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Summary

Foradil (formoterol fumarate) Capsules for Inhalation is indicated for treating patients with reversible obstructive airway disease (ROAD), including patients with symptoms of nocturnal asthma and exercise-induced bronchospasm. To support the marketing of Foradil, the sponsor (Novartis) presents evidence based on sixteen domestic and foreign studies to demonstrate the effectiveness and safety of this drug at 12 and 24 μg , b.i.d. for patients aged 12-74 years.

Following a discussion with the medical reviewer, Dr. Raymond Anthracite of the Division of Pulmonary Drug Products (HFD-570), this reviewer evaluated the U.S. Studies #40 and #41. The statistical evaluations were focused on the efficacy of Foradil (at 12 and 24 μg , b.i.d.). The conclusions of the statistical evaluation are based on selected FEV1 endpoints, the sponsor-proposed primary outcome variable. The reviewer's analyses are summarized below.

- The statistical evidence 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 statistically superior to the placebo.
- The 24- μg dose appears to be more efficacious, though the difference between the two Foradil doses is not significant.
- Albuterol at 180 μg , q.i.d., as a positive control, is also superior to the placebo.
- Foradil is most effective approximately 3 hours after the morning dose, it remains effective for at least 12 hours.
- Based on the two 12-week trials (Studies 40 and 41), the effectiveness of Foradil was demonstrated at 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. Statistical 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 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 patients with _____ asthma, including patients with symptoms of nocturnal asthma, and for controlling exercise-induced bronchospasm.

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Introduction

The sponsor proposes that Foradil (formoterol fumarate) dry power capsule for inhalation is indicated for treating patients, children and adults with mild to moderate asthma. The drug is delivered by a single-dose breath actuated inhaler administered with 12 or 24 μg , b.i.d, the proposed market dose.

Overview of the Studies

The goals of the study are summarized as follows (ref. page 9, vol. 1.95):

- To determine whether Foradil was superior to placebo with respect to lung functions and symptom control;
- To determine whether Foradil was superior to Albuterol with respect to lung functions and symptom control;
- To determine the dose-response relationship between the two doses of Foradil; and
- To examine the safety and tolerability of Foradil compared with Albuterol.

The sponsor submitted evidence from six Phase II and III studies to support efficacy and safety claims. Table 1 summarizes these studies.

Table 1. List of Studies Submitted

Study Number	Location	Phase	Date	Type
Protocol 40	U.S.	III	5/15/95-6/15/96	Double-blind parallel
Protocol 41	U.S.	III	5/2/95-5/8/96	Double-blind parallel
Protocol 45	U.S.	II	11/21/95-4/21/96	Double-blind crossover
Protocol 46	U.S.	II	12/13/95-5/24/96	Double-blind crossover
PD/DF2	Foreign	III	8/91-4/93	Double-blind parallel
PD/DF3	Foreign	II	8/92-11/92	Double-blind crossover

Based on a discussion with the medical reviewer, Dr. Raymond Anthracite of the Division of Pulmonary Drug Products (HFD-570), this reviewer evaluated the statistical evidence presented in the two phase-III U.S. studies: Protocols 40 and 41.

In both of these trials, the participating patients were randomly assigned to one of the following four treatments:

- Foradil at 12 μg , b.i.d,
- Foradil at 24 μg , b.i.d.,
- Albuterol at 180 μg , q.i.d. (a positive control), and
- Placebo.

The trial drugs were blinded using the double-dummy technique for the four daily doses each patient received during the active treatment phase. The details can be found on page 18, vol. 1.95 for Study 40 and page 17, vol. 1.182 for Study 41. In brief, the patient inhaled from ISF inhaler four times per day, receiving Albuterol or placebo. During the first and third dosing period, the patient inhaled from Inhaler A, receiving Foradil or placebo.

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Note that the sponsor in his June 24, 1997 cover letter particularly claimed that Foradil is indicated for treating patients with symptoms of nocturnal asthma and exercise-induced bronchospasm. The nocturnal-asthma symptoms were measured by scores ranging 0-4¹ recorded by the patient before morning dosing as part of the diary.

The claim for treating exercise-induced bronchospasm was based on two Phase II crossover studies. The studies were conducted during November 21, 1995-April 12, 1996.

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¹ Nocturnal-asthma scores: "0=I did not awaken because of breathing problems... 4=I had difficulty sleeping because of breathing problems even though I used my rescue medication (page 39, vol. 1.95)."

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Table 2 further details the characteristics of these studies.

Table 2. Description of the two U.S. Studies

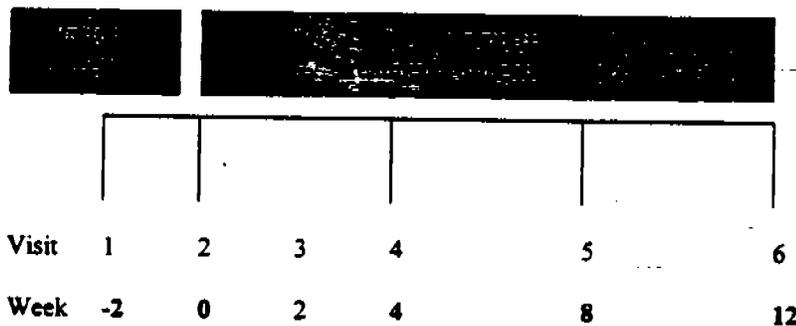
Study	Is a study of...	Specifically, it has...
Protocol 40 (pp. 11, vol. 1.91)	12 week long Randomized Double-blind Double-Dummy Parallel Multi-center FEV1 as primary outcome variable	12-hour FEV1 measurements at each of 4 visits, which were separated by four weeks 4 groups: Foradil 12 µg b.i.d., 24 µg b.i.d., Albuterol 180 µg q.i.d., & Placebo, with a total of 541 randomized patients (535 included in the efficacy analysis). 26 centers
Protocol 41 (pp. 14, vol. 1.178)	12 week long Randomized Double-blind Double-Dummy Parallel Multi-center FEV1 as primary outcome variable	12-hour FEV1 measurements at each of 4 visits, which were separated by four weeks 4 groups: Foradil 12 µg b.i.d., 24 µg b.i.d., Albuterol 180 µg q.i.d., & Placebo, with a total of 554 randomized patients (553 included in the efficacy analysis). 25 centers

