

Additional Observations of FEV1

Additional observations were made on FEV1 in different forms. These observations were made based on a proposal from Dr. Raymond Anthracite. It was found during an exploratory data assessment that the dose effect reached its highest point near 3rd hour since the morning dose. The effect decreased gradually with time. This reviewer computed the difference between the 3rd hour FEV1 and the pre-dosing FEV1, namely the very first spirometric measure of FEV1 at the visit. A difference between the 12th hour FEV1 and pre-dosing FEV1 was also computed. These differences are tabulated and plotted as follows.

Changes in 3rd Hour FEV1 from Visiting Baseline

Table 14 and Figure 17 describe the changes in 3rd hour FEV1 from the visiting baseline, which is the pretreatment observation at the visit. Note that the pretreatment FEV1 values increased with time, possibly due to the carryover effect of the drug. Therefore, the decrease of the 3rd hour FEV1 changes may partly be explained by the increase in pretreatment-values over time (See Figure 18).

Table 14. Change in 3rd-Hour FEV1 from Visit Baseline (Study 40)

	Chg Fev1 03 hrs from visit baseline							
	v2		v4		v5		v6	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std
TRT								
Formo 12mcg	0.63	0.44	0.38	0.38	0.44	0.37	0.46	0.41
Formo 24mcg	0.76	0.46	0.49	0.37	0.43	0.29	0.42	0.29
Albut 180mcg	0.51	0.41	0.44	0.38	0.46	0.38	0.37	0.36
Placebo	0.23	0.32	0.16	0.29	0.12	0.33	0.14	0.33

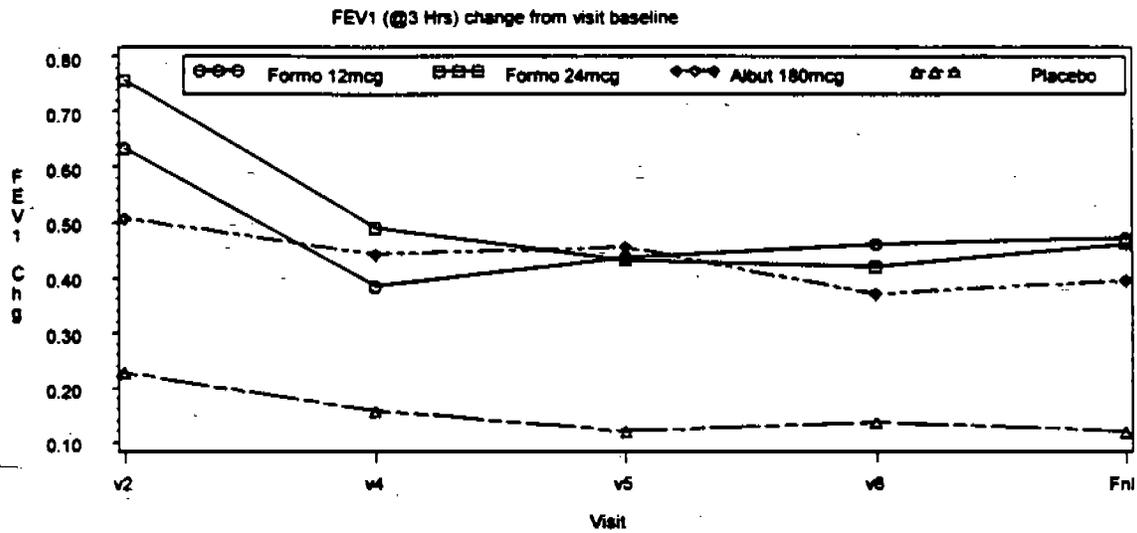
(source: s4bt40)

It can be seen that the changes from pretreatment FEV1 were clearly greater among the drug groups than among the placebo group. In addition, the differences became smaller after the second visit.

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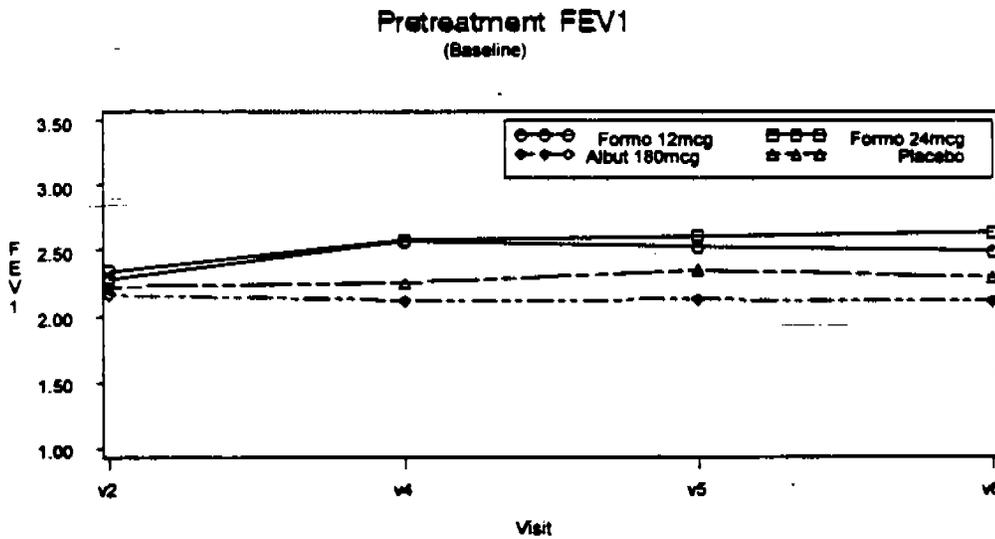
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Figure 17. Change in 3rd-Hour FEV1 from Pre-Dosing FEV1 (Study 40)



Source: Sub140
WMF: Fev1Chg3Hr40

Figure 18. Pretreatment FEV1 (Study 40)



Source: Sub40
WMF: SbVb40

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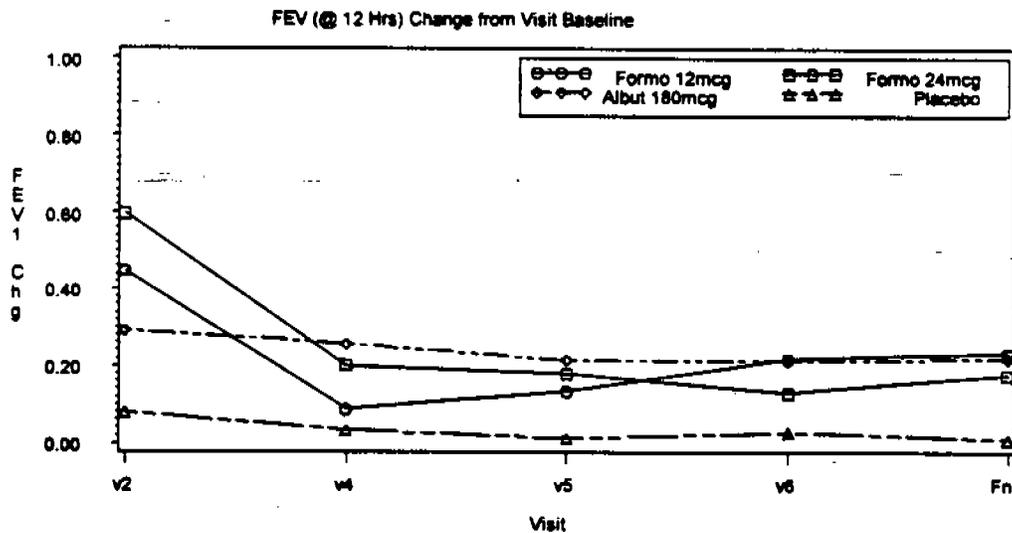
Changes in 12th Hour FEV1 from Visit Baseline

Table 15 and Figure 19 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 found smaller than those of the 3rd hour FEV1 changes are. However, the similar trend remains the same.

