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APPLICATION NUMBER:

21-279

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #: 21-279	Application Type: sNDA
Sponsor: Novartis	Proprietary Name: Foradil Aerolizer
Investigator: Multiple	USAN Name: Formoterol fumarate inhalation powder
Category: Long-acting beta ₂ agonist	Route of Administration: Oral Inhalation
Reviewer: Eugene J. Sullivan, MD FCCP	Review Date: September 24, 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
July 26, 2001	July 27, 2001	Labeling amendment	
September 12, 2001		Labeling amendment	

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments
September 22, 2000	Original sNDA	
May 4, 2001	Labeling	Initial proposed labeling

REVIEW SUMMARY: Labeling negotiations were undertaken with the Applicant based upon the initial proposed labeling (Submitted May 4, 2001). The submissions dated July 26, 2001, and September 12, 2001, represent the Applicant's responses to the Division's comments. After each of these submissions were reviewed, the Division communicated the necessary revisions to the Applicant. The final approved label represents the results of the labeling negotiations.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION: If the Applicant agrees to incorporate the Division's proposed revisions to the label, the sNDA will be sufficient for approval from the clinical standpoint.

New clinical studies: _____	Clinical Hold	_____	Study May Proceed
NDA, Efficacy/Label supplement: _____	Approvable	<input checked="" type="checkbox"/>	Not Approvable

SIGNATURES Medical Reviewer:	Date:
Medical Team Leader:	Date:

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Badrul Chowdhury
9/24/01 03:55:34 PM
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I concur

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MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #: 21-279 Sponsor: Novartis Investigator: Multiple	Application Type: NDA Proprietary Name: Foradil® Aerolizer™ USAN Name: Formoterol fumarate inhalation powder
Category: Long-acting beta-2 adrenoceptor agonist	Route of Administration: Oral inhalation
Reviewer: Eugene J. Sullivan, MD, FCCP	Review Date: July 19, 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
July 5, 2001	July 6, 2001	NDA	Final Safety Update

REVIEW: This is a review of the final safety update submitted in support of NDA 21-279, Foradil Aerolizer for the treatment of chronic obstructive pulmonary disease. This submission updates the safety information included in the Integrated Summary of Safety submitted with the original NDA, and the 120-Day Safety Update submitted in January, 2000. This submission includes: 1) summaries of safety information for clinical trials in asthma patients and COPD patients that have been completed since the last cut-off date (July 15, 2000), including case report forms for all patients who died or prematurely discontinued from a clinical trial during the time period between the last safety cutoff date and the new cutoff date (July 16, 2000 to May 15, 2001); 2) SAEs reported since the last cut-off date; 3) an update of post-marketing safety information since the last cut-off date; 4) an update of the clinical literature published since the last update; and 5) an update on the registration of this product in foreign countries along with the corresponding foreign product labeling information.

The safety data from the recently completed asthma and COPD studies are not integrated together. The two COPD trials for which safety data are submitted (CFOR258 IA02 and CFOR258 IA04) were single-dose studies in 47 and 25 patients, respectively. The six asthma studies for which safety data are submitted, ranged from single-dose to 4-week treatment period studies. Three of the asthma studies were not placebo controlled. Review of the data from the COPD and asthma trials did not raise new safety concerns.

Review of the postmarketing data and clinical literature submitted did not raise any new safety concerns.

A dossier variation for the addition of the COPD indication was dispatched to global health authorities (except the US) in March, 2000. On the basis of this dossier 19 countries have approved the COPD indication. These countries include Canada, the United Kingdom (UK), and Australia. Twelve of these countries use International Product Labeling (IPL). The submission includes copies of the IPL and the product labels from six of the seven countries that use unique product labels (the label from Turkey was not included). All of these countries, with the exception of the UK, have approved both the 12mcg BID dose and the 24mcg BID dose for the COPD indication. The labeled dose in the UK is 12mcg BID.

SUMMARY: No new safety concerns have been raised based on the data submitted with this Final Safety Update.

OUTSTANDING ISSUES: None.

RECOMMENDED REGULATORY ACTION: No action necessary.

New clinical studies: _____	Clinical Hold _____	Study May Proceed _____
NDA, Efficacy/Label supplement: _____	Approvable _____	Not Approvable _____

SIGNATURES	Medical Reviewer: Eugene J. Sullivan, MD, FCCP	Date:
	Medical Team Leader: Badrul Chowdhury, MD, PhD	Date:

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Badrul Chowdhury
7/27/01 12:28:11 PM
MEDICAL OFFICER
I concur

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MEDICAL TEAM LEADER MEMORANDUM

DATE: July 16, 2001

TO: NDA 21-279

FROM: Badrul A. Chowdhury, MD, PhD
Clinical Team Leader, Division of Pulmonary and Allergy Drug Products

SUBJECT: Secondary medical review of Foradil® Aerolizer™ (formoterol fumarate inhalation powder) for COPD

CC: HFD-570: Meyer, Sullivan, Ostroff

Administrative

NDA 21-279 for Foradil Aerolizer was submitted by Novartis On September 25, 2000. The proposed indications are the treatment and prevention of bronchoconstriction in patients with reversible and irreversible chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis in adults. The applicant is seeking approval of Foradil – 12mcg BID β_2 BID. The 10-month user fee goal date for action on this application is July 25, 2001.

Novartis has developed Foradil for the treatment of asthma. A separate application (NDA 20-831) was submitted on June 24, 1997. The application was approved on February 16, 2001.

Novartis has submitted results from two pivotal clinical studies to gain the COPD indication: (a) Study 056, a 3-month placebo and active controlled (ipratropium bromide MDI) efficacy and safety study, and (b) Study 058, a 12-month placebo and active controlled (theophylline) efficacy and safety study. In both the studies cigarette smoking related COPD patients ages 37 years and older were included. Primary efficacy time point in both studies was at 12 weeks of treatment.

Chemistry and Manufacturing

Foradil Aerolizer consists of a capsule dosage form containing a dry powder formulation of Foradil (formoterol fumarate) intended for oral inhalation with the Aerolizer. The capsule contains 12mcg formoterol fumarate and 25mg lactose as a carrier. The Aerolizer is a plastic device used for inhaling Foradil only. To use the delivery system, a Foradil capsule is placed in the well of the Aerolizer Inhaler, and the capsule is pierced by pressing and releasing the

buttons on the side of the device. The formoterol fumarate formulation is dispersed into the air stream when the patient inhaled rapidly and deeply through the mouthpiece.

Clinical studies

As mentioned above, the applicant has submitted efficacy and safety data from two pivotal clinical studies (Table 1). The two studies are briefly reviewed in the subsequent sections. Detailed review of the clinical studies can be found in Dr. Sullivan's excellent medical review. The sponsor also submitted a supporting study comparing Foradil 12mcg BID and salbutamol 200mcg QID when added to regular treatment of ipratropium MDI 40mcg QID in patients with COPD. The supporting study is not discussed further in this document.

Table 1. Overview of the clinical studies

Study No.	Diagnosis, age of subjects	Length of treatment	Foradil dose mcg BID	Comparator	Number All/Fora12/Fora24
056	COPD, 37-87 yrs	3 months	12, 24	Ipratropium bromide MDI	780/194/192
058	COPD, 34-88 yrs	12 months	12, 24	Theophylline tablet	854/211/214

Study 056: Three-month placebo and active controlled (ipratropium bronide MDI) efficacy and safety study

This was a four-arm, randomized, multicenter, double-blind, double-dummy, placebo- and active-controlled (ipratropium bromide 40mcg QID), parallel-group study. The primary objective of the study was to investigate the efficacy of two doses of formoterol fumarate (12mcg BID, and 24mcg BID) dry powder delivered by the Aerolizer device compared with placebo in COPD patients. The secondary objectives were to compare the effects of formoterol fumarate with ipratropium bromide, investigate dose-response relationship of the two formoterol doses, and assess safety and pharmacokinetics of formoterol in COPD patients. Other variable assessed were St. George Respiratory Symptom Questionnaire (SGRQ) scores, and various measures of COPD exacerbation. The study was conducted in various countries (10 centers in Australia, 4 centers in Belgium, 7 centers in Canada, 5 centers in Denmark, 4 centers in Finland, 14 centers in Netherlands, 5 centers in Norway, 5 centers in Poland, 3 centers in Russia, 9 centers in UK, and 6 centers in US) between November 1997 and April 1999. Of the total patients 6.4% came from US centers. To be eligible, patients were required to be current or previous smokers with a history of >10 pack-years of smoking, have a FEV₁ <70% of predicted and at least 0.75 liters, with an FEV₁/VC <88% of predicted for men or <89% predicted for women, and no clinically relevant concomitant disease.

The study had a 10-21 day placebo run-in period followed by a 12-week double-blind treatment period. Follow-up visits were at weeks 4, 8, and 12. Study drug (active or dummy placebo) was administered four times a day approximately the same time each day. Pre-dose spirometry was performed at each follow-up visit, and 12-hour serial spirometry after dosing was performed after the first dose (Day 0) and last dose (Week 12) of study medication. The primary efficacy variable was the normalized FEV₁ AUC 0-12 hours at week 12. Safety variables included adverse event recording, vital signs, ECG, urinalyses, CBC, and clinical

chemistry. In 21 patients at 2 Danish centers, timed urine and blood samples were obtained for pharmacokinetic measurements at visits on day 0 and week 12.

A total of 780 male and female patients 37 to 87 years of age (overall mean age 64 years) were randomized, approximately equally to the four treatment groups, of which 698 patients completed the study. The ITT population, defined as patients randomized who have received at least one dose of the study medication, included 775 patients. Results of the mean FEV₁ over 12 hours for each treatment group after 12 weeks of treatment (primary efficacy variable) are shown in Figure 1. Both doses of Foradil were statistically significantly superior to placebo and to ipratropium for the primary efficacy variable. Comparisons of the efficacy of the two doses of Foradil did not show any statistically significant difference between the two doses. In fact, the lower dose was numerically superior to the higher dose for the primary efficacy variable. Numerous secondary endpoints, including spirometric variables, patient diary scores, and rescue medication use demonstrated superiority of both Foradil doses over placebo, but no meaningful incremental benefit of the 24mcg BID dose over the 12mcg BID dose. Both doses of Foradil were superior to placebo for total SGRQ score, however, only for the 12mcg BID dose was the difference clinically significant at the predefined level of 4. Both doses of Foradil were well tolerated in this study.

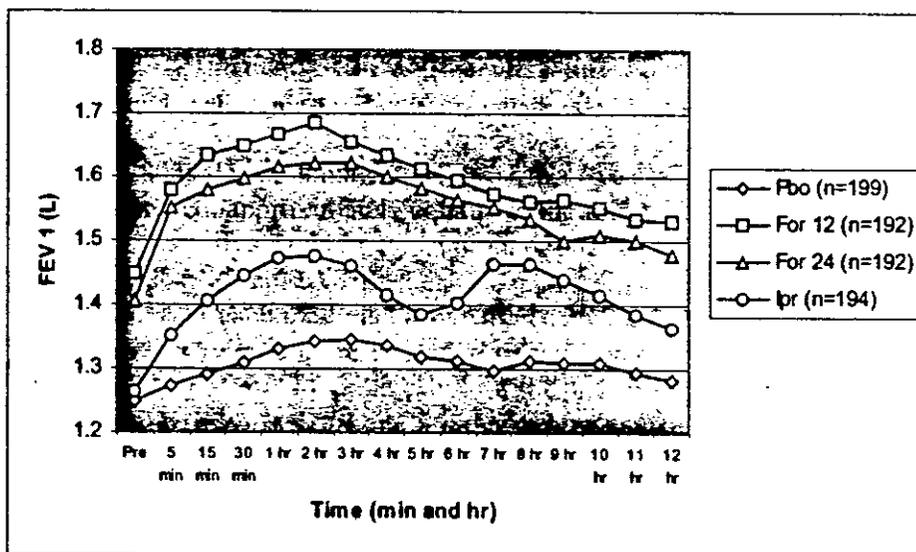


Figure 1. Mean FEV₁ at week 12 [vol 15, page 8:1-4]

Study 058: Twelve-month placebo and active controlled (oral slow release theophylline) efficacy and safety study

The design and conduct of the study was similar to study 056, except for duration of treatment (3 months in study 056 versus 12 months in study 058), and use of a different active comparator (blinded ipratropium bromide in study 056 versus open-label theophylline in this study). This was also a four-arm, randomized, multicenter, double-blind, placebo- and active-controlled (oral slow-release theophylline with dose adjusted based on serum level), parallel-group study. The study was conducted in various countries (2 centers in Austria, 1 center in Belgium, 5 centers in Czech Republic, 9 centers in France, 5 centers in Germany, 5

centers in Greece, 4 centers in Hungary, 16 centers in Italy, 3 centers in Slovakia, 6 centers in South Africa, 6 centers in Spain, and 19 centers in US) between February 1997 and June 1999. Of the total patients 23.3% came from US centers. Patient population, study objectives, efficacy and safety variables of the two studies were similar. Follow-up visits were at months 3, 6, 9, and 12. Serial 12-hour spirometry after dosing was performed at visits on months 3, 6, and 12. Primary efficacy variable was the normalized FEV₁ AUC 0-12 hours at week 12. Additional safety assessment in this study was timed post-dose ECGs performed at the visits on months 3, 6 and 12 at the US sites. ECGs were performed pre-dose, 5 minutes post-dose, and 2 hours post-dose to coincide with the expected C_{max} of formoterol and the expected time of maximum efficacy. The ECGs were read and interpreted by investigators at the study site, and also centrally for calculating QT interval using appropriate methodologies. The applicant initially sent ECG results based on the investigators reading only and QT data were not submitted. Later at our request the applicant submitted QT results based on central reading.