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Time Line of Studies 40 and 41

The following diagram describes the time lines for Studies 40 and 41. All participating patients received placebo in period one, the trial baseline period. The randomization process took place at the beginning of period two, the treatment period. The patients were randomly assigned to the active-drug doses or placebo in a double-blind fashion. The spirometric measurements (i.e., FEV1) were taken at 5, 15, 30, and 60 minutes and then hourly for 12 hours at visits 2, 4, 5, and 6. These measurements were used for statistical analyses and evaluations. The 12-hour observation periods were each separated by four-weeks. Figure 1 describes the time lines for both studies.

Figure 1. Design Diagram (Studies 40 & 41)



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According to the protocol (pages 23-25, vol. 1.91), the patients were allowed to take Albuterol as the rescue medication. They were also allowed to take other concomitant medications. Such a rule was applied to both the screening and treatment periods. If a patient took the rescue medication prior to a trial visit, an eight-hour washout time of the rescue medication was required before the next spirometric observation could begin.

Figure 2 illustrates how the FEV1 values were measured during a visit. The FEV1 were taken at the following 16 time points: 0 (pretreatment baseline); 5, 15, 30 and 60 minutes, 2 hours, and hourly thereafter to 12 hours after the morning dosing (Page 31, vol. 1.91).

Figure 2. Spirometric Measurements at a visit (Studies 40 and 41)



In addition to FEV1, the sponsor-proposed primary outcome measurement, the sponsor proposed twelve additional variables as secondary endpoints, including area-under-the-curve (AUC) of FEV1, percent of predicted FEV1, and combined asthma symptom score. In addition, more variables were introduced *post hoc* as "other variables" in the sponsor's efficacy assessment (page 41, vol. 1.91).

Both the primary and secondary efficacy variables were analyzed for all randomized patients who had at least one treatment observation (defined as the intent-to-treat (ITT) patients by the sponsor [page 42, vol. 1.91]). The pretreatment observation at visit 2 (Figure 1) was chosen as the baseline.

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Sponsor's Efficacy Studies

Statistical Method

The statistical method for Study 40 can be found on page 50 of vol. 1.95; and for Study 41, on page 53 of vol. 1.182. The methods used in both studies were the same: The analyses of FEV1 relied on the use of analyses of covariance (ANCOVA). The statistical model of these analyses included terms of TREATMENT and CENTER as factors of interest; and VISIT-2 PRETREATMENT BASELINE as a covariate. The sponsor also included TREATMENT-CENTER INTERACTION and TREATMENT-BASELINE INTERACTION.

According to the sponsor's final study report, the sponsor performed separate ANOVA for every time point of observation for the four visits, resulting in 64 p-values for the analysis of FEV1 alone. Such an approach caused difficulty in drawing a final statistical conclusion. In neither the protocols nor the final study report, did the sponsor address how these correlated measurements on the same patient could have been handled differently. Furthermore, the sponsor did not report the overall significance of other pre-specified factors in the model, such as TREATMENT-CENTER INTERACTION and CENTER.

The indication for nocturnal-asthma symptoms was supported by analyses based on nocturnal-asthma symptom scores (Study 40: page 90, vol. 1.91; Study 41: page 99, vol. 1.178). The scores at visit 2 were used as baseline scores. Analyses of variance on nocturnal-asthma symptom scores were performed for visits 4, 5, and 6, separately.

Conclusions

The sponsor's conclusions can be found on page 182 of vol. 1.91 and page 198 of vol. 1.178. The sponsor concluded that for the both studies, "Both the 12 µg and the 24 µg doses of formoterol were superior to placebo with respect to lung function measurements. This superiority prevailed throughout the 12-week period."

The sponsor concluded that "both formoterol doses [12 and 24 µg] were superior to placebo in terms of nocturnal symptom scores (Study 40: page 182, vol.1.91; Study 41: page 199, vol.1.178)."

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Reviewer's Evaluation of Study 40

Descriptions of Patients

Evaluation of Patient Accountability

The numbers of patients in Study 40 are populated in Table 3. 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 2 then discontinued accounted for the numbers of patients in column 1. Patients attended Visit 6 completed the entire 12-week long study.

Of the 539 patients, 458 completed the study, accounting for 85% of the total patients. Among the four treatment groups, at least 80% of the patients completed the study. Note that 7.8% of the total patients did not continue after Visit 2, showing a higher dropout rate than the dropout rate after Visit 4 and 5 (4.8% and 2.4%). In general, the dropout rates were considered relatively low.

Table 3. Number of Patients by Treatment and Visit (Study 40)

	Last visit								Total	
	2		4		5		6			
	N	Pct	N	Pct	N	Pct	N	Pct	N	Pct
Treatment										
Formot. 12mcg	16	11.8	6	4.4	5	3.7	109	80.1	136	100.0
Formot. 24mcg	8	5.9	7	5.2	5	3.7	115	85.2	135	100.0
Albut. 180mcg	12	9.0	8	6.0	1	0.7	113	84.3	134	100.0
Placebo	6	4.5	5	3.7	2	1.5	121	90.3	134	100.0
Total	42	7.8	26	4.8	13	2.4	458	85.0	539	100.0

(Source: temp40)