Table 15. Changes in 12th hour FEV1 from visit baseline (Study 40)

TRT	Chg Fev1 12 hrs from visit baseline									
	v2		v4		v5		v6		Fnl	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
Formo 12mcg	0.45	0.45	0.09	0.39	0.13	0.34	0.22	0.41	0.23	0.42
Formo 24mcg	0.59	0.47	0.20	0.40	0.18	0.40	0.13	0.31	0.18	0.40
Albut 180mcg	0.29	0.51	0.26	0.44	0.21	0.36	0.21	0.42	0.22	0.44
Placebo	0.08	0.40	0.03	0.36	0.01	0.33	0.03	0.37	0.01	0.39

Figure 19. Changes in 12th Hour FEV1 from visit baseline (Study 40)



Source: Sub140
WMF: FEV1Chg12Hr40

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 16 gives the means and standard deviations of the scores by visit by treatment.

Table 16. Nocturnal-asthma symptom scores (Study 40)

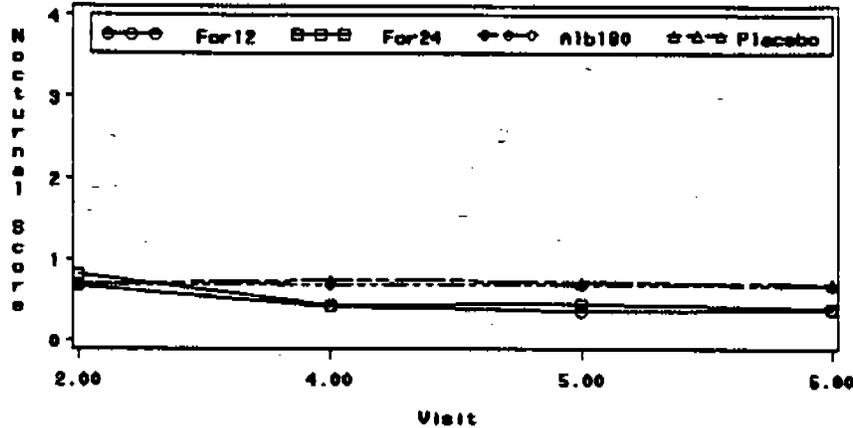
	Treatment							
	For12		For24		Alb180		Placebo	
	MEAN	STD	MEAN	STD	MEAN	STD	MEAN	STD
Visit								
2.00	0.68	0.94	0.81	0.97	0.68	0.96	0.69	0.93
4.00	0.42	0.77	0.44	0.74	0.68	0.93	0.74	0.90
5.00	0.35	0.66	0.44	0.80	0.69	0.83	0.73	0.89
6.00	0.38	0.74	0.40	0.76	0.67	0.89	0.69	0.86

The same information is depicted in Figure 20. The mean scores were higher among patients treated with Albuterol or placebo than among those treated with Foradil. The difference between the two Foradil groups was relative small.

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Figure 20. Nocturnal-asthma symptom scores (Study 40)



Source: Diary40

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	-0.26691	-0.06712	0.13267	ooo
1 - 4	-0.50592	-0.30371	-0.10149	***
2 - 4	-0.51388	-0.31370	-0.11352	***
Visit = 5				
3 - 4	-0.25686	-0.05363	0.14960	ooo
2 - 4	-0.51432	-0.31280	-0.11128	***
1 - 4	-0.58900	-0.38442	-0.17983	***
Visit = 6				
3 - 4	-0.25716	-0.05350	0.15016	ooo
2 - 4	-0.50085	-0.29897	-0.09708	***
1 - 4	-0.54561	-0.34102	-0.13643	***

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

Reviewer's Evaluation of Study 41

Descriptions of Patients

Evaluation of Patient Accountability

The patient population is described in Table 17. The columns represent the numbers and percentages of the patients who stayed on the study up to the indicated visits. For example, patients last seen at visit No. 2 and then discontinued accounted for the number of patients in column 1, while patients who completed all visits are reported in column 4. In other words, patients who had their last visits as visits 2, 4, and 5 did not complete the study.

Of the 554 patients, 485 completed the study, accounting for 88% of the total patients. Among the four treatment groups, at least 85% of the patients completed the study. Note that 7.4% of the total patients did not continue after visit 2, showing a higher rate of dropout than those discontinued after visit 4 and 5 (3.8% and 1.3%). In general, the dropout rates were considered relatively low.

Table 17. Patient Population (Study 41)

	Last Visit								Total	
	2		4		5		6			
	n	%	n	%	n	%	n	%	n	%
TRT										
Formo 12mcg	12	8.6	4	2.9	1	0.7	122	87.8	139	100.0
Formo 24mcg	12	8.8	6	4.4	2	1.5	116	85.3	136	100.0
Albut 180mcg	5	3.6	5	3.6	1	0.7	127	92.0	138	100.0
Placebo	12	8.5	6	4.3	3	2.1	120	85.1	141	100.0
Total	41	7.4	21	3.8	7	1.3	485	87.5	554	100.0

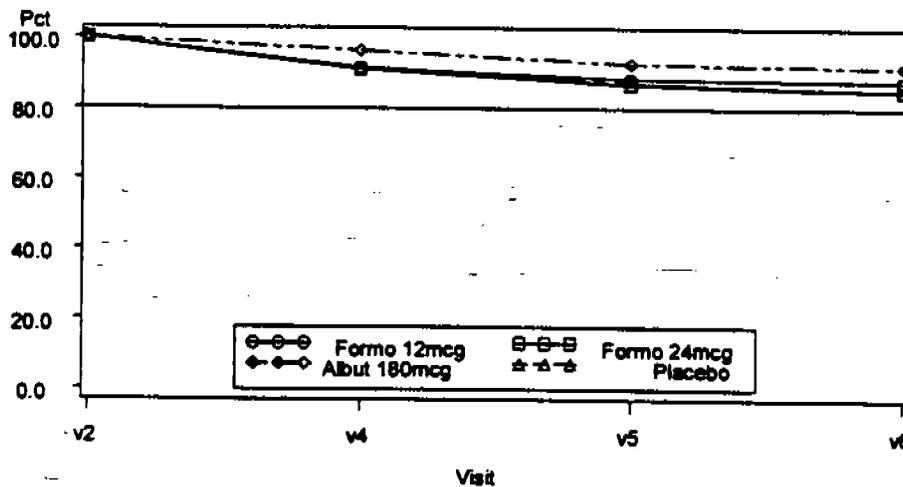
(Source: Temp41)

* Note: Column 6 accounts for patients who completed the study, while patients in other columns discontinued. For example, 41 patients only completed visit 2 then dropped out (Column 2).