A total of 854 male and female patients 37 to 88 years of age (overall mean age 63 years) were randomized, approximately equally to the four treatment groups, of which 622 patients completed the study. The ITT population, defined as patients randomized who have received at least one dose of the study medication, included 725 patients. Results of the mean FEV₁ over 12 hours for each treatment group after 12 weeks of treatment (primary efficacy variable) are shown in Figure 2. Both doses of Foradil were statistically significantly superior to placebo and to theophylline for the primary efficacy variable. Comparisons of the efficacy of the two doses of Foradil did not show any statistically significant difference between the two doses, although the higher dose was numerically superior to the lower dose for the primary efficacy variable. Numerous secondary endpoints also demonstrated superiority of both Foradil doses over placebo, but no meaningful incremental benefit of the 24mcg BID dose over the 12mcg BID dose was seen. Both doses of Foradil were superior to placebo for total SGRQ score, but neither group met the criteria for clinical significance of 4 at any visit. Both doses of Foradil were well tolerated in this study.

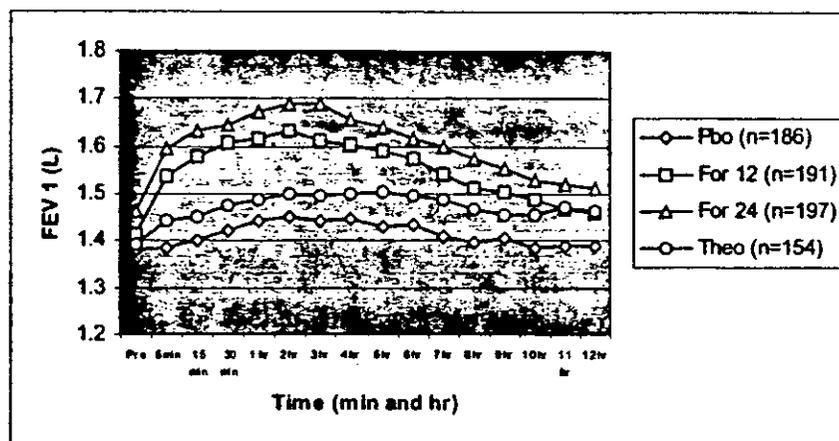


Figure 2. Mean FEV₁ at week 12 [vol 21, pages 8:202-5]

Efficacy assessment

The applicant has submitted two adequate and well controlled studies to support the efficacy of Foradil in COPD. The primary and secondary endpoints of the two studies consistently demonstrate that Foradil 12mcg BID and 24mcg BID are effective in the treatment of bronchospasm in patients with COPD. The studies included approximately equal number of patients with and without bronchodilator responsiveness. In both the studies, benefit was demonstrated statistically for both these subgroups. Therefore, it is reasonable to include a statement in the clinical trial section of the label to indicate that the studies included both bronchodilator reversible and non-reversible COPD patients. The clinical studies did not demonstrate that Foradil 24mcg offers any advantage over Foradil 12mcg.

12mcg BID dose should be approved, which is also in line with the asthma indication. The applicant also seeks a claim. However, the studies submitted do not strongly support this claim. This claim should not be allowed in the label.

Safety assessment

The safety of Foradil in COPD patients is supported by the results of the two pivotal studies and the supporting study. Adverse events reported by the patients in the studies were consistent and expected for this class of drug. Dose ordering was noted for several adverse events, most notably for muscle cramps and tremor. Muscle cramps were not reported in any patients in the placebo group, but were reported in 2% of Foradil 12mcg BID group and 4% of Foradil 24mcg BID group. Tremor was reported in 0.5% of placebo group, as compared with 1% in Foradil 12mcg BID group and 3% in Foradil 24mcg BID group. These adverse events are expected with beta-agonist use.

The frequency of serious adverse events were comparable in the different treatment groups. The incidence of respiratory serious adverse events was 6% in the placebo group, 4% in the Foradil 12mcg BID group, and 2% in the Foradil 24mcg BID group. The frequency of patients withdrawing due to adverse events were 24% in the theophylline group, 8% in the placebo group, 6% in the Foradil 24mcg BID group, 5% in the Foradil 12mcg BID group, and 5% in the ipratropium group. The primary reason of withdrawal in the theophylline group was digestive and nervous system adverse events. The frequency of respiratory system adverse event resulting in withdrawal was 4% in the Foradil 24mcg BID group and 2% in the Foradil 12mcg BID group. In contrast to the Foradil asthma studies, COPD patients did not seem to have higher incidence of respiratory system related serious adverse events or withdrawal with the higher dose of Foradil.

Laboratory data presented do not raise any safety concern.

Four of 811 formoterol treated patients died during the studies, all in study 058. Three of the deaths (coronary scleriosis, asthma, and cardiac failure in a 67 year old male randomized to Foradil 12mcg BID; suicide by strangulation and hanging in a 53 year old male randomized to Foradil 12mcg BID; and brain swelling from a fall in a 60 year old male randomized to Foradil 24mcg BID) were attributed by the investigator to be not related to study drug. One

death (acute myocardial infarction and interventricular septum rupture in a 61 year old male randomized to Foradil 12mcg BID) was attributed by the investigator to be possibly related to study drug. Dr. Sullivan reviewed narrative summaries of all deaths that occurred during the studies and also during post-study period. None of the deaths can be clearly attributed to the study drug.

Cardiac safety

The primary cardiac safety data is from timed ECGs done at the US sites in study 058. ECGs were done 5, 15, and 120 minutes after dosing at visits on months 6, 9, and 12. On our request made at the pre-NDA meeting the applicant had the ECGs read by trained cardiologist at a central site. However, this data was not submitted with the original submission. The data was subsequently submitted in the June 18, 2001, in response to our request. Results of the QT data are shown in Table 2. There were no meaningful effects of Foradil on the QT. Although heart rate and other methods of correction, such as Fredericia's, were not provided, the results indicate that alternate correction methods would not change the conclusion.

Table 2. Mean QT and QTc (Bazett's correction) results at months 3, 6, and 12 from study 058

	Foradil 12 mcg BID			Foradil 24 mcg BID			Placebo		
	n	QT	QTc	n	QT	QTc	n	QT	QTc
3 months									
Pre-dose	43	379.6	413.1	48	373.8	411.6	46	375.7	414.6
5-15 minutes	39	376.5	404.3	47	374.3	411.7	39	379.7	411.6
120 minutes	40	384.0	408.8	46	378.8	412.9	39	384.7	413.0
6 months									
Pre-dose	37	382.1	410.4	47	381.7	413.3	42	382.4	415.8
5-15 minutes	36	377.6	404.9	43	380.5	414.6	39	380.0	411.3
120 minutes	35	382.8	416.7	44	381.6	414.5	42	379.1	414.1
9 months									
Pre-dose	35	372.0	411.8	44	377.7	412.7	36	369.3	413.3
5-15 minutes	34	372.0	413.1	41	380.2	414.4	34	374.5	412.9
120 minutes	35	370.1	412.1	43	379.2	415.7	34	371.7	410.9

Ref: June 18, 2001, submission, pages 27, 30

The applicant has not performed Holter monitoring studies in COPD patients. Although this is not clearly an approvability issue, the applicant should be asked to perform such a study as a Phase 4 commitment. The product label of another long-acting beta-agonist, salmeterol, includes information on Holter monitoring done in 284 COPD patients. Such information would be valuable for Foradil product label.

Financial disclosure

The applicant has submitted form FDA 3454 with the NDA. No investigator disclosed a proprietary interest in the product or a significant equity in Novartis.

Data integrity

DSI audit was not request for this NDA. This decision was made because no single center contributed a large fraction of the patient in the NDA database, and review of the data did not raise concerns about the integrity of the data in the individual study center. Further, four centers were audited by DSI as part of the review of NDA 20-831 (Foradil for asthma).

Recommendation

From a clinical standpoint this NDA is recommend an APPROVAL action. The submitted data support the efficacy and safety of Foradil in the treatment of COPD. The applicant has proposed the approval of 12mcg BID. As discussed above, the data do not demonstrate any incremental benefit with the 24mcg BID dose over the 12mcg BID dose. 12mcg BID dose is recommended for approval.

The cardiac safety database of Foradil in COPD patients is somewhat limited. Specifically there are no Holter monitoring data that may be included in the label. The applicant should be asked to generate Holter monitoring data in COPD patients as a Phase 4 commitment.

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Medical team leader memorandum

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MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #: 21-279
Sponsor: Novartis
Investigator: Multiple

Application Type: NDA
Proprietary Name: Foradil® Aerolizer™
USAN Name: Formoterol fumarate
inhalation powder

Category: Long-acting beta-2 adrenoceptor
agonist

Route of
Administration: Oral inhalation

Reviewer: Eugene J. Sullivan, MD, FCCP

Review Date: July 19, 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
July 5, 2001	July 6, 2001	NDA	Final Safety Update

REVIEW: This is a review of the final safety update submitted in support of NDA 21-279, Foradil Aerolizer for the treatment of chronic obstructive pulmonary disease. This submission updates the safety information included in the Integrated Summary of Safety submitted with the original NDA, and the 120-Day Safety Update submitted in January, 2000. This submission includes: 1) summaries of safety information for clinical trials in asthma patients and COPD patients that have been completed since the last cut-off date (July 15, 2000), including case report forms for all patients who died or prematurely discontinued from a clinical trial during the time period between the last safety cutoff date and the new cutoff date (July 16, 2000 to May 15, 2001); 2) SAEs reported since the last cut-off date; 3) an update of post-marketing safety information since the last cut-off date; 4) an update of the clinical literature published since the last update; and 5) an update on the registration of this product in foreign countries along with the corresponding foreign product labeling information.

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Review of the postmarketing data and clinical literature submitted did not raise any new safety concerns.

A dossier variation for the addition of the COPD indication was dispatched to global health authorities (except the US) in March, 2000. On the basis of this dossier 19 countries have approved the COPD indication. These countries include Canada, the United Kingdom (UK), and Australia. Twelve of these countries use International Product Labeling (IPL). The submission includes copies of the IPL and the product labels from six of the seven countries that use unique product labels (the label from Turkey was not included). All of these countries, with the exception of the UK, have approved both the 12mcg BID dose and the 24mcg BID dose for the COPD indication. The labeled dose in the UK is 12mcg BID.

SUMMARY: No new safety concerns have been raised based on the data submitted with this Final Safety Update.

OUTSTANDING ISSUES: None.

RECOMMENDED REGULATORY ACTION: No action necessary.

New clinical studies: _____	Clinical Hold	_____	Study May Proceed
NDA, Efficacy/Label supplement: _____	Approvable	_____	Not Approvable

SIGNATURES	Medical Reviewer:	Date:
	Eugene J. Sullivan, MD, FCCP	
	Medical Team Leader:	Date:
	Badrul Chowdhury, MD, PhD	

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I concur

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MEDICAL OFFICER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #: 21-279	Application Type: NDA
Sponsor: Novartis	Proprietary Name: Foradil® Aerolizer™
Investigator: Multiple	USAN Name: Formoterol fumarate inhalation powder
Category: Long-acting beta2-agonist bronchodilator	Route of Administration: Oral Inhalation
Reviewer: Eugene J. Sullivan, MD, FCCP	Review Date: June 11, 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
September 22, 2000	September 25, 2000	Original NDA	COPD Indication
November 15, 2000	November 15, 2000	BM (electronic)	Patient Profiles
January 31, 2001	February 1, 2001	SU	120-Day Safety Update
May 4, 2001	May 7, 2001	BL	Labeling
June 18, 2001	June 19, 2001	AM	ECG data

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments

REVIEW SUMMARY: This Application is submitted to support the COPD indication for Foradil® Aerolizer™ (formoterol fumarate inhalation powder). The Applicant proposes 12mcg BID. This product, at a dose of 12mcg BID, was recently approved for the treatment of asthma under NDA 20-831. The Phase 3 program for the COPD indication included two large, multicenter, randomized, double-blind, placebo controlled studies in adults with COPD. The primary endpoint in both studies was the FEV₁ AUC_{0-12 hours} after 12 weeks of treatment. The data submitted, including analyses of the primary and secondary endpoints, indicate that both the 12mcg BID and the 24mcg BID dose are clinically and statistically superior to placebo in the maintenance treatment of COPD. However, the data do not suggest that the 24mcg BID dose offers any advantage over the 12mcg BID dose. The 24mcg BID dose is associated with more frequent beta₂-agonist associated adverse effects. The Medical Officer recommendation is that the 12mcg BID dose be approved for the treatment of COPD. A phase 4 commitment to study the cardiac effects of Foradil 12mcg BID using 24-hour Holter monitoring should be requested. Finally, although the Applicant requests labeling language the data do not support

OUTSTANDING ISSUES: Labeling discussions are ongoing.