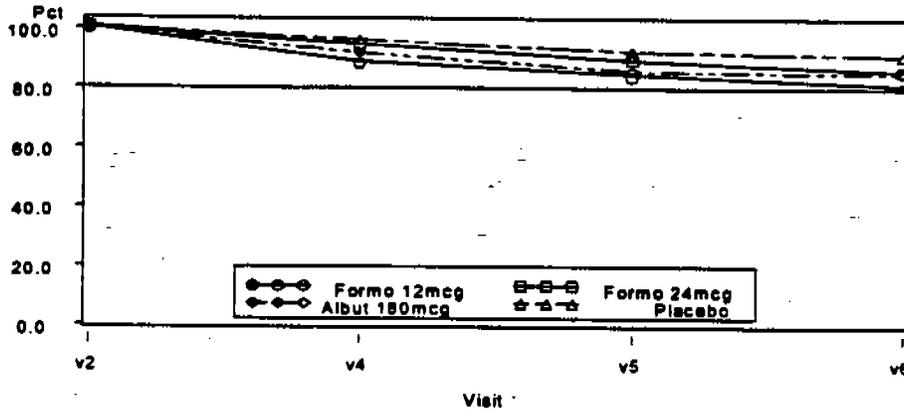
Figure 3 below depicts the percentages of patients who stayed in the study. The percentages of completion fall between 80-90% (See Table 3 above). The percentage of patients who completed Visit 6 was slightly higher in the placebo group than in other groups.

Based on Table 3 and Figure 3, this reviewer determines that the numbers of patients lost to follow-up were low and evenly distributed among the treatment groups. Therefore, it is likely that the dropouts are not of particular concern to the efficacy evaluation.

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Figure 3. Percentages of Patients Stayed on Study (Study 40)



Source: Drop40

Note that the percentage of patients treated with placebo stayed in the study was greater than those of other patients. This phenomenon might be explained by a variety of factors, including the amount of rescue-medication use. Table 4 and Table 5 below describe that the number of puffs of rescue medication (Albuterol) used by patients. The amount of rescue medication used among patients in the placebo group was greater than that among patients in any active treatment group. This reviewer does not think that the amount of rescue-medication use alone fully explains such a phenomenon.

Table 4. Puffs of Rescue Medication: Nighttime use (Study 40)

TREATMENT	PUFFS AM			
	No.	Pct	Mean	Std
Formo 12mcg	133	25.4	0.92	1.08
Formo 24mcg	130	24.8	0.89	1.23
Albut 180mcg	130	24.8	1.25	1.21
Placebo	131	25.0	1.57	1.29
Over All	524	100.0	1.16	1.23

Source: Diary0.sd2

Table 5. Puffs of Rescue Medication: Daytime use (Study 40)

	PUFFS PM			
	No.	Pct	Mean	Std
TREATMENT				
Formo 12mcg	132	25.3	1.12	1.20
Formo 24mcg	130	24.9	1.15	1.66
Albut 180mcg	130	24.9	1.36	1.33
Placebo	130	24.9	2.07	1.69
Over All	522	100.0	1.42	1.53

Source: Diary0.sd2

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Evaluation of Missing Observations

There were missing FEV1s during the observation periods. The sponsor detailed the method used to handle missing observations on page 43, vol. 1.91. 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.

With the above imputation method in mind, this reviewer researched the sponsor's data and extracted the cases where missing observations still cannot be imputed based on the sponsor's rules. The following list identifies the patients with missing observations that cannot be imputed.

The column named "Missing" represents for each of such patient the total number of missing FEV1 observations.

Non-Imputable Missing Observations

Treatment	Center	Patient	Missing
Formo 12mcg	M0145I	2076	11
	M0145I	2078	11
	M0145I	2450	4
Formo 24mcg	M0145I	2075	6
	M0145I	2080	2
	M0146M	2085	4
	M0137N	2498	1
Albut 180mcg	M0135F	2059	1
	M0145I	2073	18
	M0145I	2079	6
	M01280	2252	3
	M0141S	2362	15
	M0145I	2449	9
Placebo	M0145I	2074	9
	M0146M	2084	2
	M0146M	2088	5
	M0127K	2305	4

Note that patient #2076 had 11 non-imputable missing observations on one visit. Comparing the size of the patient pool, the number of such patients was small.

Note that the pretreatment measures were not imputed. Therefore, fewer patients were actually included in the reviewer's statistical analyses than those counted in Table 3. Patients with missing study baseline observations were excluded from the reviewer's analyses. The actual numbers of patients included in the analyses are shown in Table 6.

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Table 6. Number of Patients Included in Reviewer's Statistical Evaluation (Study 40)

	Last Visit				Total
	2	4	5	6	
	n	n	n	n	
TRT					
Formo 12mcg	16	6	5	108	135
Formo 24mcg	8	7	4	115	134
Albut 180mcg	12	8	1	111	132
Placebo	6	5	2	121	134
Total	42	26	12	455	535

(Source: sub40)

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Analysis of Baseline FEV1

Based on the sponsor's study design, the visit 2 pretreatment FEV1 value was treated as the trial baseline. In the data submission, it is also called study baseline. This reviewer uses "study baseline," "trial baseline" and "baseline" interchangeably.

Table 7 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=0.2902).

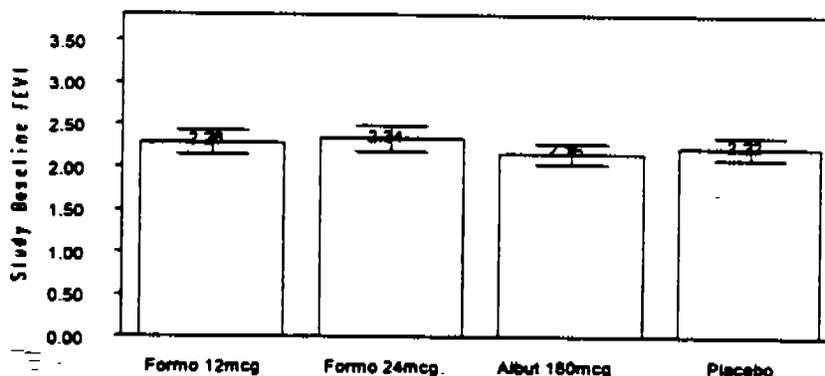
Table 7. Baseline FEV1 by treatment (Study 40)

Treatment	Baseline FEV1 (visit 2)			
	N	%	Mean	Std
Formot. 12mcg	135	25.2	2.28	0.78
Formot. 24mcg	134	25.0	2.34	0.89
Albut. 180mcg	132	24.7	2.16	0.70
Placebo	134	25.0	2.22	0.78
Over All	535	100.0	2.25	0.79

(Source: sub40/visit=2 & spno=1/imfevl:trt)

A "picture" of the above Table 7 is shown in Figure 4. Standard errors are shown on top of the bars.