Note that there were fewer patients actually included in the reviewer's statistical analyses than those counted in Table 17. Patients with missing study baseline observations were excluded from this reviewer's analyses. The actual numbers of patients included in the analyses are shown in Table 20.

Figure 21 below depicts the percentages of patients (by treatment group) who stayed on study by time. The percentages of completion fall between 80-90% (Also, see Table 17 above). Patients who completed visit 6 stayed on study until the end of the study. This reviewer determines that the number of patients lost to follow-up was low and evenly distributed among the treatment groups. Therefore, the number of dropouts does not cause alarming concern to the efficacy evaluation.

Figure 21. Percentages of Patients Stayed on Study (Study 41)



Source: Drop41

Table 18 and Table 19 below describe that the number of puffs of rescue medication used. Patients in both the Albuterol and placebo group used more rescue medication than those in the Foradil groups. Note that the percentages of patients stayed in the study were similar for the Foradil 24 µg group and the placebo group. Therefore, the use of rescue medication alone may not explain why the percentage of patients stayed in the study was higher among those in the Albuterol group than in other groups.

Table 18. Puffs of Rescue Medication: Nighttime use (Study 41)

TREATMENT	PUFFS AM			
	No.	Pct	Mean	Std
Foradil 12mcg	134	24.9	0.78	0.94
Foradil 24mcg	133	24.7	0.76	0.98
Albuterol 180mcg	135	25.1	1.03	1.05
Placebo	136	25.3	1.60	1.44
Over All	538	100.0	1.04	1.17

Source: Diary0.sd2

Table 19. Puffs of Rescue Medication: Daytime use (Study 41)

	PUFFS PM			
	No.	Pct	Mean	Std
TREATMENT				
Formo 12mcg	134	24.8	0.92	1.10
Formo 24mcg	134	24.8	0.96	1.07
Albut 180mcg	135	25.0	1.24	1.24
Placebo	137	25.4	1.99	1.78
Over All	540	100.0	1.28	1.40

Source: Diary0.sd2

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Evaluation of Missing Observations

There were missing FEV1's during the observation periods. The sponsor details the method to handle missing observations on page 48, vol. 1.178. Here is a brief summary of the sponsor's method.

For patients terminated during a 12-hour observation period at a visit, the last observed value was carried forward through the 12th hour. For the missing values between observations, the linear interpolation method was applied to impute those missing data. Certain rules were applied, according to the protocol.

There were cases where the missing observations could not be estimated. The following patients had non-imputable observations.

<u>Non-Imputed Missing Observations</u>			
Treatment	Center	Patient	Missing
Formo 12mcg	M0158X	6670	4
Formo 24mcg	M0154H	6183	30
	M0159B	6437	1
	M0160U	6048	2
	M0161Y	6326	22
	M0168A	6113	1
Albut 180mcg	M0153D	6260	16
	M0153D	6385	24
	M0156P	6025	5
Placebo	M0147Q	6281	2
	M0147Q	6380	30
	M0149Y	6111	4
	M0152Z	6156	8
	M0162C	6492	1
	M0165O	6376	30
	M0176V	6174	20

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Because this reviewer excluded patients with missing baseline values, the number of actually included in the statistical analyses are shown in Table 20.

Table 20. Number of Patients Included in Reviewer's Statistical Evaluation (Study 41)

	Last Visit								Total		
	2		4		5		6				
	n	%	n	%	n	%	n	%	n	%	
Treatme- nt											
Formo 12mcg	12	8.6	4	2.9	1	0.7	122	87.8	139	100.0	
Formo 24mcg	12	8.9	6	4.4	2	1.5	115	85.2	135	100.0	
Albut 180mcg	5	3.6	5	3.6	1	0.7	127	92.0	138	100.0	
Placebo	12	8.5	6	4.3	3	2.1	120	85.1	141	100.0	
Total	41	7.4	21	3.8	7	1.3	484	87.5	553	100.0	

(Source: sub41)

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Analysis of Baseline FEV1

Table 21 shows the means and standard deviations of pretreatment FEV1 measures (study baseline values). The differences in study baseline values among the treatment groups were not statistically significant (p-value=0.9885).

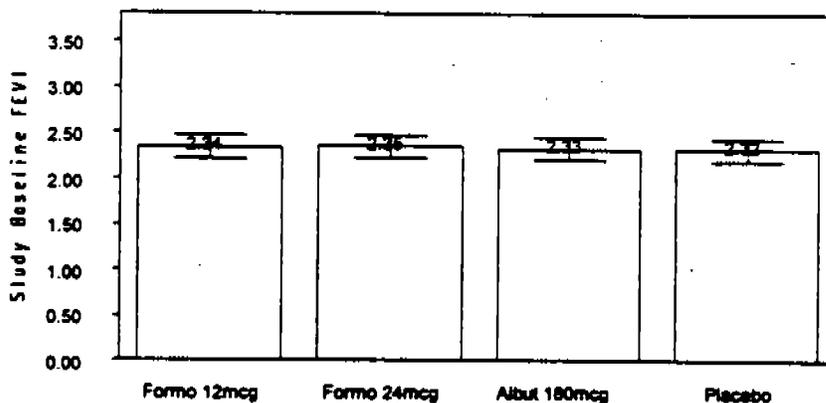
Table 21. Baseline FEV1 by treatment (Study 41)

TRT	Baseline FEV1 (Visit 2)			
	N	%	Mean	Std
Formo 12mcg	139	25.1	2.34	0.77
Formo 24mcg	135	24.4	2.35	0.75
Albut 180mcg	138	25.0	2.33	0.75
Placebo	141	25.5	2.32	0.77
Over All	553	100.0	2.34	0.76

(Source: sub41/visit=2 & spno=1/imfev1:trt)

A "picture" of Table 21 is shown in Figure 22.

Figure 22 . Baseline FEV1 by Treatment (Study 41)



Source: sub41
 DDF: Sbf0441

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Evaluation of Study-Baseline FEV1 by Patient Characteristics

This section evaluates the variations in baseline FEV1 values by patient characteristics: Sex, race, and age group. It is this reviewer's intention to assess the situation of potential imbalance in baseline values among various patient.

Table 22, Table 23, Table 24: and Figure 23, Figure 24, and Figure 25 describe the FEV1s by sex, race, and age.