RECOMMENDED REGULATORY ACTION:

NDA, Efficacy/Label supplement: Approval Not Approvable

SIGNATURES **Medical Reviewer:** Eugene J. Sullivan, MD, FCCP **Date:** _____
Medical Team Leader: Badrul Chowdhury MD, Ph.D. **Date:** _____

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1 Executive Summary

1.1 RECOMMENDATIONS

1.1.1 Recommendations on Approvability

The data presented in this Application support the safety and efficacy of Foradil® Aerolizer™ in the maintenance treatment of Chronic Obstructive Pulmonary Disease (COPD). The Applicant has proposed _____ (12mcg capsules, to be administered as 12mcg BID _____

_____ The data do not demonstrate that the higher dose offers any efficacy advantage, despite the evidence of increased adverse events. The data also do not allow any _____

1.1.2 Recommendations on Phase 4 Studies and/or Risk Management Steps

The COPD population, because of their age, concomitant cardiac risk factors (e.g. smoking), and frequent concomitant cardiac disease, may be particularly susceptible to the potential adverse cardiac effects of beta₂-agonists. The Applicant has not performed studies in the COPD population in which Holter monitoring was performed. The Applicant should be required to perform a Phase 4 study to examine the cardiac effects of the therapeutic dose of Foradil in this patient population. The product label for another long-acting beta₂-agonist, Serevent Inhalation Aerosol (Glaxo Wellcome), includes information on Holter monitoring performed in 284 patients during five 24-hour periods. The Applicant should commit to studying a similar number of patients with Holter monitoring during chronic use of Foradil.

1.2 SUMMARY OF CLINICAL FINDINGS

1.2.1 Brief Overview of Clinical Program

Two adequate and well controlled Phase 3 studies, Study 056 and Study 058, have been submitted in support of the proposed indication, the maintenance treatment of COPD.

The Applicant has also proposed that _____

_____ two Phase 3 studies.

_____ The table below summarizes the

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Adequate and well-controlled trials submitted in support of NDA				
Study	Design/ Duration/ Purpose	Control	Number of Patients	Primary Efficacy Measure
056	Randomized, double-blind, controlled 3 months Study of: efficacy, dose response, QOL, safety, PK, pharmacogenomics	1. Placebo 2. Ipratropium bromide MDI 40mcg QID	ITT=780 12mcg=194 24mcg=192 Pbo=200 IB=194	FEV ₁ AUC _{0-12hours} after 3 months of treatment
058	Randomized, double-blind, controlled 12 months Study of: efficacy, dose response, QOL, safety, pharmacogenomics	1. Placebo 2. Theophylline 200-400mg po BID	ITT=854 12mcg=211 24mcg=214 Pbo=220 Theo=209	FEV ₁ AUC _{0-12hours} after 3 months of treatment

Both of the Phase 3 studies were four-arm studies comparing the efficacy of Foradil 12mcg BID (F12), Foradil 24mcg BID (F24), an active comparator, and placebo in adults with COPD. The active comparator in Study 056 was ipratropium bromide MDI (40mcg QID), and the active comparator in Study 05 was slow-release oral theophylline (200-400mg BID). The treatment periods for Studies 056 and 058 were 12 weeks and 12 months, respectively. Inclusion criteria for both studies included American Thoracic Society criteria for the diagnosis of COPD, and the presence of sufficient COPD symptoms during the run-in period. The studies included patients both with and without baseline bronchodilator reversibility, defined as a $\geq 15\%$ increase in FEV₁ following the administration of albuterol sulfate MDI. The patients enrolled in these studies had a mean baseline FEV₁ of 46% of predicted.

In both studies, the primary endpoint was FEV₁ AUC_{0-12 hours} after 12 weeks of treatment. Secondary endpoints included other spirometric variables (pre-dose FEV₁, post-dose FEV₁ at various timepoints, FVC AUC_{0-12 hours}), daily symptom scores, rescue medication use (recorded daily in a diary), COPD exacerbations, and St. George Respiratory Symptom Questionnaire (SGRQ) scores.

A total of 1634 patients were enrolled in these two studies, including 405 patients receiving Foradil 12mcg BID, 406 patients receiving Foradil 24mcg BID, and 420 patients receiving placebo. A total of 316 patients were exposed to Foradil for more than 48 weeks.

The application also includes a final report from one additional, "supportive" study, FOR-INT-03. This was a non-US, multicenter, randomized, double blind, double-dummy, two-period crossover study of Foradil 12mcg BID versus salbutamol 200mcg QID, when

added to regular treatment with ipratropium bromide 40mcg QID in patients with "partially reversible" COPD. This study offered little relevant efficacy information regarding the regulatory approval decision of Foradil for COPD.

1.2.2 Efficacy

Both studies demonstrated that both doses of Foradil (12mcg BID and 24mcg BID) were superior to placebo on the pre-specified primary endpoint, FEV₁ AUC_{0-12 hours} after 12 weeks of treatment, and that the treatment effects were greater than the minimal meaningful effect size that was pre-specified by the Applicant. In Study 056, the effect size for this endpoint demonstrated in the Foradil 12mcg BID (F12) group (0.223 liters) was numerically greater than the effect size demonstrated in the Foradil 24mcg BID (F24) group (0.194 liters). In Study 058, the effect sizes that were demonstrated in the two Foradil groups were virtually identical (0.200 liters in the F12 group and 0.208 liters in the F24 group).

The various secondary spirometric variables also supported the superiority of both doses of Foradil over placebo and also did not suggest that the 24mcg BID dose was superior to the 12mcg BID dose. For instance, the pre-dose FEV₁, a measure of end-of-dosing-interval efficacy, was numerically higher in the F12 group than in the F24 group at 8 and 12 weeks in Study 056 (the 12-week study), and at 6, 9, and 12 months in Study 058 (the 12-month study). Also, the FEV₁ AUC_{0-12 hours} at 12 months (Study 058) was numerically higher in the F12 group than the F24 group.

Both studies demonstrated that the daily use of rescue medication was statistically lower in both Foradil groups, as compared to placebo. In regard to the patient diary symptom scores, both doses were statistically superior to placebo at 4 and 8 weeks (Study 056), only F12 was superior to placebo at 12 weeks in Study 056, and neither dose was superior to placebo at 3, 6, 9, and 12 months in Study 058.

No

are justified

1.2.3 Safety

The safety database in this application is derived from the two Phase 3 studies. In these studies, patients were exposed to Foradil for either 3 months (Study 056) or 12 months (Study 058). There was no significant safety concern regarding deaths or serious adverse events (SAEs). Adverse events associated with the beta₂-agonist class of drugs were seen with Foradil and were more common in the Foradil 24mcg BID (F24) group than in the 12mcg BID (F12) group.

The percentage of patients discontinuing treatment was higher in the placebo group (21%) than in the Foradil groups (16%). Similarly, the percentage of patients withdrawing due to adverse events was slightly higher in the placebo group (8%) than in the Foradil groups (5%, for both Foradil groups combined). There were four deaths, all of which occurred in

patients treated with Foradil (3 patients receiving 12mcg BID and 1 patient receiving 24mcg BID). Two of the deaths were cardiac in nature, one was related to trauma, and one was due to suicide. The Foradil groups had a lower incidence of SAEs compared with placebo, primarily due to fewer respiratory events.

The overall incidence of adverse events (AEs) in the placebo and Foradil groups was similar. The incidences of overall cardiovascular AEs and individual specific cardiovascular AEs were also similar among these groups. There were several individual AEs that showed dose ordering and for which the incidence was greater in one or both of the Foradil groups than in the placebo group. For instance, the incidence of muscle cramps in the placebo, F12, and F24 groups was 0%, 1.7%, and 3.7%, respectively. The incidence of tremor in the placebo, F12, and F24 groups was 0.5%, 1%, and 3%, respectively.

The cardiac safety database is somewhat limited in that no studies utilizing 24-hour Holter monitoring were performed. As discussed above, it would be appropriate for the Applicant to commit to performing such a study in Phase 4. There was no important difference between the placebo and the Foradil groups regarding the numbers of patients whose pre-dose ECG changed from normal at baseline to abnormal during treatment. Post-dose ECGs (5-15 minutes and 2 hours post-dose) were performed in a subset of patients in Study 058. There was no evidence of a drug effect on the QT or QTc (Bazett's correction) intervals in these patients.

1.2.4 Dosing

Dosing issues are discussed in the previous sections. The drug is supplied as 12mcg dry powder capsules. The Applicant has proposed the approval of — (12mcg BID) ~~—~~. There is no evidence to suggest that the efficacy of the 24mcg BID dose is superior to that of the 12mcg BID dose. In fact, on several efficacy parameters the 12mcg BID dose was numerically superior to the 24mcg BID dose. The safety data suggest that while both doses appeared relatively safe, there was an increased frequency of beta₂-agonist related effects in the higher dose group.

1.2.5 Special Populations

Only 20% of the patients in the database were women. A slightly higher percentage of women experienced AEs in all treatment groups, except for the F12 group. For the primary efficacy variable, both doses of Foradil were statistically superior to placebo for both men and women. For the 24mcg BID dose there was no difference in treatment effect size between men and women; however, for the 12mcg BID dose the estimated treatment effect size was substantially greater in men than in women (0.230L vs. 0.138L) [Vol. 30: page 8:61]. In its discussion of this difference in treatment effect, the Applicant notes that there was a greater proportion of patients ≥65 years of age in the female 12mcg BID group (45%) than in the 24mcg BID group (31%). The significance of this observation is not clear, as the Applicant has also concluded that there was no observable difference in treatment effect size based on age category (<65 years vs. ≥65 years) [Vol.

30: page 8:69]. (The estimated treatment effect size of the 12mcg BID dose was 0.202L in patients ≥ 65 years old and it was 0.208 in patients < 65 years old.)

Because the large majority of patients in both studies were Caucasians, subset safety and efficacy analyses based on race were not possible.

There was a slight increase in the frequency of adverse events as age increased for both the Foradil groups. This age effect was not evident in the placebo group.

Few women of childbearing years were recruited into the pivotal studies. The only information available regarding the use of Foradil during pregnancy arises from the Applicant's global spontaneous reporting database, in which there have been a total of 20 reports of such use. In 5 of these the outcome was reported as "normal baby", in 7 there was a problem with the pregnancy reported, and in 8 no outcome information was reported. The problems reported were spontaneous abortion, missed abortion, stillbirth, and malformation. Beta₂-adrenergic agents are commonly used to treat asthma in pregnant women.

A minority of the patients in the two Phase 3 studies were US patients. US patients represented 6.4% of the total number of patients in Study 056 and 23.3% of the total number of patients in Study 058. Statistical analyses for the US-patient groups were not performed. However, the Biometrics reviewer, Dr. Guo, generated figures illustrating the serial FEV₁ values for the US patients by treatment group after 12 weeks of treatment. These figures, which can be found in Dr. Guo's review, confirm that the treatment effect seen in the US population was qualitatively similar to the treatment effect seen in the entire study population.

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2 Introduction and Background

2.1 DRUG INFORMATION: CATEGORY, ROUTE, PROPOSED INDICATION

Foradil® Aerolizer™ (formoterol fumarate inhalation powder) is a long-acting beta₂-adrenoceptor agonist, which is currently approved in the US for the treatment of asthma in adults and children five years of age and older who require regular treatment with inhaled, short-acting beta₂-agonists. It is also indicated for the acute prevention of exercise-induced bronchospasm in adults and children 12 years of age and older. These indications were supported by NDA 20-831. The drug is supplied as 12mcg dry powder capsules, which are intended for oral inhalation using a plastic, single-dose, breath activated device called the Aerolizer™. To use the Aerolizer, a Foradil capsule is placed in the well of the device, and the capsule is pierced by pressing and releasing the buttons on the side of the device. The formoterol fumarate formulation is dispersed into the air stream when the patient inhales rapidly and deeply through the mouthpiece.

Foradil®, in various formulations, has been approved for marketing for at least one indication in 79 countries.

This NDA proposes the following additional indication: Foradil Aerolizer is indicated for the long-term, twice daily (morning and evening) administration in the

Obstructive Pulmonary Disease including chronic bronchitis and emphysema. Chronic
Submission dated

5/4/01, page 13 of proposed US Package Insert]

2.2 CURRENT ARMAMENTARIUM/RELATED DRUGS

The only currently approved category of agents for the treatment of COPD are the bronchodilators. Currently approved bronchodilators include several short-acting beta-adrenergic agonists (e.g. albuterol, pirbuterol, bitolterol, metaproterenol, and terbutaline), a short-acting anti-cholinergic agent (ipratropium bromide), one long-acting beta-adrenergic agonist (salmeterol), and theophylline. These drugs are available in various formulations, including solutions and metered dose inhalers for oral inhalation, and various formulations for oral ingestion.

The Applicant proposes that Foradil will represent a significant addition to the current armamentarium because: 1) only one alternative long-acting bronchodilator (salmeterol) is available and 2) Foradil's onset of action is shorter than the onset of action of salmeterol.

Other classes of agents, such as corticosteroids and mucokinetic agents, have been investigated for their utility in the pharmacologic management of COPD but none have demonstrated efficacy [Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease, Am J Respir Crit Care Med, 152:S77-S120, 1995].

2.3 IMPORTANT MILESTONES IN PRODUCT DEVELOPMENT

The development of this product for both the asthma and the COPD indications was performed under IND #47,031. The protocols for the pivotal COPD studies were submitted the IND on April 21, 1997 (Study 058) and October 12, 1998 (Study 056).

A pre-NDA meeting was held on June 9, 2000. Issues discussed at that meeting included the format of the application, the proposed statistical analysis and presentation, and the content of the proposed Integrated Summary of Safety. In addition to the proposed integration of the safety data from the two pivotal studies, the Applicant agreed to submit an integration of the safety data from the COPD program and the asthma program combined. It was agreed that this could be submitted with the 120-Day Safety Update. In addition, at the pre-NDA meeting the Division reminded the Applicant that establishing the cardiac safety of Foradil would be very important.