Figure 4. Baseline FEV1 by Treatment (Study 40)



Source: sub40
 DT: 3/27/40

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. Variations among various patient groups are expected to exist. When the patients are randomly assigned to different treatments, such variations can be explained by randomness alone. The imbalance, if it exists, is expected to be minimal. It is this reviewer's intention to assess the situation of potential imbalance in baseline values between treatments.

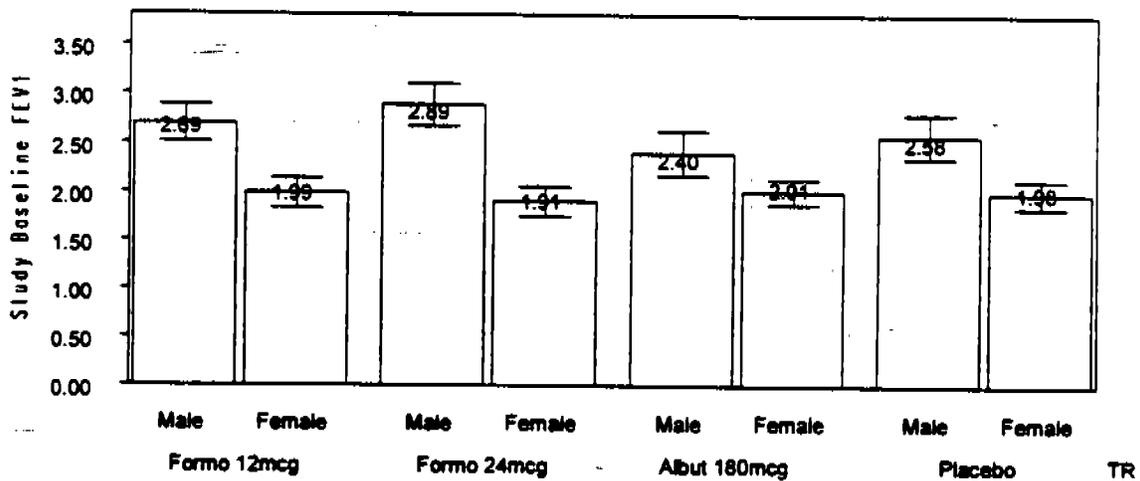
Table 8 describes the number of patients by sex by treatment. The males account for about 40% of the total patients.

Table 8. Number of Patients by Sex by Treatment (Study 40)

	Treatment Group									
	Formot. 12mcg		Formot. 24mcg		Albut. 180mcg		Placebo		Total	
	n	%	n	%	n	%	n	%	n	%
Sex										
Male	58	25.9	59	26.3	53	23.7	54	24.1	224	100.0
Female	78	24.8	76	24.1	81	25.7	80	25.4	315	100.0
Total	136	25.2	135	25.0	134	24.9	134	24.9	539	100.0

Figure 5 indicates that the baseline FEV1 values were greater in males than in females.

Figure 5. Baseline FEV1 by Sex by Treatment (Study 40)



Source: Subtt40
 NMF: 5050x60

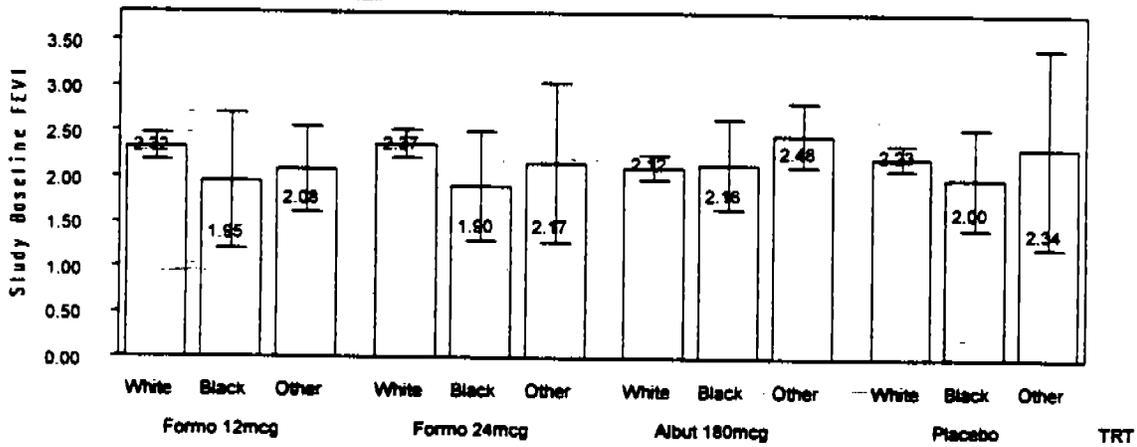
Table 9 describes the number of patients by race by treatment. About 88% of the total patients were white.

Table 9. Number of Patients by Race by Treatment (Study 40)

Race	Treatment Group									
	Formot. 12mcg		Formot. 24mcg		Albut. 180mcg		Placebo		Total	
	n	%	n	%	n	%	n	%	n	%
White	118	25.0	123	26.1	111	23.5	120	25.4	472	100.0
Black	8	26.7	5	16.7	9	30.0	8	26.7	30	100.0
Other	10	27.0	7	18.9	14	37.8	6	16.2	37	100.0
Total	136	25.2	135	25.0	134	24.9	134	24.9	539	100.0

Figure 6 shows that the baseline FEV1 tends to be greater among the whites than among other groups. The variations are also smaller among white patients.

