
Analysis of Nocturnal Asthma Symptom Scores

This reviewer analyzed the nocturnal-asthma symptom scores to compare the differences between the active treatments and the placebo. Table 30 describes the means and standard deviations of the scores by visit by treatment (Also see Figure 38).

Table 30. Nocturnal-asthma symptom scores (Study 41)

	Treatment							
	1		2		3		4	
	MEAN	STD	MEAN	STD	MEAN	STD	MEAN	STD
Visit								
2.00	0.63	0.86	0.68	0.93	0.74	0.95	0.76	0.97
4.00	0.44	0.75	0.41	0.80	0.63	0.86	0.76	1.00
5.00	0.41	0.74	0.34	0.66	0.64	0.83	0.72	0.95
6.00	0.41	0.73	0.36	0.68	0.62	0.83	0.72	0.96

Figure 38. Nocturnal-asthma symptom scores (Study 41)



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The reviewer's Dunnett's Test indicates that Foradil in (12 and 24 μg) had significantly lower nocturnal-asthma symptom scores than did the placebo and Albuterol. This conclusion holds for visits 4, 5, and 6. Details can be found in Appendix 2. The confidence intervals given below are based on Dunnett's method and are part of the computer output. The symbol, "***" indicates a significant difference between the two groups compared.

Dunnett's T tests for variable: NOCTAM (Nocturnal asthma symptom score)
Comparisons significant at the 0.05 level are indicated by '***'.

TRT Comparison	Simultaneous Lower Confidence Limit	Difference Between Means	Simultaneous Upper Confidence Limit	
Visit = 4				
3 - 4	-0.36886	-0.16335	0.04217	ooo
1 - 4	-0.56170	-0.35461	-0.14751	***
2 - 4	-0.60483	-0.39650	-0.18817	***
Visit = 5				
3 - 4	-0.25248	-0.05685	0.13878	ooo
1 - 4	-0.50408	-0.30613	-0.10819	***
2 - 4	-0.58078	-0.38160	-0.18242	***
Visit = 6				
3 - 4	-0.28816	-0.09233	0.10350	ooo
1 - 4	-0.49232	-0.29374	-0.09517	***
2 - 4	-0.54097	-0.34113	-0.14129	***

where 1: For12, 2: For24, 3: Alb180, 4: Placebo, ooo: not significant

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Reviewer's Evaluation of Study 45 and Study 46

The claim of treating exercise-induced bronchospasm (EIB) was supported by two Phase II crossover studies: Studies 45 and 46. They were single dose, randomized, double-blind, double-dummy, and four-period crossover trials. Both were conducted during 1995-96. The study designs were identical for both trials. Table 31 describes some of the characteristics of these studies.

Table 31. Clinical Trials for EIB

Study No.	Trial Center Location	Number of Patients	Treatment
45	Salt Late City, UT	Enrolled: 26	Foradil, 12 and 24 µg, b.i.d.; Albuterol, 180 µg, q.i.d.; and Placebo
		Randomized: 18	
		Completed: 17	
46	Seattle, WA	Enrolled: 35	Foradil, 12 and 24 µg, b.i.d.; Albuterol, 180 µg, q.i.d.; and Placebo
		Randomized: 20	
		Completed: 17	

Because these clinical trials were crossover studies, each participating patient was expected to receive all four treatments during the study period. The treatment sequence is described on page 10, vol. 1.137 (Study 45) and page 10, vol. 1.319 (Study 46). These sequences are described in Table 32.

Table 32. Treatment Sequences

Treatment Sequence	Visit			
	2	3	4	5
1	Foradil 12	Foradil 24	Albuterol 180	Placebo
2	Foradil 24	Placebo	Foradil 12	Albuterol 180
3	Albuterol 180	Foradil 12	Placebo	Foradil 24
4	Placebo	Albuterol 180	Foradil 24	Foradil 12

At the end of the screening period (1), each patient was randomized to one of the four treatment sequences. At the visit time, the patient changed from his/her current treatment to the next treatment in the designated sequence. The visits were separated by a five-day interval.

The sponsor decided in the protocol that the study required at least 16 patients to complete the designed treatment sequences. This requirement has been met in both studies.