The Applicant has also developed Foradil for the treatment of asthma. A separate NDA for the asthma indication (NDA #20-831) was submitted on June 24, 1997. This application was approved on February 16, 2001.

2.4 FINANCIAL DISCLOSURE

The Applicant has submitted a signed form FDA 3454, the certification of financial interests and arrangements of clinical investigators. This form certifies that the Applicant has not entered into any financial arrangements with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. It also certifies that no investigator disclosed a proprietary interest in the product or a significant equity in the Applicant. [Submission dated 5/25/01]

2.5 DATA AUDITING

Auditing by the Agency's Division of Scientific Investigation (DSI) was not requested for the studies supporting this NDA.

2.6 RELATED REVIEWS

Because Foradil has been previously approved for a different indication, this NDA did not contain any new CMC or Pharm/Tox information. Reviews of these aspects of this product have been performed for NDA #20-831. Reviews of the current application are

being prepared by Dr. Guo (Biometrics) and Dr. Choi (Clinical Pharmacology and Biopharmaceutics).

2.7 READER'S GUIDE TO THIS REVIEW (CONVENTIONS USED)

Throughout this review, information drawn from the NDA submission will be referenced within the text as Volume: page inside [brackets]. Many of the pages in the submission are numbered with a single digit, followed by a hyphen and 1 or more digits (e.g. page 8-23, followed by 8-24). These pages, if located in Volume 22, would be referenced as: [Vol. 22: pages 8:23-24]. All references refer to the 9/25/00 submission, unless otherwise noted. One important exception is the section of this document that reviews the 120-Day Safety Update. This Update was submitted on 1/31/01, and, as noted in the introduction to that section, references in the section refer to the 1/31/01 submission, unless otherwise noted. Throughout this review, *italics* are used to add emphasis. Important comments from the reviewer will appear in **bold** text and will be preceded by the phrase **Reviewer's Comments**. Where p-values are given within tables, values less than 0.05 are emphasized by shading of the cell (unless otherwise noted). Other noteworthy cells within tables may also be shaded in order to draw the reader's attention.

Throughout this document the abbreviations F12 and F24 will be used to indicate the Foradil Aerolizer 12mcg BID treatment group and the Foradil Aerolizer 24mcg BID treatment group, respectively.

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3 Clinically Relevant Findings From Other Review Disciplines

This application did not contain any new CMC, Animal Pharmacology/Toxicology, or Microbiology data. These aspects were reviewed as part of the asthma NDA (NDA 20-831) and will not be discussed further here.

Limited Biopharmaceutics data was submitted with this NDA. Dr. Choi, from the Office of Clinical Pharmacology and Biopharmaceutics, has reviewed this data in a separate document. Two issues discussed in his review are summarized below:

1. Based on a small subset of patients in one of the Phase 3 studies (21 patients from 2 centers in Study 056) who underwent pharmacokinetic sampling, Dr. Choi has determined that the systemic exposure of Foradil is slightly lower in COPD patients, as compared with patients with asthma.
2. The Applicant performed analyses of the metabolizer status of CYP2D6 and CYP2C19 in 239 patients who participated in the pivotal studies. Of these 239 patients, 11 were identified as being poor metabolizers of CYP2D6, and 7 were identified as being poor metabolizers of CYP2C19. Because of the small numbers of affected patients, extensive analyses of the safety and pharmacodynamic impact of the poor metabolizer genotype were not performed. However, one signal of potential significance was noted. Four of the five patients who were poor metabolizers of CYP2C19 and who received Foradil 24mcg BID had some evidence of drug-induced tachycardia at one or more visits [Vol. 12; page 6:453]. Based on this observation, the Division considered requiring the Applicant to further investigate this subgroup of patients. A decision was made not to require further studies, for three reasons. First, the current label already contains warnings regarding the potential for Foradil to cause tachycardia. Second, the currently available data provides ample clinical experience in patients with systemic exposures comparable to the systemic exposure expected from a 12mcg BID dose in a patient who is a poor metabolizer of CYP2C19. (Based upon conservative estimates, the systemic exposure of a 12mcg BID dose in a patient who is a poor metabolizer of CYP2C19 is not expected to exceed the systemic exposure of a 24mcg BID in a patient with normal metabolizing status.) Third, the

No consultations outside the Division of Pulmonary and Allergy Drug Products were requested.

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4 Clinical Studies

The Applicant has submitted two adequate and well controlled Phase 3 studies and one supportive study intended to support the proposed COPD indication. The two Phase 3 studies (Study 056 and Study 058) were four-arm studies comparing the efficacy of Foradil 12mcg BID, Foradil 24mcg BID, an active comparator, and placebo in adults with chronic obstructive pulmonary disease (COPD). These studies are summarized in the table below and are discussed in this section of the Medical Officer Review. The safety aspects of these two studies are discussed collectively in the section of this review entitled "Overview of Safety."

Adequate and well-controlled trials submitted in support of NDA				
Study	Design/ Duration/ Purpose	Control	Number of Patients	Primary Efficacy Measure
056	Randomized, double-blind, controlled 3 months Study of: efficacy, dose response, QOL, safety, PK, pharmacogenomics	3. Placebo 4. Ipratropium bromide MDI 40mcg QID	ITT=780 12mcg=194 24mcg=192 Pbo=200 IB=194	FEV ₁ AUC _{0-12hours} after 3 months of treatment
058	Randomized, double-blind, controlled 12 months Study of: efficacy, dose response, QOL, safety, pharmacogenomics	3. Placebo 4. Theophylline 200-400mg po BID	ITT=854 12mcg=211 24mcg=214 Pbo=220 Theo=209	FEV ₁ AUC _{0-12hours} after 3 months of treatment

One additional, "supportive" study (FOR-INT-03) was also submitted in this application. It was a non-US, multicenter, randomized, double-blind, double-dummy, two-period crossover study of Foradil 12mcg BID versus salbutamol 200mcg QID, when added to regular treatment with ipratropium bromide 40mcg QID in patients with "partially reversible" COPD. This study offered little relevant efficacy information regarding the regulatory approval decision of Foradil for COPD. It is discussed briefly in this section.

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4.1 STUDY 056: "RANDOMIZED, DOUBLE-BLIND, BETWEEN-PATIENT TRIAL COMPARING TWO DOSES OF INHALED FORMOTEROL FUMARATE DRY POWDER (12 AND 24MCG BID) WITH PLACEBO AND IPRATROPIUM BROMIDE MDI (40MCG QID) FOR 12 WEEKS INPATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE, IN TERMS OF CLINICAL EFFICACY, TOLERABILITY AND QUALITY OF LIFE."

4.1.1 Study Description

4.1.1.1 Design

This was a multicenter, randomized, double blind, double-dummy, placebo- and active-controlled study. The protocol is provided in Volume 15, pages 8:227-310. The clinical study report is provided in Volume 14, pages 8:1-77.

4.1.1.2 Duration

The treatment period was 12 weeks. A placebo run-in period of 10-21 days preceded the active treatment period.

4.1.1.3 Population

Male and female subjects, aged ≥ 40 years, with a diagnosis of COPD according to the criteria of the American Thoracic Society (ATS) were enrolled.

4.1.1.4 Study Sites

The original protocol (Dated 12/9/96) indicated the study would take place in one country (Denmark). A protocol amendment dated 9/2/97 expanded the study to include sites in other countries as well [Vol. 15: page 8:295]. There is some discrepancy in the reported total number of centers. The NDA submission reports a total of 72 centers but Dr. Guo's review of the data reveals a total of 62 centers. Dr. Guo, the Biometrics reviewer, does not feel that this discrepancy adversely affects the ability to draw conclusions from the data. Elsewhere in the submission, the total number of centers is listed as 44. This number reflects post-randomization pooling of some of the smaller centers. Six of the centers were in the US, representing 6.4% of all patients. Other sites were in Australia, Belgium, Canada, Denmark, Finland, Great Britain, Norway, Holland, Poland, and Russia. [Source: Biometrics Review by Dr. Guo]

4.1.1.5 Investigational and Reference Therapy

The following materials were used:

- Formoterol dry powder capsules, each containing 12mcg formoterol fumarate (Foradil®, Batch #s B970020 and B970097)

- Ipratropium bromide MDI 20mcg per puff, 200 puffs/canister (Atrovent®, Batch #s 17/409/51 and 17/422/51, produced by Boehringer Ingelheim)
- Placebo dry powder capsules matched to formoterol dry powder capsules (Batch #s B970021 and B970110, produced by Novartis)
- Placebo MDI matched to ipratropium bromide MDI (Batch #s 17/402/52 and 17/305/52, produced by —)
- Marketed albuterol MDI, 100mcg/puff, as rescue medication (Ventolin®)

All dry powder capsules were inhaled through the Aerolizer, which is a single-dose, breath-activated inhaler device.

4.1.1.6 Objectives

The primary objective of this study was to investigate the efficacy of two doses of inhaled formoterol fumarate (Foradil®) dry powder inhaler delivered by the single-dose breath actuated inhaler (Aerolizer®) compared with placebo, with respect to FEV₁ Area Under the Curve (AUC) measured at the end of continuous treatment for 12 weeks in patients with COPD [Vol. 14: page 8:16].

The secondary objectives of the study were to:

- Compare the effects of Foradil with the effects of ipratropium bromide (Atrovent®) with respect to FEV₁ AUC measured at the end of continuous treatment for 12 weeks.
- To investigate the dose-response relationship of the two doses of formoterol.
- To evaluate the effects of Foradil on other clinical variables.
- To assess the tolerability of Foradil with regard to ECG, laboratory tests, vital signs, and adverse experiences.
- To investigate the pharmacokinetics of Foradil in COPD patients.

4.1.1.7 Inclusion Criteria

Patients were required to [Vol. 14: page 8:19]:

- be current or previous smokers with a history of smoking >10 pack-years
- have an FEV₁ <70% of predicted and at least 0.75 liters, with an FEV₁/VC <88% of predicted for men or <89% of predicted for women (pre-bronchodilator). (These values were based upon European Respiratory Society standards)
- have a total symptom score of more than 0 on at least 4 of the last 7 days prior to randomization

4.1.1.8 Exclusion Criteria

Notable exclusion criteria were [Vol. 14: pages 8:19-20]:

- Current or childhood asthma according to ATS criteria
- Hospitalization or emergency room visit for COPD exacerbation in the month prior to the first visit
- Need for long term oxygen therapy
- Clinically significant conditions that might compromise the patients' safety or compliance, interfere with evaluations, or preclude completion of the trial

- QTc above 0.46s
- Inhaled or nasal corticosteroids that had been started or discontinued or subjected to any change in the daily dose or dosing schedule in the one month prior to Visit 1
- Use of the following medications, with corresponding wash-out periods prior to Visit 1: parenteral or oral corticosteroids (1 month), theophylline (72 hours), oral or inhaled anti-cholinergics (48 hours), oral or inhaled long-acting β_2 -agonists (48 hours), or inhaled short-acting β_2 -agonists (6 hours).

4.1.1.9 Conduct

The tables below outline the overall scheme of the study and the schedule of study procedures.

Study Scheme (Study 056)					
Period:	Run-In	Double-blind Active Treatment			
Visit:	1	2	3	4	5 (Final)
Day:	-21 to -10	0 Randomization	28 (±2)	56 (±2)	84 (±2)
Week:		0	4	8	12
Treatment:	Placebo MDI + Placebo Aerolizer + Albuterol Rescue	Foradil 12mcg BID			
		Foradil 24mcg BID			
		Atrovent 40mcg QID			
		Placebo (BID + QID)			

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Schedule of Study Procedures (Study 056)		[Vol. 15: page 8:247]			
Period	Run-In	Double-blind Active Treatment			
Visit	1	2	3	4	5
Week		0	4	8	12
Informed Consent	X				
Selection Criteria	X	X			
Demographic data, medical history, screening spirometry/reversibility test	X				
Fasting laboratory test	X				X
Randomization		X			
Quality of life questionnaire (SGRQ)		X			X
Check patient diary		X	X	X	X
Check smoking status		X	X	X	X
ECG pre-dose	X				X
BP, pulse rate pre-dose	X	X			X
Inspiratory VC, FEV ₁ , FVC pre-dose		X	X	X	X
Dispense trial drug	X	X	X	X	
Collect trial drug		X	X	X	X
Trial drug administration at center	X	X	X	X	X
12-hr BP and pulse rate		X			X
12-hour serial spirometry		X			X
Adverse experiences	X	X	X	X	X
Concomitant medication	X	X	X	X	X
COPD-related hospitalizations			X	X	X
Residual urine (PK centers only)	X				
Urine and blood samples for PK (PK centers only)		X			X
Termination sheet					X

At Visit 1, patients were screened for inclusion and instructed in study procedures, including home peak flow measurements and patient diary completion. Also at Visit 1, patients underwent bronchodilator reversibility testing, and, for those patients seen at centers where pharmacokinetic sampling was planned, residual urine measurement by ultrasound. A 10-21 day, single-blind placebo run-in period followed Visit 1. Albuterol was used as the rescue medicine during this run-in. Randomization occurred at Visit 2, 10-21 days after Visit 1. Follow-up Visits 3, 4, and 5 occurred after 4, 8, and 12 weeks of active treatment, respectively. Patients were issued two Aerolizer devices (one intended for "back-up") at Visit 1, as well as one Aerolizer at each of Visits 2-4. An additional back-up Aerolizer was retained at the study center, for use if required [Vol. 15: page 8:306].