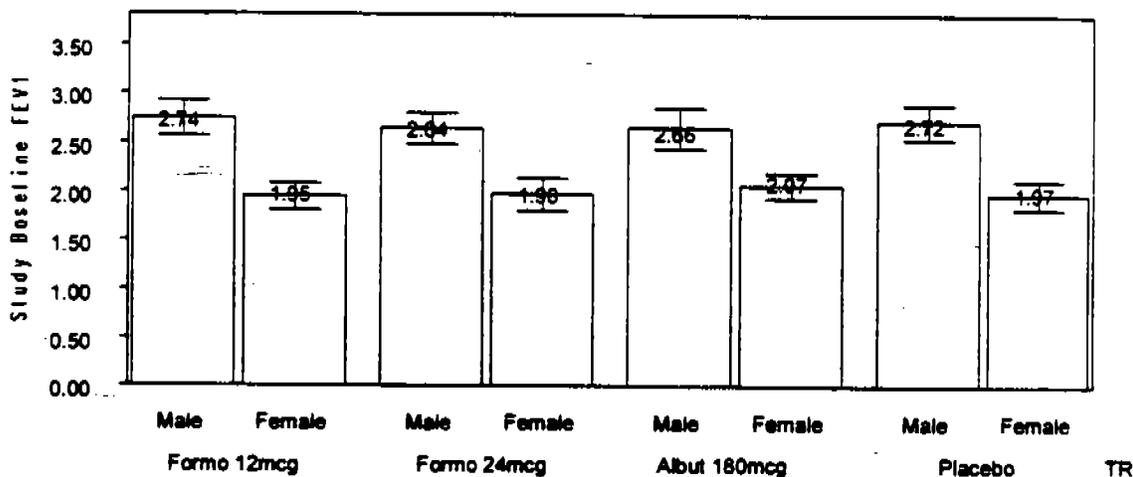
Table 22. Number of Patients by Sex by Treatment (Study 41)

	Treatment									
	Formo 12mcg		Formo 24mcg		Albut 180mcg		Placebo		Total	
	n	%	n	%	n	%	n	%	n	%
Sex										
Male	69	25.3	76	27.8	62	22.7	66	24.2	273	100.0
Female	70	25.0	59	21.1	76	27.1	75	26.8	280	100.0
Total	139	25.1	135	24.4	138	25.0	141	25.5	553	100.0

(source: subtt41)

Figure 23 indicates that the baseline FEV1 values were greater in males than in females.

Figure 23. Baseline FEV1 by Sex by Treatment (Study 41)



Source: Subtt41
 WDF: 5bSex41

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Table 23 describes the number of patients by race by treatment. About 86% of the total patients was white.

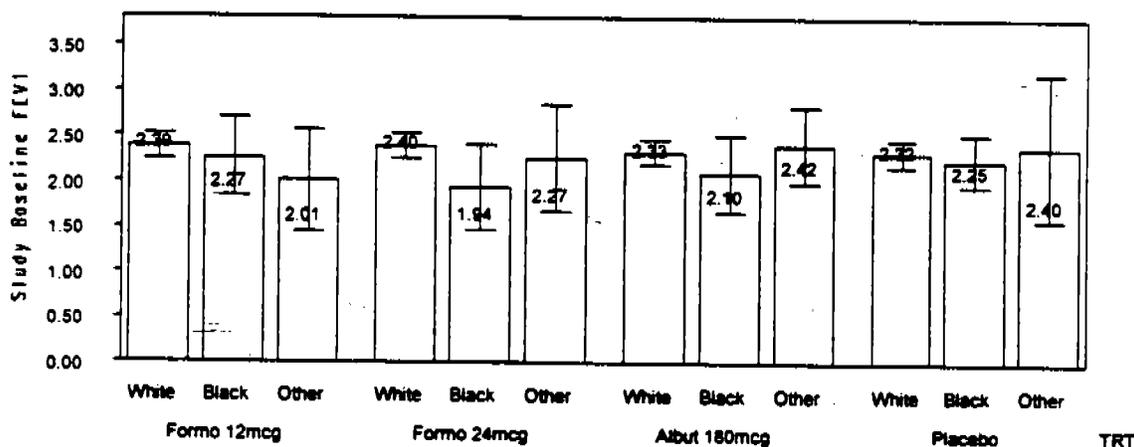
Table 23. Number of Patients by Race by Treatment (Study 41)

Race	Treatment									
	Formo 12mcg		Formo 24mcg		Albut 180mcg		Placebo		Total	
	n	%	n	%	n	%	n	%	n	%
White	113	23.9	116	24.5	123	26.0	121	25.6	473	100.0
Black	13	31.0	12	28.6	4	9.5	13	31.0	42	100.0
Other	13	34.2	7	18.4	11	28.9	7	18.4	38	100.0
Total	139	25.1	135	24.4	138	25.0	141	25.5	553	100.0

(source: subtt41)

Figure 24 indicates that the baseline FEV1 values were balanced across racial categories.

Figure 24. Baseline FEV1 by Race by Treatment (Study 41)



Source: subtt41
WUF: 50R00041

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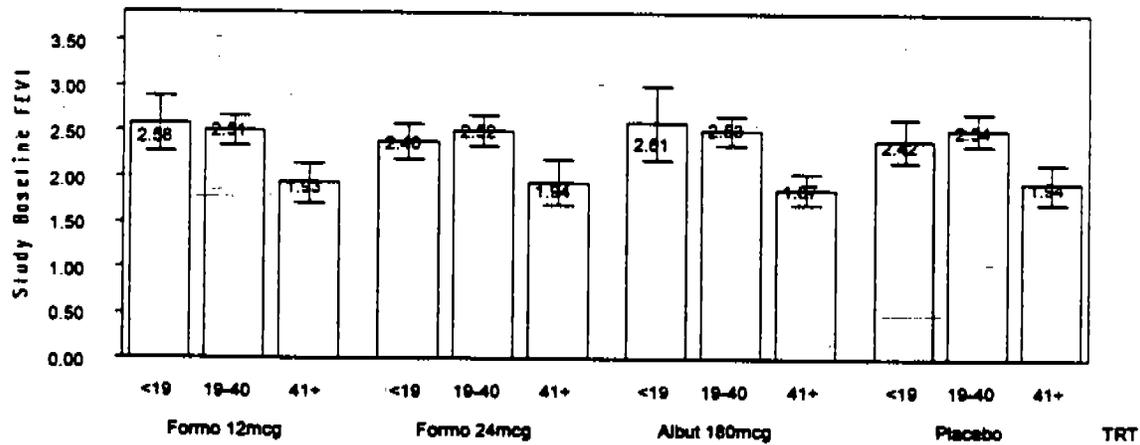
Table 24 describes the patient ages by treatment. The patients were 33 years of age on average. The youngest patient was aged 12 and the oldest was 74.