Figure 6. Baseline FEV1 by Race by Treatment (Study 40)



Source: sub140
Vol: 56Rec40

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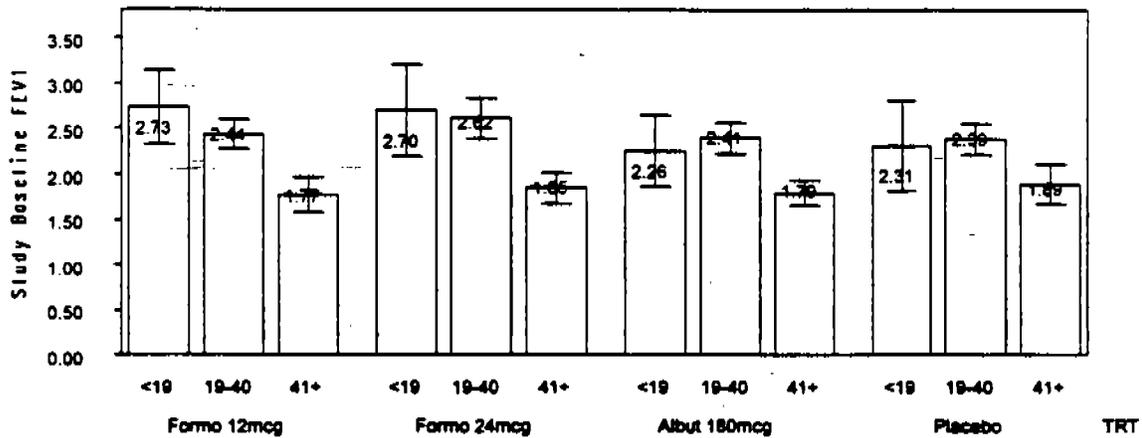
Table 10 describes the patient ages by treatment. On average, the patients were 35 years of age. The youngest patient was aged 12 and the oldest was 74.

Table 10. Analysis of Patient Age (Study 40)

Treatment	Age				
	N	%	Average	Minimum	Maximum
Formot. 12mcg	136	25.2	34.24	12.00	73.00
Formot. 24mcg	135	25.0	35.79	12.00	74.00
Albut. 180mcg	134	24.9	35.66	12.00	73.00
Placebo	134	24.9	35.88	12.00	73.00
Over All	539	100.0	35.39	12.00	74.00

Figure 7 shows that the baseline FEV1 values were smaller among the patients, aged 41 and older than among the younger groups.

Figure 7. Baseline FEV1 by Age Group by Treatment (Study 40)



Source: sub1140
 UMF: 5bA0040

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.

Focus of Statistical Evaluation

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. By doing so, more precision is gained in evaluation the differences among the treatments. (The assumptions for using this method, however, were not addressed by the sponsor in the section on statistical methods.)

In addition to treatment, center and interaction between treatment and center were also included in the statistical model. As every patient was measured at 16 time points for each of the four 12-hour observation periods, there were 64 measurements drawn from the study for every patient. The sponsor performed analyses of covariance (ANCOVA) for every time points as independent analyses. Statistical results were summarized on page-66-83, vol. 1.91.

The sponsor in the statistical-method section of the protocol (page 50, vol. 1.95) did not address how the multiple observations on the same patient were handled. Nor did the sponsor give a compelling reason for which FEV1 values were more important than others. The sponsor provided separate analyses of covariance for every time point resulting in 80 p-values (16 time points for each visit multiplied by 5 visits).

To confirm the efficacy claim, this reviewer considered all the observations and evaluated FEV1 based on what was likely to be the weakest evidence. If this weak evidence still supports the efficacy claim, there is little doubt that proof of efficacy has been established.

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

1. FEV1 at hour 12 of visit 6,
2. Mean FEV1 at visit 6, and
3. AUC at visit6.

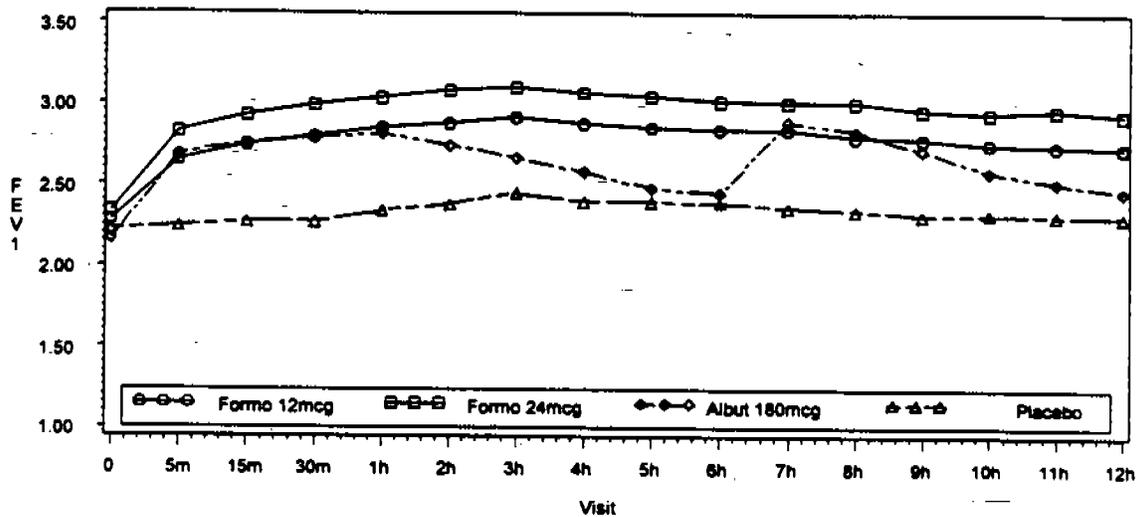
In the following graphs: Figure 8, Figure 9, Figure 10, and Figure 11. this reviewer explores the pattern of the FEV1 values over the observation time points for each visit. Observations on these graphs can be summarized in the following highlights:

1. The pretreatment observations, represented by the values at time point zero, change over time, indicating a carryover effect of treatments from one visit to the next.
2. In general, FEV1 values are greater in the two Foradil groups than in the placebo group.
3. The drug effect increases to its peak about 3 hours from the morning dose, and then declines and stabilizes toward the end of the day.
4. In general, Albuterol does not demonstrate as strong an effect as do the Foradil treatments.
5. The FEV1 profiles appears similar for all of the visits.