Efficacy Assessments

Pre-dose spirometry was performed at each follow-up visit. In addition, 12-hour serial spirometry was performed after the first dose (Visit 2) and last dose (Visit 5) of study medication. Serial spirometry included measures before dosing and 5, 15, 30 minutes, 1 hour and hourly up to 12 hours after dosing. Visits 2 and 5 were postponed if the patient had taken albuterol rescue medication within 6 hours before the visit. For Visits 3 and 4,

patients were encouraged to avoid the use of rescue medication for 6 hours before the visit, but the visit was not re-scheduled for this reason.

A patient diary was used to collect additional efficacy data. The patients were instructed to complete the diary daily in the morning before taking study medication, considering events over the last 24 hours. This diary included the following items:

Contents of daily patient diary (Study 056)		[Vol. 15: page 8:254]
Item	Score and definition	
Ability to perform usual daily activity: "Did your respiratory symptoms prevent you from performing your usual daily activities yesterday?"	0. Not at all 1. A little 2. Quite a lot 3. Completely	
Breathlessness: "When did you first feel breathless during the past 24 hours?"	0. Never or only when running 1. When walking uphill or upstairs 2. When walking on flat ground 3. At rest	
Waking at night due to respiratory symptoms: "How would you rate your respiratory symptoms last night?"	0. No symptoms, slept all night 1. Woke up once due to symptoms 2. Woke up more than once due to symptoms 3. Woke up frequently or could not sleep due to symptoms	
Cough: "How was your cough during the past 24 hours?"	0. None 1. Mild 2. Moderate 3. Severe	
Amount of sputum: "How much sputum did you produce during the past 24 hours?"	0. No sputum 1. Little on rising only 2. Less than 1 eggcup full 3. More than 1 eggcup full	
Breathlessness on rising: "How breathless were you on rising?"	0. Not at all breathless 1. A little breathless 2. Moderately breathless 3. Very breathless	
# of inhalations of rescue medication	(# of puffs in last 24 hours)	
Morning PEFR (pre-dose; L/min; using mini-Wright® Peak Flow Meter)	(highest of 3 consecutive efforts)	

Safety Assessments

Vital signs were measured once during Visit 1, and five times at Visits 2 and 5 (pre-dose, and 1, 2, 4, and 12 hours post-dose). Pre-dose electrocardiograms were obtained at Visits 1 and 5. *Note that no post-dose ECGs were performed. Post-dose ECGs were performed in a subset of patients in Study 058.* Fasting blood samples were drawn for hematology and blood chemistry laboratories at Visit 1 (before reversibility testing) and at Visit 5 (pre-dose). *Note that no post-dose laboratory studies were performed.*

The patient diary was also used to record perceived adverse events. The diary included space to record any adverse event, along with its start date and stop date.

Pharmacokinetic Assessment

In 21 patients at 2 Danish centers, timed urine and blood samples were obtained for pharmacokinetic measurements at Visit 2 and Visit 5 [Vol. 14: page 8:32].

Other Assessments

The Saint George's Respiratory Questionnaire (SGRQ) was self-administered at Visit 2 and Visit 5.

COPD exacerbations were characterized in several ways [Vol. 14: page 8:31, 39]:

- "Bad days": Days with at least twice a score of 2 or more as recorded in the diary and/or a reduction of PEFR from baseline of more than 20%.
- Need for additional therapy (steroids/antibiotics/oxygen/xanthines).
- COPD-related hospitalizations (An emergency room visit not requiring overnight stay is not considered a hospitalization).

4.1.1.10 Concomitant Treatments

Short courses (≤ 15 days) of antibiotics, oral corticosteroids, and oxygen to treat COPD exacerbations were permitted. (If these events occurred within 7 days of Visits 2 or 5, these visits were to be postponed.) If the short courses were not sufficient to manage the exacerbation, the patient was withdrawn for the trial.

Albuterol (100mcg/puff, maximum 8 puffs/day) was used as the rescue medication. Nebulized albuterol was not permitted. The following medications were disallowed: theophyllines, parenteral corticosteroids, β -blockers, quinidine and quinidine-like medications, antidepressants (tricyclics, MAO inhibitors, or selective serotonin re-uptake inhibitors), and β_2 -agonists and anti-cholinergics other than the trial medications.

4.1.1.11 Ethical Aspects

The study was performed in accordance with the sponsor's standard operating procedures. These procedures were designed to be in adherence with Good Clinical Practice, the Declaration of Helsinki, the Rules Governing Medicinal Products in the European Community, and US 21 CFR. Informed consent was obtained from each patient prior to initiating any study procedure. The protocol and patient informed consent forms were approved by a properly constituted committee responsible for approving clinical trials (e.g. Ethical Review Board/ Institutional Review Board).

4.1.1.12 Data Analysis

Efficacy Variables

The projected sample size was determined based upon the primary efficacy variable, normalized FEV₁ AUC 0-12hours. The sample size calculation was made based upon the assumption of a between-patient standard deviation of 400mL and the assumption that a difference of 120mL between formoterol 24mcg BID and placebo would be clinically relevant. The original protocol indicated that 824 patients (206 patients per group) were to be randomized so as to obtain 700 completed patients after 12 weeks, allowing for a drop-out rate of 15% [Vol. 15: page 8:238]. Because of lower than expected drop-out rate, the target was subsequently decreased to 770 randomized patients. A total of 780 patients were actually randomized, with 698 completers [Vol. 14: page 8:18].

The pre-specified primary variable was the normalized FEV₁ AUC 0-12 hours at Week 12. Secondary efficacy variables were:

- Pre-dose FEV₁ at 4, 8, and 12 weeks
- Post-dose FEV₁ at each time point on Day 1 and Week 12
- Inspiratory vital capacity at each measured time point after randomization
- Normalized FVC AUC 0-12 hours on Day 1 and Week 12
- Morning pre-dose PEFr, averaged monthly over 12 weeks
- Total score of the patient's diary averaged monthly over 12 weeks
- Daily number of puffs of rescue medication averaged monthly over 12 weeks

The study report adds a *new secondary variable (not listed in the protocol)*: Normalized AUC calculated using absolute FEV₁ through the 12-hour interval, after 1 dose of trial medication on day 1 of treatment [Vol. 14: page 8:37].

According to the protocol amendment dated 9/2/97, the confirmatory analysis on the primary variable was to be carried out on the modified intent-to-treat (ITT) population. The modified ITT population was defined to include all patients randomized who have received at least one dose of trial medication. All secondary variables were to be analyzed "following the intention-to-treat principle." [Vol. 15: page 8:300]

As stated in the 9/2/97 amendment, in order to control Type I error in light of multiple testing, a hierarchy of testing was set up. No contrast was to be considered statistically significant unless each preceding contrast examined within that family of contrasts is also statistically significant. The hierarchy is described below:

- For the primary objective: the comparison of Foradil 24mcg BID vs. placebo will be performed first, followed by the comparison of Foradil 12mcg BID vs. placebo.
- For the secondary objective: the comparison of Foradil 24mcg BID vs. placebo will be performed first, followed by the comparison of Foradil 12mcg BID vs. placebo.
- An additional secondary objective will be to compare the two doses of Formoterol.
- The contrast of ipratropium bromide versus placebo will be used to test the sensitivity of the trial.

Analysis of covariance was planned, using center, sex, reversibility, smoking status, and baseline FEV₁ as covariates. *A decision was subsequently made* to replace the effects of center with the effects of country and center within country in the model. This was done

because a large number of centers had recruited fewer than 12 patients, which was the block-size used in the randomization. While the study report indicates that this decision was made prior to un-blinding [Vol. 14: page 8:37], the timing of this decision is not otherwise documented. Additional subgroup analyses were planned to compare reversible and non-reversible patients using the modified ITT population. *After the study was un-blinded* the following additional variables were analyzed according to these reversibility subgroups: morning pre-dose PEFr, total score on the patient diary, daily number of puffs of rescue medication, and quality of life total score. *These were not pre-specified analyses.*

Missing values within a visit were to be estimated by linear interpolation if no more than 3 values are missing and the values for baseline, 1, 2, 3, and 12 hours are given. (Otherwise, missing within-visit values were to be left as missing and the derived variables would not be calculated for that visit). The protocol states that "for all other variables, no missing value will be replaced by interpolation, extrapolation or last carried forward approach" [Protocol, Vol. 15: page 8:266]. *However, the study report states that patients having no AUC at Visit 5 had their last available AUC carried forward [Vol. 14: page 8:36]. The last observation carried forward was also applied to the analysis of post-medication FEV₁ measurement although this was not planned in the original protocol.*

Safety Variables

All patients randomized who had received at least one dose of study medication were to be included. Safety data was to be presented in listings, summary tables, and plots. Inferential statistics and plots were to be used to compare treatment groups. Descriptive summary statistics were also planned.

Other Variables

Additional pre-specified variables to be investigated are listed below, along with the planned analyses:

- SGRQ scores (symptoms, activity, impacts, and total): analysis of covariance
- time to premature discontinuation due to AE or unsatisfactory therapeutic effect: Kaplan-Meier estimate
- percentage of "bad days" averaged monthly over 12 weeks: analysis of covariance
- number of days on which additional therapy is required for COPD exacerbations: van Elteren test
- time to first COPD exacerbation requiring additional therapy: Kaplan-Meier estimate
- number of COPD-related hospitalizations: van Elteren test
- time to first COPD-related hospitalization: Kaplan-Meier estimate

The modified ITT population was to be analyzed.

The 9/2/97 protocol amendment specified that the primary quality of life comparison between groups would be based upon the total SGRQ score, assuming that a difference of 4 points would be clinically significant.

The study report added the following *new variable*: percentage of “bad days” averaged over all visits. An *additional change* made prior to un-blinding (according to the study report) was the addition of xanthines to the list of additional therapies in the definition of an asthma exacerbation. *In addition*: 1) the analysis of the number of days on which additional COPD therapy was required was changed to the percentage of days on which additional COPD therapy was required, and 2) the original variable regarding the time to first COPD exacerbation was amended to be the time to the first “bad day”, and 3) because there were few such events, the pre-specified analyses of premature discontinuation, number of COPD-related hospitalizations, and time to first COPD-related hospitalization were not performed. It is not stated when these changes were made.

4.1.2 Patient Disposition and Demographics

The table below outlines, by treatment group, the numbers of patients screened, randomized, and completed. Also provided in the table are the numbers of patients discontinuing the trial and the reasons given for discontinuation. A total of 935 patients were screened and 780 patients were randomized. The percentage of patients who discontinued the trial was highest in the Placebo group and lowest in the Foradil 12mcg BID group. Discontinuation due to COPD-related AE (cough, breathlessness, dyspnea, bronchospasm, or chronic obstructive airways disease exacerbated) was slightly more common in the Foradil 24mcg BID group and the Placebo group as compared to the Foradil 12mcg BID group. The mean duration of double-blind treatment exposure was similar among all four treatment groups (79-81 days, data not shown [Vol. 14: page 8:45]).

Patient Disposition (Study 056) [number (%) of patients]					[Vol. 14: page 8:40-41]
	F12	F24	Placebo	lpr	Total
Total # of patients studied					
Screened					935
Randomized	194	192	200	194	780
Completed	181 (93)	162(88)	171 (86)	177 (91)	698 (89)
Discontinued					
Total	13 (7)	23 (12)	29 (15)	17 (9)	82 (11)
AE (COPD-related)	2 (1)	9 (5)	7 (4)	5 (3)	23 (3)
AE (Not COPD-related)	4(2)	5 (3)	4 (2)	4 (2)	17 (2)
Abnormal test result(s)	0	0	1 (1)	1 (1)	2 (<1)
Unsatisfactory therapeutic effect	1 (1)	0	3 (2)	1 (1)	5 (1)
Protocol criteria not met	3 (2)	6 (3)	2 (1)	2 (1)	13 (2)
Non-compliance	2 (1)	2 (1)	4 (2)	2 (1)	10 (1)
Withdrawal of consent	0	0	7 (4)	2 (1)	9 (1)
Lost to follow-up	1 (1)	0	0	0	1 (<1)
Administrative problems	0	1(1)	1 (1)	0	2 (<1)

As specified in the protocol, efficacy and safety analyses were carried out on all patients who were randomized and had received at least one dose of study medication (modified ITT population). In this study, all randomized patients received at least one dose of study

medication. Therefore, the modified ITT population was identical to the ITT population. The numbers of modified ITT patients in each treatment group are indicated in the table above, in the row labeled "randomized." The Applicant also planned to do additional analyses on all randomized patients who had completed the 12-week treatment period and had not taken rescue medication in the six hours before the spirometry at Visit 5 (the "acceptable" patient population). **Reviewer's Comment: These analyses will not be discussed in this Review.** The protocol also called for subgroup analyses of reversible and non-reversible patients for various efficacy parameters, using the modified ITT population. The table below provides the numbers of patients in these two subgroups, by treatment. **Reviewer's Note: Interestingly, the study enrolled equal numbers of reversible and irreversible patients.**

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Number (%) of patients in modified ITT subgroups					[Vol. 14: page 8:42]
	F12	F24	Placebo	Ipr	Total
Subgroups:					
Reversible patients*	98	99	99	93	389
Non-reversible patients	96	92	101	100	389

*FEV₁ increased by ≥15% after inhalation of 200mcg albuterol at Visit 1

The table below summarizes selected baseline demographic variables by treatment group. The mean age of the patients was 64 years and seventy-five percent of the patients were men. There were no important differences between groups on the variables presented. Morning PEF was slightly higher in the two Foradil groups compared to the placebo group. A slightly greater percentage of patients in the two Foradil groups had a history of cardiovascular disease, as compared with the placebo and ipratropium groups. The Foradil 24mcg BID group used slightly more puffs of rescue medication during baseline than did the other groups.