Table 24. Analysis of Patient Age (Study 41)

TRT	AGE					
	N	%	Average	Std	Minimum	Maximum
Formo 12mcg	139	25.1	32.59	13.95	12.00	72.00
Formo 24mcg	135	24.4	32.49	14.93	12.00	74.00
Albut 180mcg	138	25.0	33.83	14.33	12.00	74.00
Placebo	141	25.5	33.52	14.89	12.00	73.00
Over All	553	100.0	33.11	14.50	12.00	74.00

Figure 25 shows that the baseline FEV1 values were smaller among the patients, aged 41 and older than among the younger groups.

Figure 25. Baseline FEV1 by Age Group by Treatment (Study 41)



Source: sub1141
 WFF: S000041

Based on the above assessment of imbalance among the selected patient group, this reviewer did not find unusually large or small FEV1s in any patient group.

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Focus of Statistical Evaluation

The statistical methods used by the sponsor in Study 41 were the same as those used in Study 40. The primary outcome variable based on which statistical conclusions were drawn was FEV1. According to the sponsor's protocol, the baseline FEV1 was included in the statistical model as the covariate.

The reviewer's confirmatory evaluations were based on the following outcome variables:

4. FEV1 at hour 12 of Visit 6,
5. Mean FEV1 at Visit 6, and
6. AUC at-Visit 6.

In the following graphs, Figure 26, Figure 27, Figure 28, and Figure 29; this reviewer explores the pattern of the FEV1 values over the observation time points for each visit. It has been found that the pattern of FEV1-value changes was similar to what can be seen in study 40. Therefore, this reviewer omits the similar discussion here.

Clearly, if the superiority of Foradil can be confirmed at the last observation at the last visit, it is reasonable to extend such a conclusion to the entire study period.

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In the following graphs, FEV1 values were plotted against time points of observations. The values at time 0 at visit 2 represents the study baseline values.

Figure 26. FEV1s at Visit 2 (Study 41)

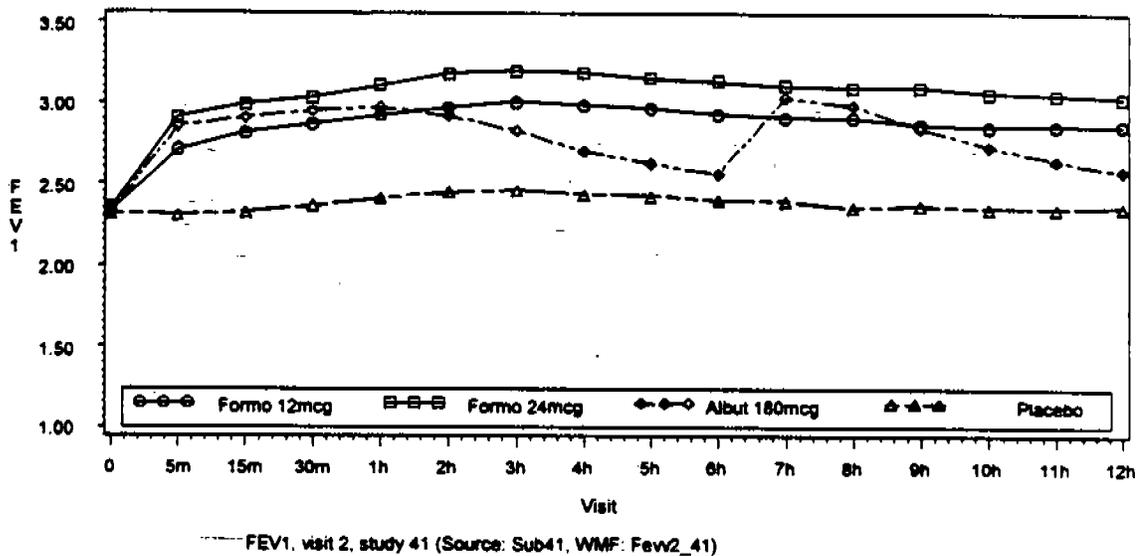
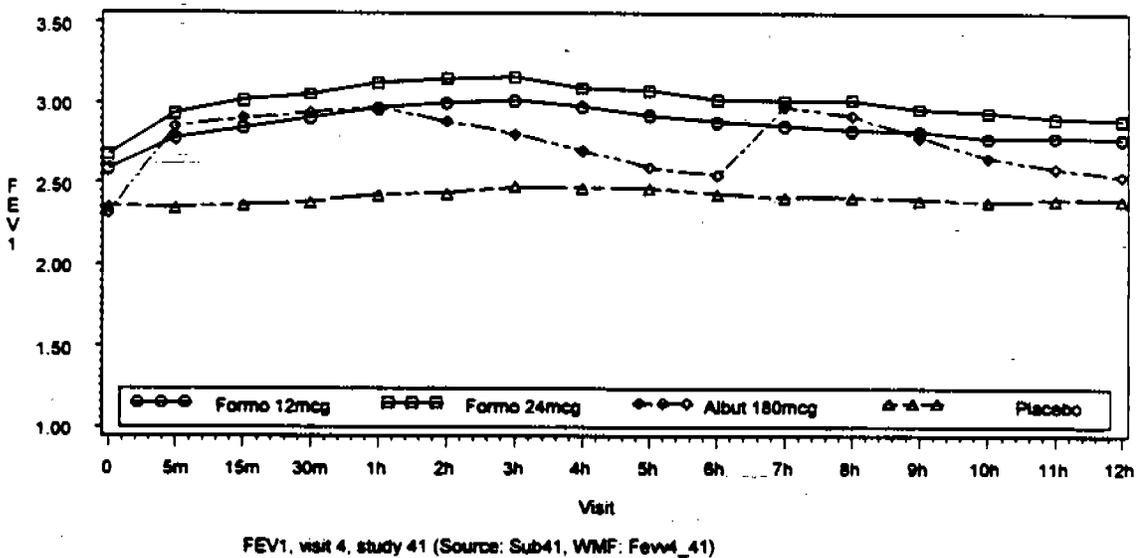
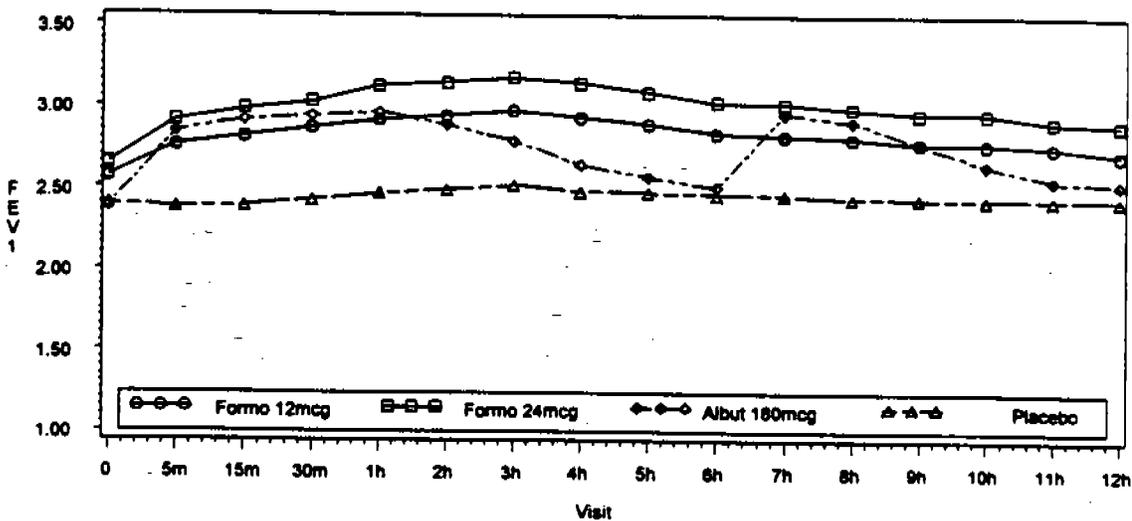