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.

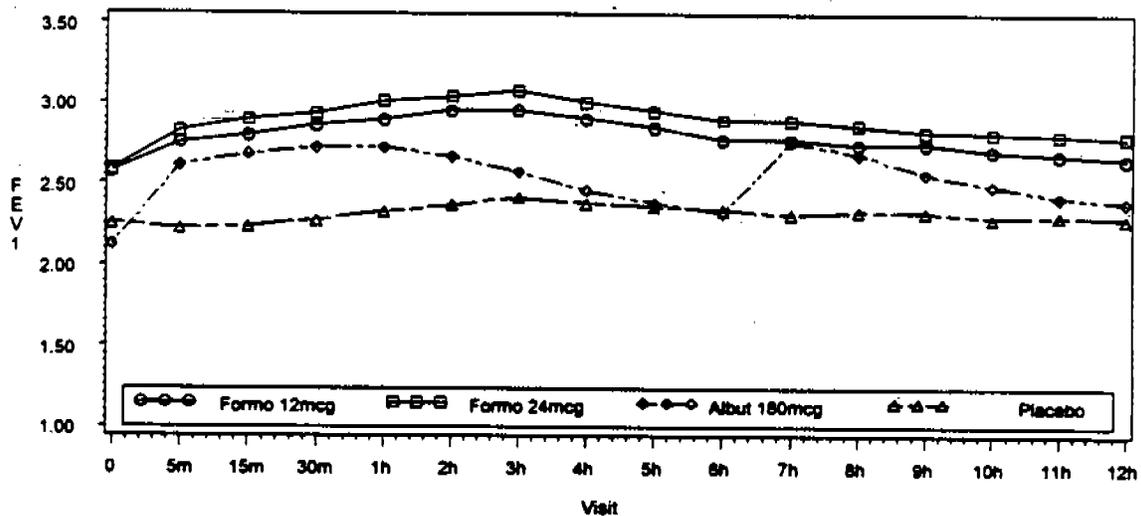
In the following graphs, FEV1 values were plotted against time points of observations. The values at time 0 at visit 2 represents the study baseline values.

Figure 8. FEV1s at Visit 2 (Study 40)



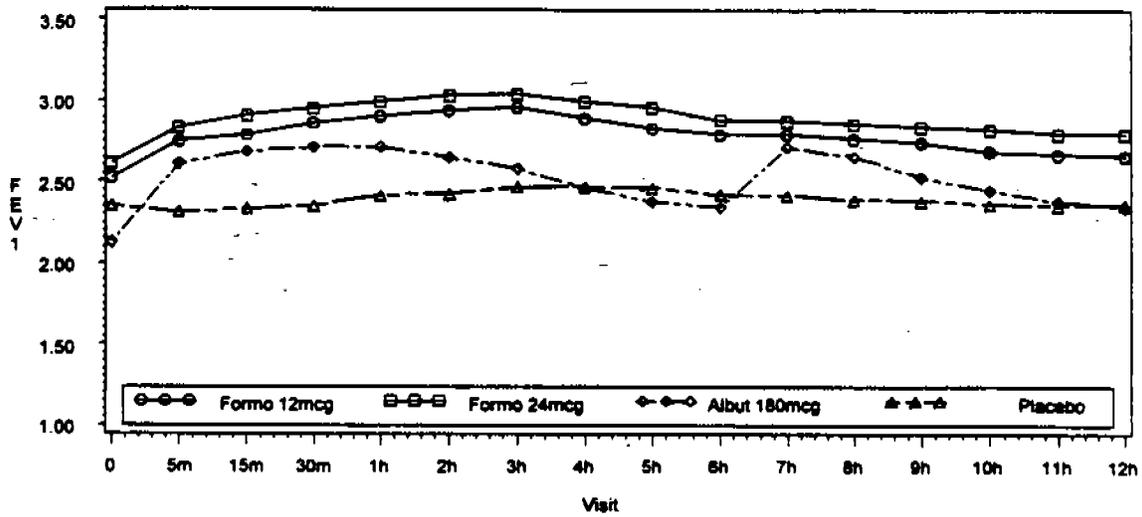
FEV1, visit 2, study 40 (Source: Sub40, WMF: Few2_40)

Figure 9. FEV1s at Visit 4 (Study 40)



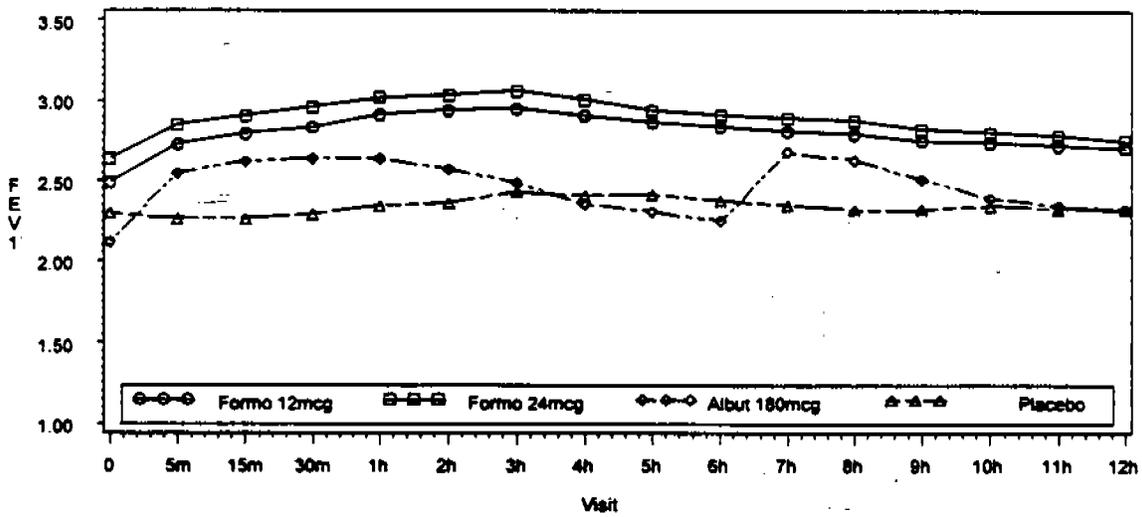
FEV1, visit 4, study 40 (Source: Sub40, WMF: Few4_40)