Demographic/Baseline Data (Study 056, modified ITT population)					[Vol. 14: page 8:43, and 8:356-378]
	F12 (N=194)	F24 (N=192)	Placebo (N=200)	Ipr (N=194)	Total (N=780)
Age (years)					
Mean	64	64	63	64	64
Range	40-84	42-79	37-82	40-87	37-87
Sex [n(%)]					
Male	144 (74)	145 (76)	157 (79)	136 (70)	582 (75)
Female	50 (26)	47 (25)	43 (22)	58 (30)	198 (25)
Baseline FEV ₁ (L) (Visit 2)					
Mean	1.32	1.31	1.26	1.25	1.28
Range	0.5 - 3.5	0.6 - 4.3	0.5 - 3.1	0.5 - 2.7	0.5 - 4.3
Morning pre-dose PEF (L/min)*					
Mean	255	258	241	243	246
Range	65-504	103-523	65-467	80-654	65-654
Daily puffs of rescue medication (mean)	2.0	2.5	2.5	2.4	2.4
Percentage reversibility					
Mean	18	18	17	16	17
Range	-9 - 146	-17 - 108	-17 - 73	-41 - 69	-41 - 146
Patients with concomitant diseases [n(%)]	119 (61)	134 (70)	120 (60)	115 (59)	488 (63)
Patients with history of cardiovascular (CV) disease [n(%)]					
CV disorders, general	48 (25)	46 (24)	40 (20)	41 (21)	175 (22)
Rate and rhythm disorders	10 (5)	7 (4)	14 (7)	6 (3)	37 (5)
Myo, endo, and pericardial & valve disorders	28 (14)	28 (15)	21 (11)	22 (11)	99 (13)
Hypertension	46 (24)	43 (22)	36 (18)	40 (21)	165 (21)

*mean over the last 7 days of the run-in period

There were no important differences between groups regarding the concomitant use of COPD medications during the study. Slightly more patients in the placebo group used corticosteroids than did patients in the Foradil 12mcg BID group (56% vs. 50.5%) [Vol.14: page 8:390]. Regarding other (non-COPD) concomitant medications, more patients in the Foradil 24mcg group used medications categorized as “coronary vessel dilators” than did patients in other groups (24.5% vs. 14.4%, 17%, and 14.9% for Foradil 12mcg BID, Placebo, and Ipratropium, respectively) [Vol. 14: page 8:409].

4.1.3 Efficacy Review

4.1.3.1 Primary Endpoint

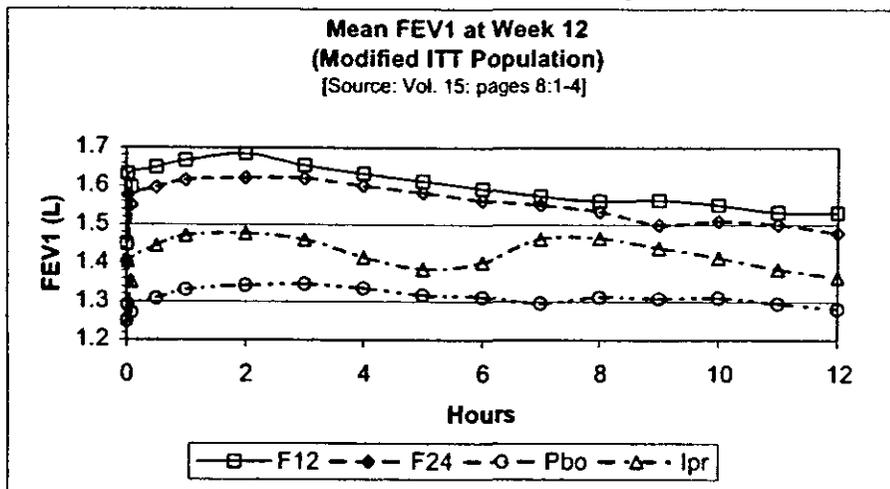
The pre-specified primary efficacy endpoint was the normalized FEV₁ AUC over 12 hours after 12 weeks of treatment (Visit 5). The efficacy analysis of the modified ITT population consisted of 775 patients out of the 780 randomized patients. The five remaining patients were excluded because of missing serial spirometry data or reversibility data. The table below summarizes the treatment group comparisons regarding FEV₁ AUC 0-12 hours at Week 12. In order to control for Type I error, the protocol specified that these comparisons were to be made in a hierarchical fashion, as described above.

Comparison (n=775)	Estimate of Treatment Difference (L)	95% Confidence Interval	p-value
Foradil 24 v Placebo	0.194	0.145 - 0.243	<0.001
Foradil 12 v Placebo	0.223	0.174 - 0.273	<0.001
Foradil 24 v Ipratropium	0.057	0.007 - 0.106	0.024
Foradil 12 v Ipratropium	0.086	0.037 - 0.136	0.001
Foradil 24 v Foradil 12	-0.029	-0.079 - 0.020	0.245
Ipratropium v Placebo	0.137	0.088 - 0.186	<0.001

On this variable, both doses of Foradil were superior to placebo. However, there was no significant difference between Foradil 12mcg BID and Foradil 24mcg BID. In fact, the estimated improvement over placebo seen with Foradil 12mcg BID (223ml) was numerically superior to that of Foradil 24mcg BID (194ml). The ipratropium treatment arm was included in order to assess the sensitivity of this trial. Ipratropium was demonstrated to be superior to placebo on FEV₁ AUC over 12 hours at Visit 5. Both doses of Foradil were statistically superior to ipratropium, but the difference was not clinically significant (57 and 86 ml, in contrast to the pre-specified assumption of clinical significance of 120ml).

Factors that were shown to be significantly related to outcome were baseline FEV₁, country, sex and reversibility, whereas center within country and smoking status were not.

The figure below depicts the mean FEV₁ over 12 hours for each treatment group after 12 weeks of treatment. The figure shows that the Foradil 12mcg BID group performed numerically better than the Foradil 24mcg BID group.



4.1.3.2 Secondary Endpoints

4.1.3.2.1 Subgroup Analysis: Reversible vs. Non-reversible patients

The protocol indicated that certain efficacy variables would be analyzed for subgroups of the modified ITT population, based on the baseline bronchodilator reversibility status. Reversibility was defined as an improvement in FEV₁ of ≥15%, 30 minutes after treatment with 200mcg albuterol. The tables below summarize the treatment group comparisons for the primary efficacy variable (FEV₁ AUC_{0-12 hours} at Week 12) for each subgroup.

Subgroup Analysis: Reversible Patients			[Vol. 14: page 8:48]
Treatment Group Comparisons of FEV ₁ AUC 0-12 hours at 12 Weeks [Modified ITT Population]			
Comparison (n=387)	Estimate of Treatment Difference (L)	95% Confidence Interval	p-value
Foradil 24 v Placebo	0.244	0.166 - 0.322	<0.001
Foradil 12 v Placebo	0.241	0.162 - 0.320	<0.001
Foradil 24 v Ipratropium	0.094	0.015 - 0.173	0.020
Foradil 12 v Ipratropium	0.091	0.012 - 0.170	0.025
Foradil 24 v Foradil 12	0.003	-0.074 - 0.081	0.934
Ipratropium v Placebo	0.150	0.071 - 0.229	<0.001

Among the reversible subgroup of patients, both doses of Foradil were shown to be superior to placebo and to ipratropium. No difference was demonstrated between the Foradil 24 group and the Foradil 12 group. Ipratropium was superior to placebo.

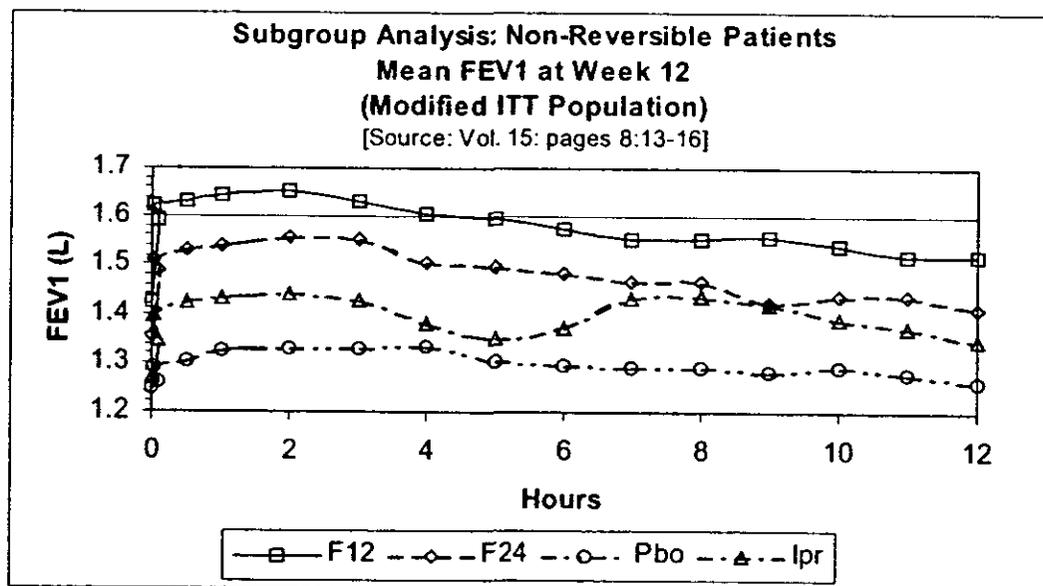
Subgroup Analysis: Non-Reversible Patients [Vol. 14: page 8:48-9]

Treatment Group Comparisons of FEV₁ AUC 0-12 hours at 12 Weeks
[Modified ITT Population]

Comparison (n=388)	Estimate of Treatment Difference (L)	95% Confidence Interval	p-value
Foradil 24 v Placebo	0.137	0.071 - 0.203	<0.001
Foradil 12 v Placebo	0.213	0.145 - 0.280	<0.001
Foradil 24 v Ipratropium	0.031	-0.036 - 0.097	0.371
Foradil 12 v Ipratropium	0.106	0.039 - 0.174	0.002*
Foradil 24 v Foradil 12	-0.076	-0.144 - -0.007	0.030
Ipratropium v Placebo	0.106	0.040 - 0.172	0.002

*Based upon the pre-specified hierarchy of comparisons and the failure to demonstrate superiority of Foradil 24 over Ipratropium, this comparison cannot be considered significant.

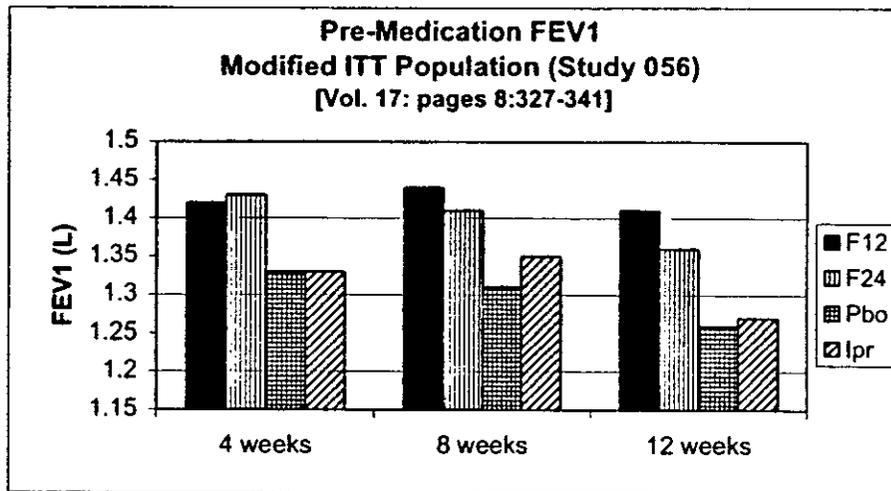
Among the non-reversible patients, both doses of Foradil were shown to be superior to placebo. *Foradil 12 was statistically, though not clinically, superior to Foradil 24* (p=0.03, estimated treatment difference=0.076 liter). Foradil 24 was not significantly different from ipratropium; therefore, based upon the pre-specified hierarchy of comparisons, the Foradil 12 versus ipratropium comparison could not be considered. Ipratropium was shown to be superior to placebo. The figure below is intended to demonstrate graphically the comparison of Foradil 24 with Foradil 12 in the non-reversible subgroup at 12 weeks.



4.1.3.2.2 Secondary Spirometry Endpoints

The FEV₁ AUC_{0-12 hours} after the first dose of study medication was analyzed in the modified ITT population. Both doses of Foradil were statistically and clinically superior to placebo. No difference was seen between the two doses of Foradil.

Pre-medication FEV₁ (12 hours after the last evening dose) after 4, 8, and 12 weeks of treatment was analyzed in the modified ITT population. Both doses of Foradil were superior to placebo after 4, 8, and 12 weeks for this variable. No statistical difference was seen between the two doses of Foradil. The Foradil 12 group was numerically superior to the Foradil 24 group after 8 and 12 weeks. This data is illustrated graphically below.