During a visit, observations were made on the FEV1. Each patient was measured at 15 minutes, 4, 8, and 12 hours when the exercise challenges (ECTs) were conducted. For each of these ECTs, the FEV1s were measured at pre-exercise time; 2, 5, 10, 15, 20, 30,45, and 60 minutes post-exercise. The pre-post differences in FEV1 were then computed. If one treatment is more effective than another, this treatment is likely to have a smaller FEV1 decline. The primary efficacy variable was defined as the maximum percentage decline in FEV1 from the pre-exercise value for an ECT.

The sponsor performed separate analyses of variance for all ECT's (15 minutes, 4, 8, and 12 hours). Following the same logic used in the evaluation of efficacy (See Focus of Statistical Evaluation on page 16.), this reviewer focus his attention to the analysis and evaluation of the pre-post exercise percentage changes in FEV1 measured at the 12th-hour. Figure 39 describes the averages and standard errors of the pre-post ECT changes in FEV1 for Study 45. (The graph was generated by Systat 6.0 for Windows.) A similar graph for Study 46 is displayed as Figure 40.

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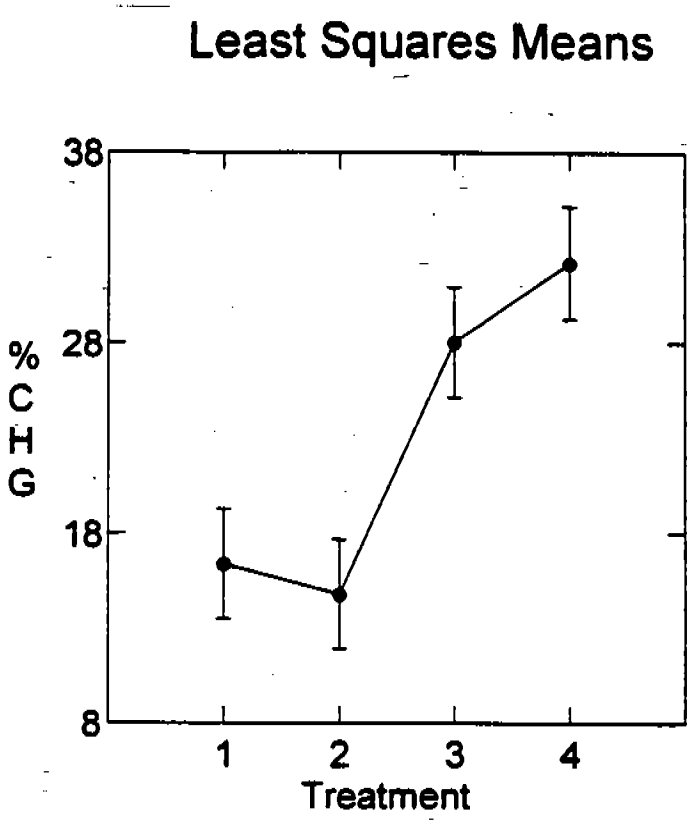
Note that, according to the Figure 39 and Figure 40, the Foradil groups demonstrated noticeably smaller percentage changes in FEV1 than the Albuterol and placebo group, indicating a possibly greater control of the EIB. The differences between Albuterol and placebo appeared to be relatively small.

Figure 39. Pre-Post Percentage Changes in FEV1 (Study 45)



TRTS: 1=Foradil 12, 2=Foradil 24, 3=Albuterol 180, 4=Placebo.

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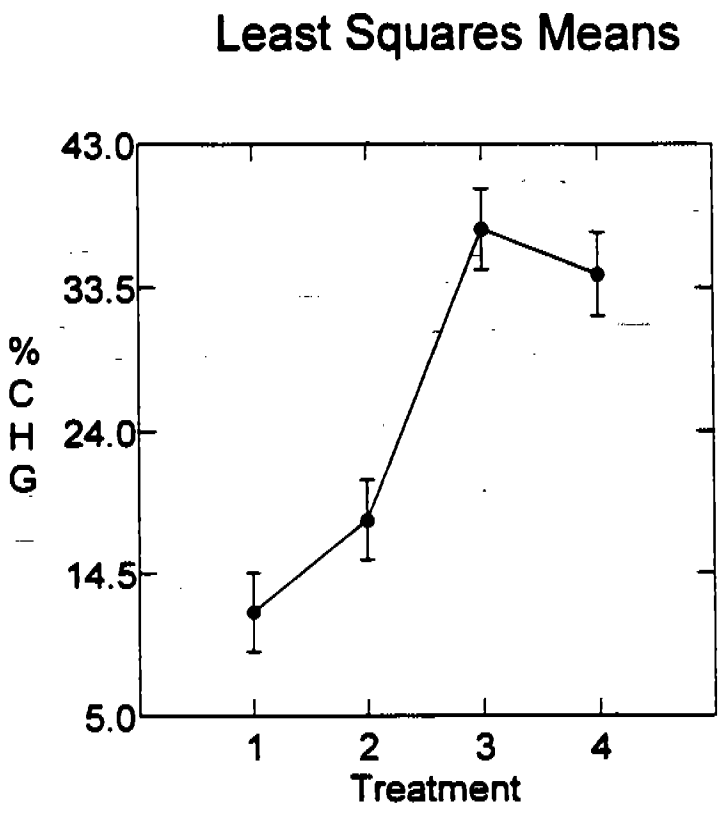
Figure 40. Pre-Post Percentage Changes in FEV1 (Study 46)