Figure 10. FEV1s at Visit 5 (Study 40)



FEV1, visit 5, study 40 (Source: Sub40, WMF: Few5_40)

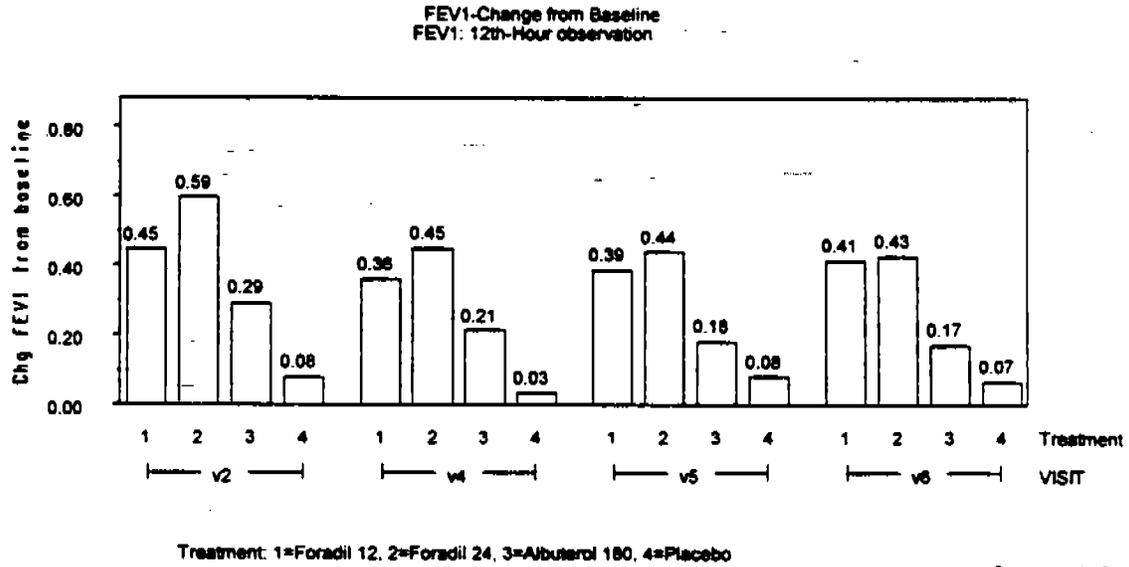
Figure 11. FEV1s at Visit 6 (Study 40)



FEV1, visit 6, study 40 (Source: Sub40, WMF: Few6_40)

Figure 12 demonstrates the changes in FEV1 from baseline. Here, the FEV1 is the measurement taken at the 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 consistently greater in the higher dose group than in the lower one.

Figure 12. Changes in 12th-Hour FEV1 from Trial Baseline (Study 40)



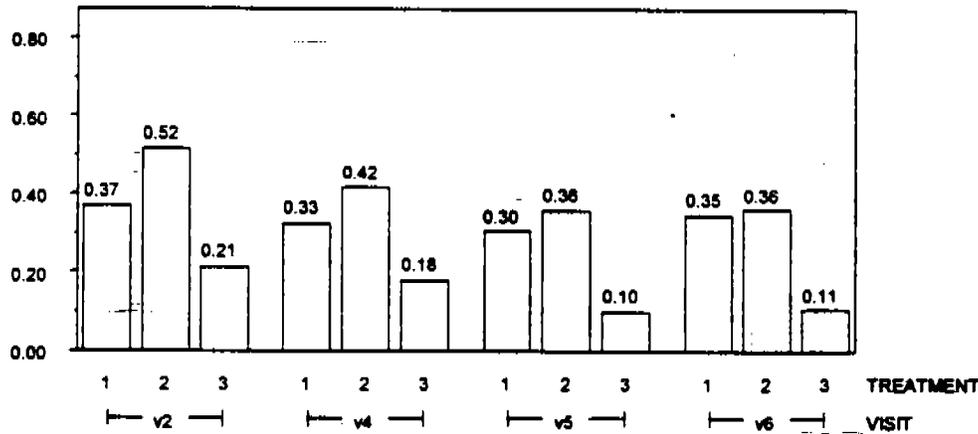
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Table 11 and Figure 13 compare the differences in 12th-hour FEV1 changes from baseline measures between the drug groups and the placebo. The differences between the Foradil doses and the placebo were greater than those between Albuterol and the placebo.

Table 11. Drugs vs. Placebo: Differences in 12-Hour FEV1 Changes from Baseline (Study 40)

Treatment	Differ in 12hr FEV1 Cg from Base:			
	Drug vs. placebo			
	v2	v4	v5	v6
Formo 12mcg	0.37	0.33	0.30	0.35
Formo 24mcg	0.52	0.42	0.36	0.36
Albut 180mcg	0.21	0.18	0.10	0.11

Figure 13. Drugs vs. Placebo: Differences in 12-Hour FEV1 Changes from Baseline (Study 40)