The FEV₁ after the morning dose of medication was measured over 12 hours at day 1 and after 12 weeks of treatment. The treatment groups were compared at each individual time-point, using the modified ITT population. Both doses of Foradil were superior to placebo for this variable at every time-point on both days. There was no statistical difference between the two doses of Foradil at any of the time-points. However, the Foradil 12 group was numerically superior to the Foradil 24 group at every time-point at Week 12 (mean difference=0.031L, range 0.012L to 0.051L) [Vol. 18: pages 8:80-150].

The protocol called for analyses of pre- and post-medication IVC at various time-points. The analyses were done but the study report states that "it is unknown in which patients FVC was measured instead of IVC" and therefore, "the results should be interpreted with caution." [Vol. 14: pages 8:51-2]. These data will not be discussed in this review.

The FVC AUC_{0-12 hours} on Day 1 and after twelve weeks of treatment were analyzed in the modified ITT population. Both doses of Foradil were statistically superior to placebo on both days. No difference was seen between the two doses of Foradil on either day.

The mean pre-medication PEF (recorded daily on the patient diary card), averaged monthly, was analyzed in the modified ITT population. The mean pre-medication PEF for the entire treatment period was also analyzed, although this was not planned in the protocol. Both doses of Foradil were statistically superior to placebo for each month analyzed and for the entire treatment period. No statistical difference was seen between the two doses of Foradil. The improvement in PEF over placebo, averaged over all visits, was estimated at 23L/min for both doses of Foradil.

4.1.3.2.3 Rescue Medication Use

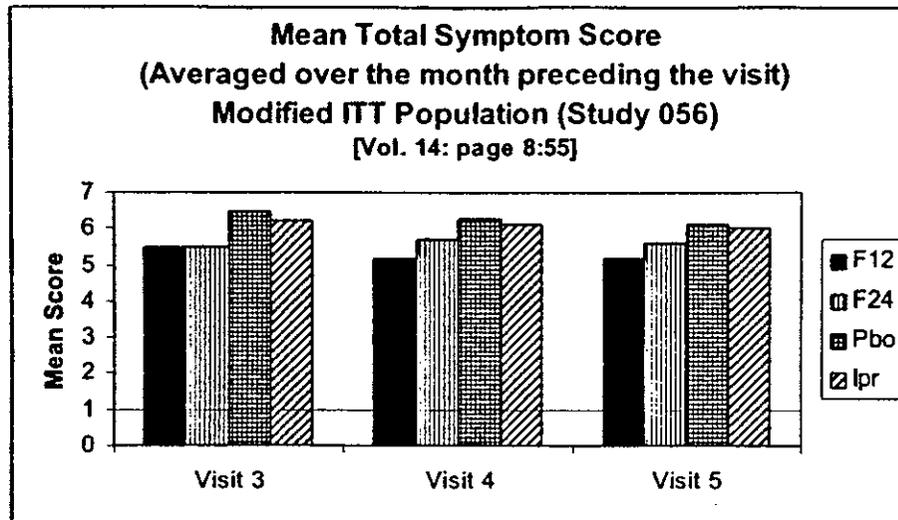
The protocol stated that the daily number of puffs of rescue medication would be averaged monthly and compared between groups. Both doses of Foradil were statistically superior to placebo over each month of the study. There was no statistical difference between the two Foradil groups; however the Foradil 12 group was numerically superior to the Foradil 24 group at Visit 3 (1.1 vs. 1.7), Visit 4 (1.1 vs. 1.6), and Visit 5 (1.2 vs. 1.7). Of note, at baseline the Foradil 24mcg BID group reported greater use of rescue medication than did the Foradil 12mcg BID group (mean daily puffs = 2.5 vs. 2.0).

The study report also includes two analyses that were not pre-specified: mean number of puffs of rescue medication over the entire treatment period, and mean % of days with no rescue medication. The Foradil 12 group was numerically superior to the Foradil 24 group regarding the mean % of days with no rescue medication use at each treatment visit (60% vs. 56.4% at Visit 3, 59.9% vs. 57.5% at Visit 4, and 61.1% vs. 55.9% at Visit 5) and for the entire study period (59.6% vs. 55.9%) [Vol. 14, page 8:56-7].

4.1.3.2.4 Patient Diary Scores

The components of the daily patient diary are described above. There were six questions, each scored on a 0-3 scale. Therefore, the total score ranged from 0 (no symptoms) to 18 (worst symptoms). Total scores were averaged monthly during the course of treatment [Vol. 14: pages 8:54-56].

Foradil 24 was superior to placebo in the months before Visit 3 and Visit 4, *but not in the month before Visit 5*. Foradil 12 was superior to placebo in all 3 months of the study. There was no statistically significant differences between the two Foradil groups but the Foradil 12 group was numerically superior to the Foradil 24 group at Visit 4 (5.2 vs. 5.7) and Visit 5 (5.2 vs. 5.6). The mean total diary score at Visit 3 was the same for both Foradil groups. The mean total symptom scores, averaged monthly, are demonstrated graphically below.



The following analyses of the patient diary scores were described in the study report but were not pre-specified in the protocol: mean total diary score over the entire treatment period, and mean percentage of days with no symptoms. Of note, Foradil 12 was superior to Foradil 24 regarding mean percent of days with no symptoms at Visits 4 and 5 (Foradil 24 was superior at Visit 3 only) [Vol. 14: page 8:55-6].

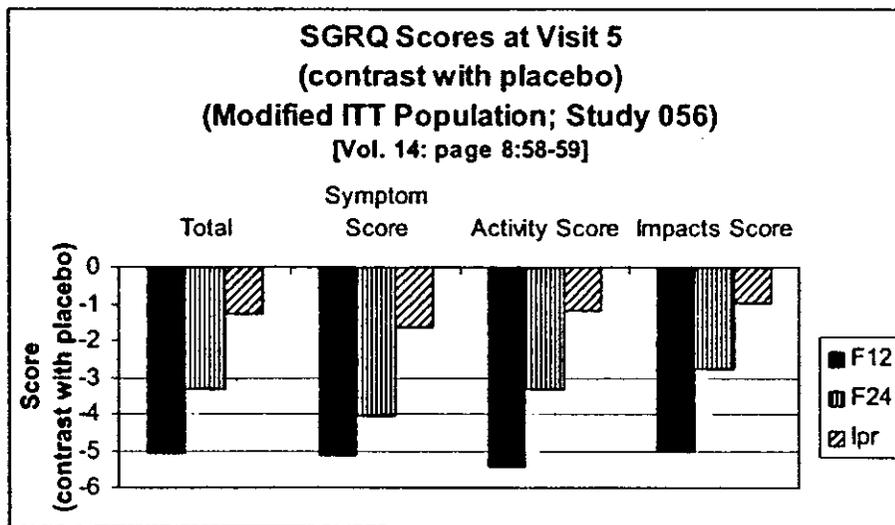
Total patient diary scores were analyzed by subgroups based on bronchodilator reversibility. Both doses of Foradil were superior to placebo in the reversible group but *only the Foradil 12 group was superior to placebo in the non-reversible group.*

4.1.3.2.5 St. George's Respiratory Questionnaire

The protocol (as amended) specified that the St. George's Respiratory Questionnaire (SGRQ) would be administered at Visits 2 and 5. Comparisons between groups were to be based on the total SGRQ score, with a difference of 4 points pre-specified as representing a clinically meaningful difference. Both doses of Foradil were statistically superior to placebo for total SGRQ score *but only Foradil 12 met the criteria for clinical significance* (Foradil 12 vs. placebo = -5.06; Foradil 24 vs. placebo = -3.34) [Vol. 14: pages 8:57-59].

Because the total SGRQ score for F12 was demonstrated to be statistically and clinically superior to placebo, comparisons regarding the individual domains will be discussed for this Foradil dose only. Foradil 12 was statistically superior to placebo on the individual domains of "symptom score", "activity score", and "impacts score." The absolute differences between F12 and placebo for these domains were -5.12, -5.42, and -5.0, respectively. The protocol did not pre-specify what absolute difference would be considered clinically meaningful for the SGRQ domains.

The figure below illustrates the comparisons of Visit 5 SGRQ scores (total, and for each domain) and placebo, for each active treatment.



4.1.3.2.6 Time to Withdrawal Due to Adverse Event or Unsatisfactory Therapeutic Effect

The protocol called for an analysis of time to withdrawal due to an adverse event or unsatisfactory therapeutic effect. Because few patients withdrew for these reasons (n=45), formal statistical analysis was not performed. The numbers of withdrawals in each treatment group were as follows: Foradil 12 = 7, Foradil 24 = 14, Placebo = 14, Ipratropium = 10. *The fewest withdrawals for these reasons were seen in the Foradil 12 group. The study report does not indicate how many of the withdrawals in each treatment group were due to adverse events and how many were due to unsatisfactory therapeutic effect. One could postulate that unsatisfactory therapeutic effect might be the reason for the majority of the withdrawals in the placebo group, and adverse effect might be the reason for the majority of the withdrawals in the F24 group.*

4.1.3.2.7 Percentage of “Bad Days”

The protocol called for comparisons between treatment groups on the percentage of “bad days” averaged monthly over the treatment period. Both doses of Foradil were superior to placebo during all three months of the trial. Of note, when the percentage of “bad days” was averaged for the entire treatment period, the Foradil 12 group was numerically superior to the Foradil 24 group (-13.14% vs. -9.98%, compared to placebo).

The Applicant has described a comparison based on time to first “bad day.” *However, this comparison was not pre-specified among the numerous secondary analyses.*

4.1.3.2.8 COPD Exacerbations

The protocol described the following analyses related to COPD exacerbations [Vol. 15; pages 8:267 and 8:269]:

- number of days on which additional therapy is required for COPD exacerbations
- time to first COPD exacerbation requiring additional therapy
- number of COPD-related hospitalizations
- time to first COPD-related hospitalization

The study report describes the mean percentage of days of additional therapy that was required for COPD exacerbation. There was no statistical difference between groups on this variable (F12=13%, F24=16%, Placebo=14%).

The pre-specified analysis of time to first COPD exacerbation requiring additional therapy (Kaplan-Meier curve) is not provided in the study report. The Applicant has described a comparison based on time to first "bad day." *However, this comparison was not pre-specified among the numerous secondary analyses.*

There were very few COPD-related hospitalizations in this study; therefore no formal statistical analyses were performed on this variable.

4.1.3.2.9 Pharmacokinetics

The pharmacokinetic analyses of formoterol in plasma and urine will not be discussed in this review. Pharmacokinetic data may be found in the separate review performed by the OCPB reviewer.

4.1.3.3 Reviewer's Comments on Efficacy

Both doses of Foradil were superior to placebo on the study's pre-specified primary endpoint analysis, the normalized FEV₁ AUC over 12 hours after 12 weeks of treatment (Visit 5).

Both doses of Foradil were also superior to placebo on many of the secondary endpoints including: FEV₁ AUC_{0-12 hours} after the first dose of study drug, pre-medication FEV₁ (12 hours after the last evening dose) after 4, 8, and 12 weeks of treatment, mean pre-medication PEF, serial individual FEV₁ measurements after the morning dose of medication on day 1 and after 12 weeks of treatment, daily number of puffs of rescue medication, and percentage of "bad days."

For the monthly, total patient diary scores, Foradil 24 was superior to placebo in the months before Visit 3 and Visit 4, *but not in the month before Visit 5.* Foradil 12 was superior to placebo for this variable in all 3 months of the study. Regarding the quality of life instrument, both doses of Foradil were statistically superior to placebo for total SGRQ score *but only Foradil 12 met the criteria for clinical significance* (Foradil 12 vs. placebo = -5.06; Foradil 24 vs. placebo = -3.34). No difference between either dose of

Foradil and placebo was demonstrated in the number of days on which additional therapy was required for treatment of COPD exacerbations.

In the pre-specified subgroup analysis of the primary variable (FEV_1 AUC_{0-12 hours} after 12 weeks of treatment), both doses of Foradil were superior to placebo among both the reversible and non-reversible subgroups of patients. Of note, among the non-reversible patients, Foradil 12 was statistically, though not clinically, superior to Foradil 24.

In summary, both doses of Foradil were shown to be superior to placebo in the primary and many of the secondary analyses. However, in several of these analyses, Foradil 12 was numerically, though not statistically, superior to Foradil 24. The variables (some not pre-specified) on which Foradil 12 was numerically superior to Foradil 24 include: 1) FEV_1 AUC_{0-12 hours} at week 12; 2) pre-medication FEV_1 at 8 and 12 weeks; 3) daily number of puffs of rescue medication at 4, 8, and 12 weeks; 4) mean percentage of days with no rescue medication use at 4, 8, and 12 weeks; 5) total patient diary score at 8 and 12 weeks; 6) mean percentage of days with no symptoms at 4, 8, and 12 weeks; 7) total SGRQ (at 12 weeks); 8) number of withdrawals due to adverse event or unsatisfactory therapeutic effect (7 vs. 14); and 9) percent of "bad days" over the entire treatment period. Further evidence of the superiority of F12 over F24 may be inferred from the data on COPD-related AEs resulting in discontinuation. In the F12 group there were 2 (1%) such events, compared with 9 (5%) such events in the F24 group.

4.1.4 Safety Review

Because this study was very similar in design to Study 058, safety data from the two studies will be examined collectively, in the Integrated Summary of Safety. No gross safety concerns were noted in this study.