Figure 27. FEV1s at Visit 4 (Study 41)



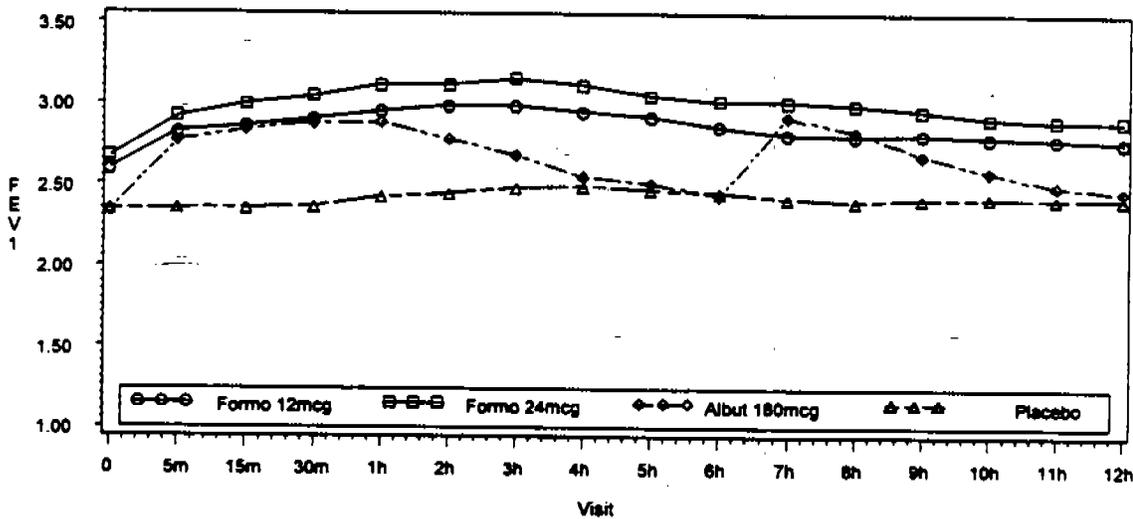
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Figure 28. FEV1s at Visit 5 (Study 41)



FEV1, visit 5, study 41 (Source: Sub41, WMF: Fev5_41)

Figure 29. FEV1s at Visit 6 (Study 41)

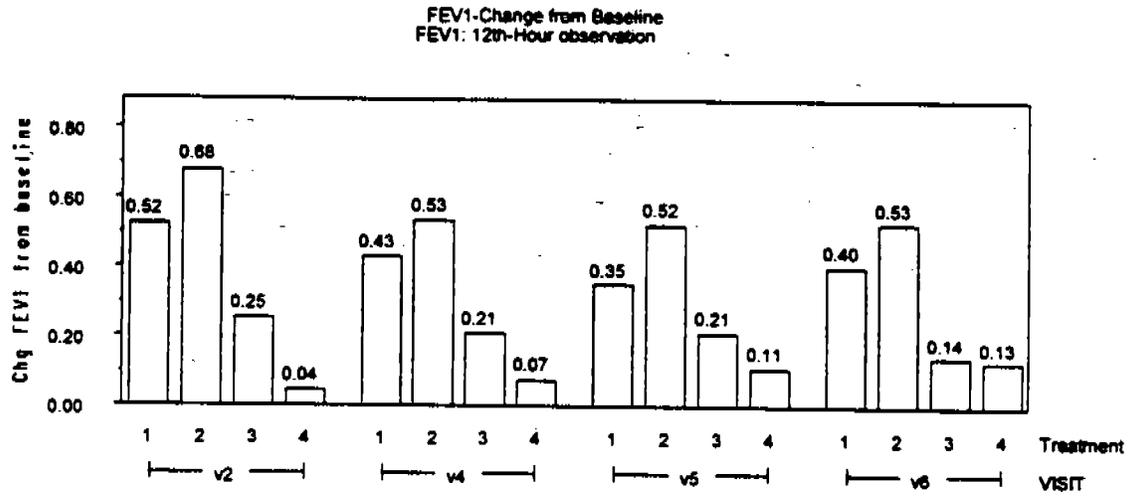


FEV1, visit 6, study 41 (Source: Sub41, WMF: Fev6_41)

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Figure 30 demonstrates the changes in FEV1 from baseline. Here, the FEV1 is the measurement taken at 12th hour of the observation period. Clearly, the Foradil dose groups had greater changes from baseline than Albuterol and the placebo. The changes appear to be somewhat greater in the higher dose group than in the lower one.

Figure 30. Changes in 12th-Hour FEV1 from Trial Baseline (Study 41)



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

Source: sub41
WMF: Chg12H41

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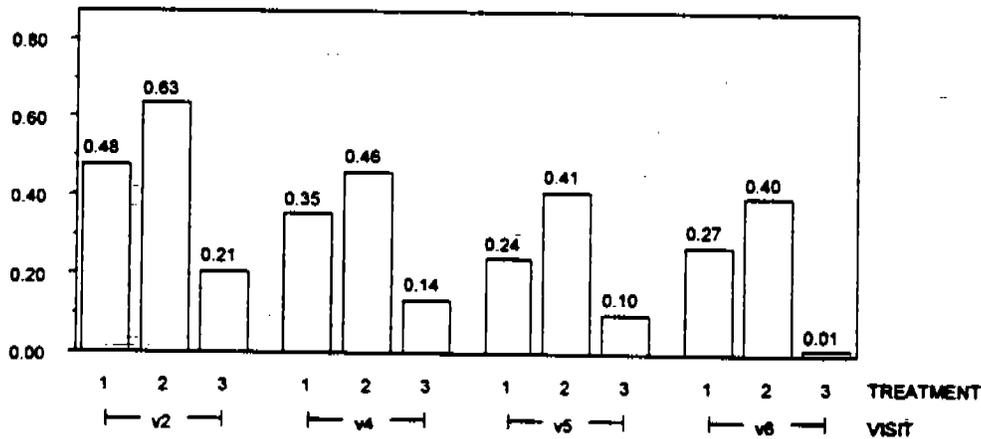
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Table 25 and Figure 31 compare the differences in 12th-hour FEV1 changes from baseline measures between the drug groups and the placebo. The differences between the Foradil doses and the placebo were greater than those between Albuterol and the placebo.