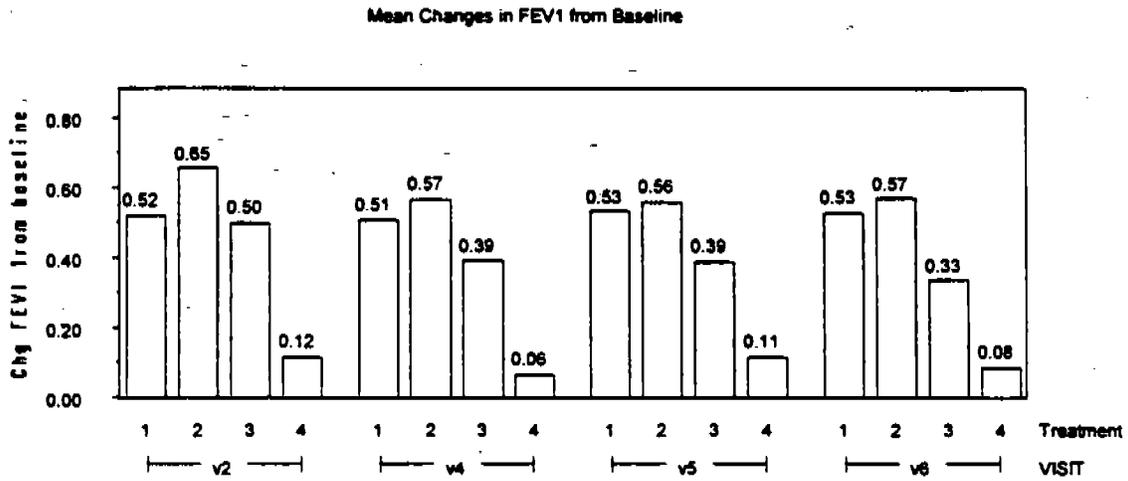
Treatment: 1=Foradil 12, 2=Foradil 24, 3=Albuterol 180

Source: sub40, difchg40
WMF: Dif12hChg40

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Figure 14 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 14. Changes in Mean FEV1 from Trial Baseline (Study 40)



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

Source: sub40
WMF: ChgMn40

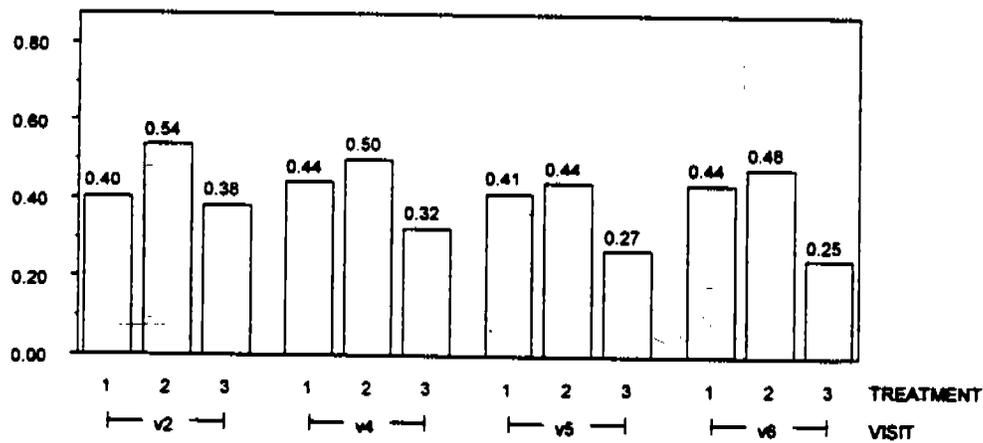
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Table 12 and Figure 15 compare the differences in mean FEV1 changes from baseline measures between the drug groups and the placebo. The differences between the Foradil doses and the placebo were greater than those between Albuterol and the placebo.

Table 12. Drugs vs. Placebo: Differences in Mean FEV1 Changes from Baseline (Study 40)

TRT	Differ in Mean FEV1 Chg from Base			
	Drug vs. placebo			
	v2	v4	v5	v6
Formo 12mcg	0.40	0.44	0.41	0.44
Formo 24mcg	0.54	0.50	0.44	0.48
Albut 180mcg	0.38	0.32	0.27	0.25

Figure 15. Drugs vs. Placebo: Differences in Mean FEV1 Changes from Baseline (Study 40)



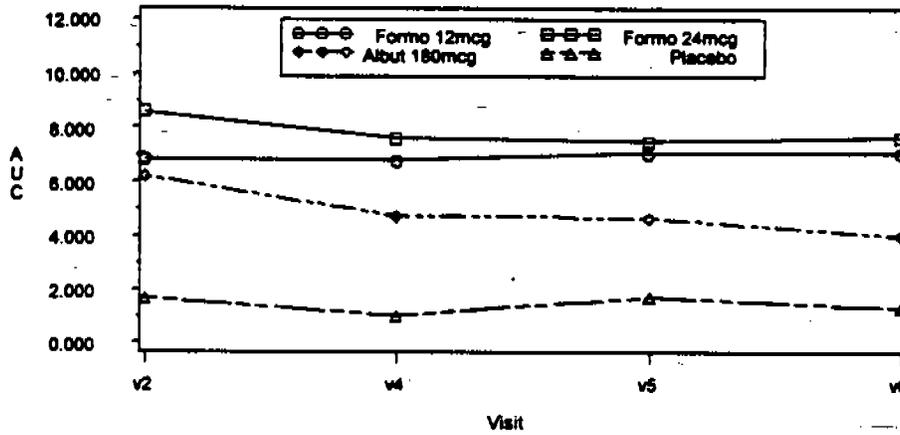
Treatment: 1=Foradil 12, 2=Foradil 24, 3=Albuterol 180

Source: sub40, difchg40
WMF: DiffInChg40

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Figure 16 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 16. AUC of FEV1 (Study 40)



Source: AUC40
WMF: AUCofFEV40

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Summary of Efficacy Evaluation

Analyses based on the hour-12 FEV1, mean FEV1, and AUC are summarized in Table 13. The listed p-values indicate that Foradil is statistically superior to the placebo.

Table 13. Results of Efficacy Evaluation (Study 40)

	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	0.1883	0.0005	0.0068

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, the test based on the 12th hour's FEV1 did not demonstrate the same superiority, though clear improvement compared with the placebo can be found in Figure 12 and Figure 13 above.

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

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