TRT$: 1=Foradil 12, 2=Foradil 24, 3=Albuterol 180, 4=Placebo.

The reviewer's analyses (for Studies 45 and 46) are based on the 12th-hour percentage changes in FEV1 from ECT. Table 33 provides a brief summary of the analyses. Details can be found in the appendix. The factors included in the ANOVA are CARRYOVER, TREATMENT, PATIENT, and SEQUENCE. Dunnett Test was applied to the pairwise comparisons between the active treatments and placebo. This way, the overall Type I error was controlled at the 0.05 level.

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The reviewer's analysis, based on the 12th-hour FEV1, are summarized in the following points:

- There was no significant carryover effect for both Studies 45 and 46. In other words, no significant treatment effect carried over from the current treatment to the subsequent ones in the treatment sequence. The five-day time span between the visits was adequate.
- The treatment effect was significant with very small p-values.
- Foradil at 12 and 24 μg was significantly more effective than the placebo in controlling EIB.
- Albuterol at 180 μg was not significantly different from the placebo in terms of percentage changes in FEV1 from ECT. This conclusion is consistent with those reached by the sponsor.

Table 33. Analysis of Percentage Changes in FEV1 from ECT

Study	P-values				
	Carryover Effect	Overall Treatment Effect	Foradil 12 vs. Placebo	Foradil 24 vs. Placebo	Albuterol vs. Placebo
45	0.568	<0.001	0.002	<0.001	0.588
46	0.207	<0.001	<0.001	<0.001	0.988

This reviewer concludes that Foradil at 12 and 24 μg, b.i.d., is statistically superior to the placebo in controlling EIB based on Studies 45 and 46. This effect has not been demonstrated by Albuterol in either Study 45 or 46.

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Conclusions

Based on the statistical evidence presented by the sponsor and the selected statistical evaluations by this reviewer on Studies 40 and 41, this reviewer reached the following conclusions:

- The statistical evidences and conclusions presented in Studies 40 and 41 are consistent, and the efficacy claim for Foradil is well supported.
- Foradil at 12 μg and 24 μg, b.i.d. is significantly superior to the placebo. The 24-μg dose appears to be even more efficacious, though the difference between the two Foradil doses is not significant.
- Albuterol at 180μg, q.i.d, as a positive control, is also superior to the placebo.
- Foradil is most effective around the 3rd hour after the morning dose, it remains effective for the entire day.
- Based on the two 12-week trials (Studies 40 and 41), the effectiveness of Foradil is demonstrated at all the four visits (visits 2,4,5, and 6).
- Patients treated with Foradil at 12 μg and 24 μg, b.i.d. had significantly improved nocturnal-asthma scores (i.e., significantly lower nocturnal asthma symptom scores) than those treated with placebo. Such significance was not demonstrated for patients treated with Albuterol.
- Foradil at 12 and 24 μg, b.i.d., is statistically superior to the placebo in controlling EIB based on Studies 45 and 46. This effect has not been demonstrated by Albuterol in either Study 45 or 46.

In summary, the sponsor in this NDA has provided sufficient statistical evidence to demonstrate that Foradil, at both 12 μg and 24 μg, b.i.d. is superior to the placebo for treating mild to moderate asthma, including patients with symptoms of nocturnal asthma, and for controlling exercise-induced bronchospasm.

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Signoff Page

Reviewer: Ted Guo, Ph.D. /S/ 5/21/98

Concur: Steve Wilson, Ph.D. /S/ 5/21/98
Ed Nevius, Ph.D. /S/ 5/29/98

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

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