Table 25. Drugs vs. Placebo: Differences in 12-Hour FEV1 Changes from Baseline (Study 41)

	Differ in 12hr FEV1 Chg from Base			
	Drug vs. placebo			
	v2	v4	v5	v6
TRT				
Formo 12mcg	0.48	0.35	0.24	0.27
Formo 24mcg	0.63	0.46	0.41	0.40
Albut 180mcg	0.21	0.14	0.10	0.01

Figure 31. Drugs vs. Placebo: Differences in 12-Hour FEV1 Changes from Baseline (Study 41)



Treatment: 1=Foradil 12, 2=Foradil 24, 3=Albuterol 180

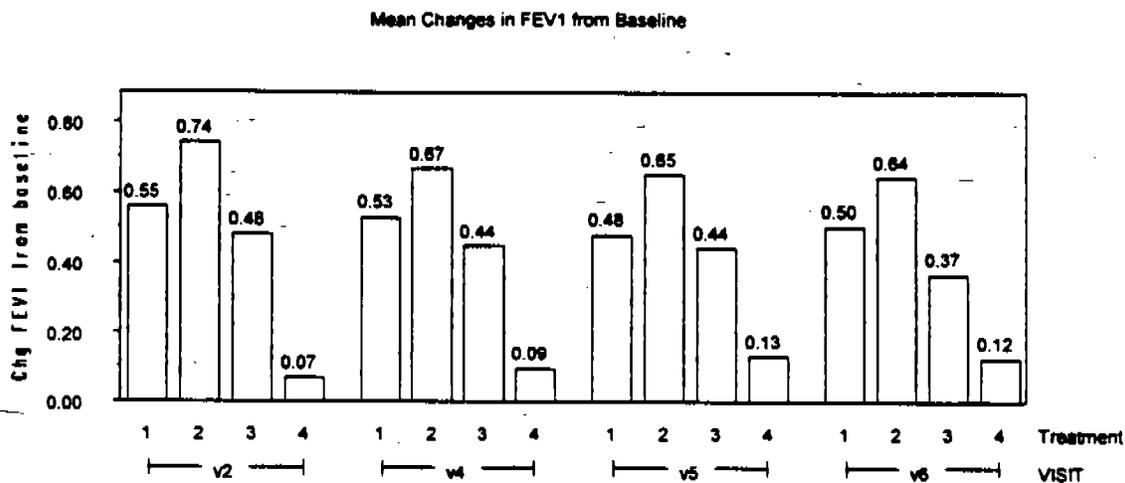
Source: sub41.difchg41
WMF: Dif12hChg41

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Figure 32 demonstrates the changes in FEV1 from baseline. Here, the FEV1 is the mean measurement taken during the 12-hour observation period at a visit. Clearly, the Foradil dose groups had greater changes from baseline than Albuterol and the placebo. The changes appear to be greater in the higher dose group than in the lower one.

Figure 32. Changes in Mean FEV1 from Trial Baseline (Study 41)



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

Source: sub41
WMF: ChgMn41

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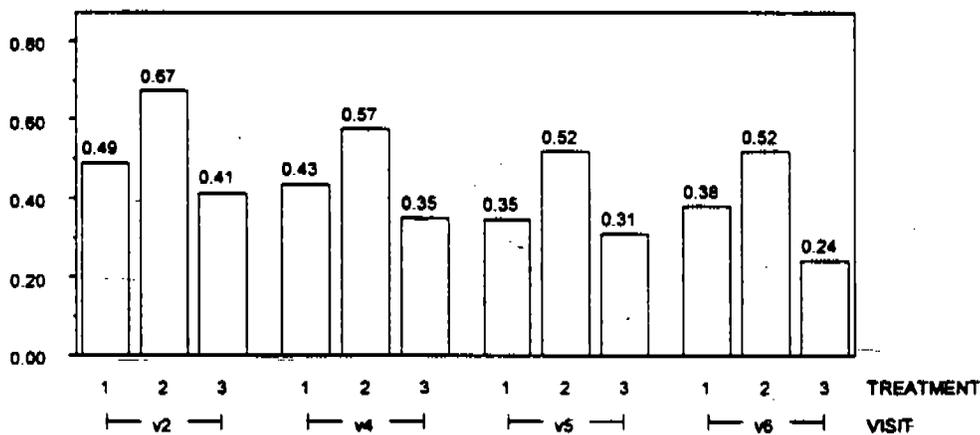
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Table 26 and Figure 33 compare the differences in mean FEV1 changes from baseline measures between the drug groups and the placebo. The differences between the Foradil doses and the placebo were greater than those between Albuterol and the placebo.

Table 26. Drugs vs. Placebo: Differences in Mean FEV1 Changes from Baseline (Study 41)

TRT	Differ in Mean FEV1 Chg from Base			
	Drug vs. placebo			
	v2	v4	v5	v6
Formo 12mcg	0.49	0.43	0.35	0.38
Formo 24mcg	0.67	0.57	0.52	0.52
Albut 180mcg	0.41	0.35	0.31	0.24

Figure 33. Drugs vs. Placebo: Differences in Mean FEV1 Changes from Baseline (Study 41)



Treatment: 1=Foradil 12, 2=Foradil 24, 3=Albuterol 180

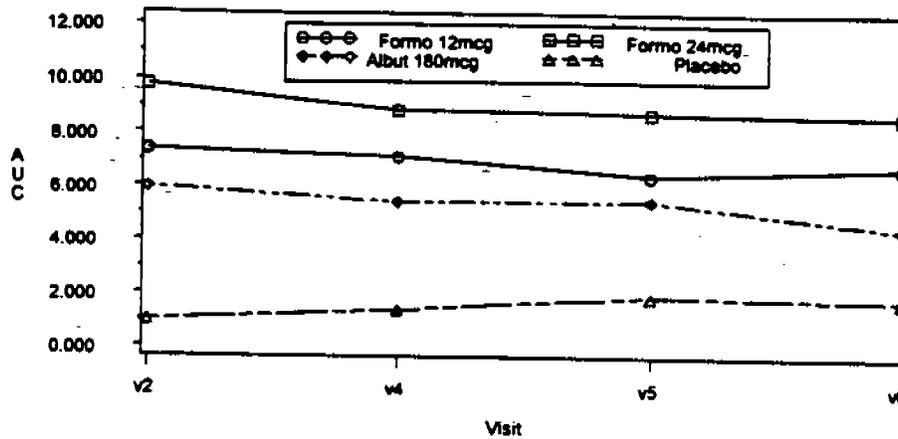
Source: sub41, difchg41
WMF: DrInChg41

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Figure 34 demonstrates AUC of FEV1 for the four visits. The AUC values were markedly greater in the Foradil groups than in the Albuterol and placebo groups

Figure 34. AUC of FEV1 (Study 41)



Source: AUC41
WMF: AUCofFEV41

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Summary of Efficacy Evaluation

Analyses based on the hour-12 FEV1, mean FEV1, and AUC are summarized in Table 27. The listed p-values indicate that Foradil is statistically superior to the placebo.

Table 27. Results of Efficacy Evaluation (Study 41)

	Hour - 12 FEV1	Mean FEV1	AUC
Foradil 12 vs. placebo	0.0001	0.0001	0.0001
Foradil 24 vs. placebo	0.0001	0.0001	0.0001
Albuterol vs. Placebo	0.8566	0.0001	0.0018

The above tests confirm that Foradil in 12 and 24 µg were superior to the placebo. Having applied Dunnett's criterion for multiple comparisons, the same conclusions hold. Based on the mean and AUC of FEV1, the superiority to the placebo was also demonstrated for Albuterol. However, Albuterol failed to demonstrate the superiority to placebo, based on the 12-hour FEV1 (p=0.8566).

This reviewer's statistical evaluations based on Studies 40 and 41 confirmed the sponsor's results.

Details of these statistical results can be found in the appendix to this report.

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Additional Observations of FEV1

Additional observations were made on other FEV1 based variables. This reviewer computed the difference between the 3rd hour FEV1 and the pre-dosing FEV1, namely the very first spirometric measure of FEV1 at the visit. A difference between the 12th hour FEV1 and pre-dosing FEV1 was also computed. These differences are tabulated and plotted as follows.

Changes in 3rd Hour FEV1 from Visiting Baseline

Table 28 and Figure 35 describe the changes in 3rd hour FEV1 from the visiting baseline, which is the pretreatment observation at the visit. Note that the pretreatment FEV1 values increased with time, possibly due to the carryover effect of the drug. Therefore, the decrease of the 3rd hour FEV1 changes may partly be explained by the increase in pretreatment-values over time (See Figure 36).

Table 28. Change in 3rd-Hour FEV1 from Visit Baseline (Study 41)

3rd Hour FEV1 Change from Pretreatment measurement

	Chg Fev1 03 hrs from visit baseline									
	v2		v4		v5		v6		Fn1	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std	Mean	Std
TRT										
Formo 12mcg	0.66	0.39	0.43	0.33	0.41	0.30	0.39	0.31	0.43	0.33
Formo 24mcg	0.84	0.43	0.46	0.40	0.53	0.41	0.49	0.35	0.52	0.39
Albut 180mcg	0.49	0.36	0.49	0.38	0.41	0.37	0.35	0.39	0.34	0.40
Placebo	0.14	0.35	0.12	0.30	0.12	0.31	0.13	0.32	0.12	0.31

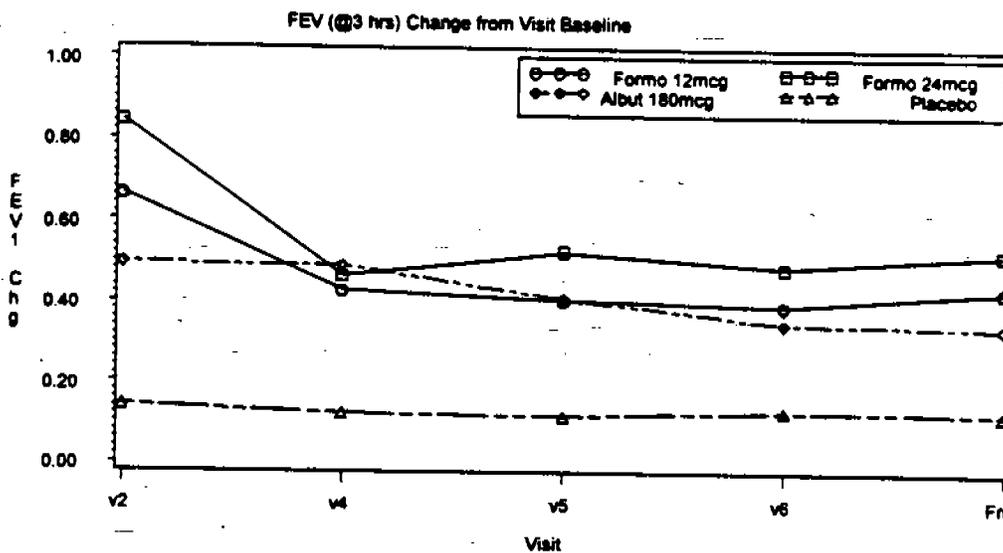
(Source: sub41)

It can be seen that the changes from pretreatment FEV1 were clearly greater among the drug groups than among the placebo group. In addition, the differences became smaller after the second visit.

APPEARS THIS WAY
ON ORIGINAL

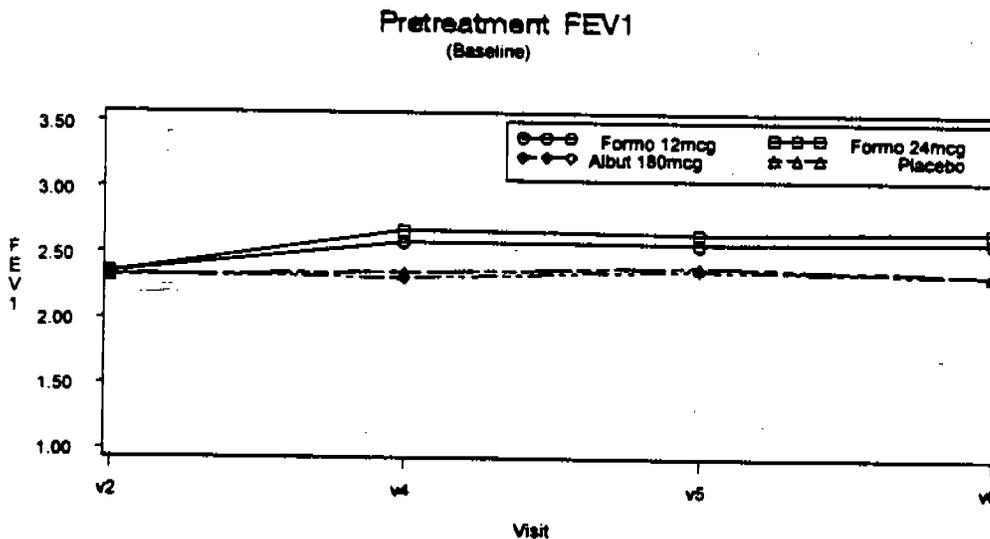
Filename _____

Figure 35. Change in 3rd-Hour FEV1 from Pre-Dosing FEV1 (Study 41)



Source: Sub41
WMF: Fev1Chg3hr41

Figure 36. Pretreatment FEV1 (Study 41)



Source: Sub41
WMF: SbVb41

APPEARS THIS WAY
ON ORIGINAL

Filename: _____