4.1.5 Summary of Study

This was a 12-week, multicenter, randomized, placebo-controlled study comparing Foradil 12mcg BID, Foradil 24mcg BID, and placebo in adults with COPD. In addition, ipratropium bromide MDI was used as an active comparator. The primary endpoint was FEV_1 AUC 0-12hours, measured after 12 weeks of treatment. The results demonstrated the superiority of both doses of Foradil over placebo for the pre-specified primary endpoint, as well as numerous secondary endpoints including other spirometric variables and rescue medication use. Foradil 12mcg BID was superior to placebo on patient diary scores during each month of the study. However, on this variable, Foradil 24mcg BID was superior to placebo for the first and second months only. Both doses of Foradil were statistically superior to placebo for total SGRQ score, but only in the Foradil 12mcg BID group was the difference clinically significant. Comparisons of the relative efficacy of the two doses of Foradil did not suggest an important incremental benefit of the higher dose. In fact, the lower dose was numerically superior to the higher dose for the primary efficacy variable as well as several secondary variables.

Safety data from this study will be discussed in the Integrated Summary of Safety.

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4.2 STUDY 058: "RANDOMIZED, BETWEEN-PATIENT TRIAL COMPARING TWO DOSES OF INHALED FORMOTEROL FUMARATE DRY POWDER (12MCG AND 24MCG) WITH PLACEBO (DOUBLE-BLIND) AND WITH ORAL SLOW-RELEASE THEOPHYLLINE AT INDIVIDUAL DOSES BASED ON SERUM LEVELS (OPEN-LABEL), EACH ADMINISTERED TWICE DAILY FOR ONE YEAR TO PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN TERMS OF CLINICAL EFFICACY, TOLERABILITY AND QUALITY OF LIFE."

4.2.1 Study Description

This study was very similar to Study 056. Both were multicenter, randomized trials comparing Foradil 12mcg BID, Foradil 24mcg BID, placebo and an active comparator. Differences between the two studies include the active comparator used (blinded ipratropium bromide in Study 056 versus open-label theophylline in Study 058) and the duration of the study (3 months in Study 056 versus 12 months in Study 058). The primary endpoint for both studies was the normalized FEV₁ AUC 0-12 hours after 12 weeks of treatment. Pharmacokinetic analyses were performed in a subset of patients in Study 056 but were not performed in Study 058. The protocol for Study 058 is provided in Volume 23, pages 8:1-145. The clinical study report for Study 058 is provided in Volume 20, pages 8:1-97.

4.2.1.1 Design

This was a multicenter, randomized trial. The placebo and the two formoterol groups were administered in a double-blind fashion. The theophylline group was open-label.

4.2.1.2 Duration

The treatment period was one year. The treatment period was preceded by a 10-21 day placebo run-in period.

4.2.1.3 Population

Male and female subjects, aged ≥ 40 years, with a diagnosis of COPD according to the criteria of the American Thoracic Society were enrolled.

4.2.1.4 Study Sites

The original protocol was to include several study centers in Italy. In a subsequent amendment, the study was expanded to include sites in other countries as well. The study was ultimately conducted at 81 centers across the world. Nineteen (23%) of these centers were in the US, accounting for 23.3% of all patients. Other sites were in Italy (16 centers), Austria, Belgium, Czech Republic, Germany, Spain, France, Greece, Hungary, Slovakia, and South Africa. (Note: The total number of centers is sometimes listed as 57,

reflecting post-randomization pooling of some of the smaller centers.) [Source: Biometrics Review by Dr. Guo]

4.2.1.5 Investigational and Reference Therapy

The following materials were used:

- Formoterol dry powder inhaler, each containing 12mcg of formoterol fumarate (Foradil®): Batch number B970020, lot number E18/96.
- Theophylline slow release (SR) divisible tablets, each containing 200 or 300 mg of active substance (Theo-Dur®), produced by Astra, Batch numbers: 200mg=XL 530; 300mg=XI 931A.
- Placebo dry powder capsules matched to formoterol: Batch number B970021, lot number E19/96.
- Marketed salbutamol MDI, 100mcg/puff, as rescue medication.

4.2.1.6 Objective

The primary objective of this study was to investigate the efficacy of two doses (12mcg BID and 24mcg BID) of inhaled formoterol fumarate (Foradil®) dry powder inhaler delivered by the single-dose breath actuated inhaler (Aerolizer®) with placebo with respect to FEV₁ Area Under the Curve (AUC) measured at the end of continuous treatment for 12 weeks in patients with COPD [Vol. 20: page 8:16]. (Note: the original protocol declared that this variable would be analyzed after 12 months but this was amended to 12 weeks [Vol. 23: page 8:71]).

The secondary objectives of the study were to:

- Compare the effects of Foradil with the effects of oral SR theophylline (Theo-Dur®) BID (at doses adjusted according to serum level) with respect to FEV₁ AUC measured at the end of continuous treatment for 12 months. The study report adds the following timepoints: 12 weeks and 6 months.
- To investigate the dose-response relationship of the two doses of formoterol.
- To evaluate the effects of Foradil on other clinical variables.
- To assess the tolerability of Foradil with regard to ECG, laboratory tests, vital signs, and adverse experiences.

4.2.1.7 Inclusion Criteria

The inclusion criteria were identical to those used in Study 056.

4.2.1.8 Exclusion Criteria

The exclusion criteria were identical to those used in Study 056 except patients with a history of "untoward" reaction to ipratropium bromide were not excluded and patients with a history of "untoward" reaction to theophyllines were excluded.

4.2.1.9 Concomitant Treatments

Rules regarding concomitant treatments of COPD were identical to those used in study 056.

4.2.1.10 Conduct

The tables below outline the overall scheme of the study and the schedule of study procedures.

Study Scheme (Study 058)						
Period:	Run-In	Double-blind Active Treatment				
Visit:	1	2	3	4	5	6
		Randomization				
Day:	-21 to -10	0				
Month:		0	3	6	9	12
Treatment:	Placebo MDI + Placebo Aerolizer + Albuterol Rescue	Foradil 12mcg BID				
		Foradil 24mcg BID				
		SR Theophylline* BID (open arm)				
		Placebo (BID + QID)				

*Doses adjusted according to serum levels

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Schedule of Study Procedures (Study 058)		[Vol. 23: page 8:79]				
Period	Run-In	Double-blind Active Treatment				
Visit	1	2	3	4	5	6
Day	-21 to -10	0				
Month		0	3	6	9	12
Informed Consent	X					
Selection Criteria	X	X				
Demographic data, medical history, screening spirometry/reversibility test	X					
Fasting laboratory test	X			X		X
Randomization		X				
Quality of life questionnaire		X		X		X
Check patient diary		X	X	X	X	X
Check smoking status		X	X	X	X	X
ECG pre-dose						
All countries	X		X	X	X	X
US only		X ^a	X ^b	X ^b		X ^b
BP, pulse rate pre-dose	X	X	X	X	X	X
Inspiratory VC, FEV ₁ , FVC pre-dose		X	X	X	X	X
Dispense trial drug		X	X	X	X	
Collect trial drug			X	X	X	X
Trial drug administration at center		X	X	X	X	X
12-hr BP and pulse rate			X	X		X
12-hour serial spirometry			X	X		X
Adverse experiences	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
COPD-related hospitalizations			X	X	X	X
Residual urine (PK centers only)	X					
Theophylline serum levels (in respective group of patients only)		X	X	X	X	X
Termination sheet						X

^a = pre-dose

^b = pre-dose, between the 5 min and 15 min post-dose spirometry test, and immediately after the 2 hour post-dose spirometry test

At Visit 1, patients were screened for inclusion and instructed in study procedures, including home peak flow measurements and patient diary completion. Also at Visit 1, patients also underwent bronchodilator reversibility testing. A 10-21 day, single-blind placebo run-in period followed Visit 1. Randomization occurred at Visit 2, 10-21 days after Visit 1. Follow-up Visits 3-6 occurred after 3, 6, 9, and 12 months of active treatment, respectively.

Patients in the theophylline group began treatment at Visit 2 with 300 mg BID. These patients returned to the center within 4-7 days for serum theophylline measurement. If the level was below 8mg/L, the dose was increased to 400mg BID. If the level was above 20mg/L, the dose was decreased to 200mg BID [Vol. 23: page 8:72]. If the dose was adjusted at Visit 2, the patient returned to the center for another serum theophylline level in 4-7 days. If this level is not within the target range (8-20mg/L), the patient was removed from the study. Serum theophylline were also drawn 3-4 hours after dosing (Visits 3-6), and at any time theophylline was suspected of causing an adverse experience.

Dose adjustments were made according to the plan above if levels were found to be out of the target range.

Efficacy Assessments

Pre-dose spirometry was performed at Visits 1, 2, and 5. In addition, 12-hour serial spirometry was performed at Visits 3, 4, and 6 (3 months, 6 months, and 12 months, respectively). *Note that serial spirometry was not performed after the first dose of study medication, which occurred at Visit 2.* Serial spirometry included measures before dosing and 5, 15, 30 minutes, 1 hour and hourly up to 12 hours after dosing. Pre-dose inspiratory VC (IVC) was intended to be performed at every visit. However, many centers could not measure IVC and instead recorded the forced vital capacity (FVC). Visits 3, 4, and 6 were postponed if the patient had taken albuterol rescue medication within 6 hours before the visit. For other Visits, patients were encouraged to avoid the use of rescue medication for 6 hours before the visit, but the visit was not re-scheduled for this reason.

A patient diary was used to collect additional efficacy data. The patients were instructed to complete the diary daily in the morning before taking study medication, considering events over the last 24 hours. This diary was identical to the diary used in Study 056.

Safety Assessments

Vital signs (pulse and blood pressure) were measured at rest during Visit 1 and pre-dose during Visits 2 and 5. Vital signs were measured 5 times at Visits 3, 4, and 6 (pre-dose, and 1, 2, 4, and 12 hours post-dose). Pre-dose electrocardiograms were obtained at Visits 1, 3, 4, 5, and 6. Additional ECGs were performed at US sites only. These were performed at Visits 3, 4, and 6 and were performed at 5 minutes post-dose and 2 hours post dose, to coincide with the expected C_{max} and the expected time of maximum efficacy. Additionally, in the US, pre-dose ECGs were performed at Visit 2. The QTc was calculated by the local investigators at Visit 1 and Visit 2 (US sites only), who were instructed to use the formula: $QTc = QT/\sqrt{RR}$ interval. Fasting blood samples were drawn for hematology and blood chemistry laboratories at Visit 1 (before reversibility testing) and at Visits 4 and 6 (pre-dose). Note that no post-dose laboratory studies were performed.

The patient diary was also used to record perceived adverse events. The diary included space to record any adverse event, along with its start date and stop date.

Other Assessments

The Saint George's Respiratory Questionnaire (SGRQ) was self-administered at Visits 2, 4, and 6.

COPD exacerbations were characterized in several ways:

- "Bad days": Days with at least twice a score of 2 or more as recorded in the diary and/or a reduction of PEFR from baseline of more than 20%.
- Need for additional therapy (steroids/antibiotics/oxygen).

- Addition of, or increased dosing of inhaled corticosteroids.
- COPD-related hospitalizations (An emergency room visit not requiring overnight stay is not considered a hospitalization).

4.2.1.11 Ethical Aspects

Informed consent was obtained from each patient prior to initiating any study procedure. The protocol and patient informed consent forms were approved by a "properly constituted committee or committees responsible for approving clinical trials." [Vol. 23: page 8:35]

4.2.1.12 Data Analysis

The sample size was based on the primary efficacy variable, normalized FEV₁ AUC 0-12 hours, after 3 months of treatment [Vol. 23: page 8:82-82]. A between patient standard deviation of 400mL was assumed. A difference of 120mL between Foradil 24mcg BID and placebo was considered clinically relevant. For a two-sided test at a 5% level of significance with 80% power, as sample size of 175 per treatment group was expected to be required for analysis. Assuming a dropout rate of 15%, a total of 824 patients (250 per group) were to be randomized [Vol. 23: page 8-90].

The pre-specified primary variable was the normalized FEV₁ AUC 0-12 hours at Week 12. [Vol. 23: page 8:84]

Secondary efficacy variables were [Vol. 23: page 8:84-85]:

- Pre-dose FEV₁ at 3, 6, 9, and 12 months
- Post-dose FEV₁ at each time point at 3, 6, and 12 months
- Normalized FEV₁ AUC 0-12 hours at 6 and 12 months
- Inspiratory vital capacity at 3, 6, 9, and 12 months
- Normalized FVC AUC 0-12 hours at 3, 6, and 12 months
- Morning pre-dose PEF, averaged 3-monthly over 12 months
- Total score of the patient's diary averaged 3-monthly over 12 months
- Daily number of puffs of rescue medication averaged 3-monthly over 12 months

The pre-specified population for the statistical analysis was the modified intention-to-treat population, defined as all patients randomized who have received at least one dose of trial medication. Foradil 24mcg BID was to be considered effective if there was a clinically and statistically significant difference ($p \leq 0.05$) in comparison to placebo in FEV₁ AUC 0-12 hours after 3 months of treatment. Foradil 12mcg BID was to be considered effective if the contrast of Foradil 12mcg BID versus placebo is significant ($p \leq 0.05$) and the higher dose is considered effective. Foradil (12mcg BID and 24mcg BID) was also compared to theophylline using the testing hierarchy below.

As stated in the 8/29/97 amendment, in order to control Type I error in light of multiple testing, a hierarchy of testing was set up. No contrast was to be considered statistically

significant unless each preceding contrast examined within that family of contrasts is also statistically significant. The hierarchy is described below:

- For the primary objective: the comparison of Foradil 24mcg BID vs. placebo will be performed first, followed by the comparison of Foradil 12mcg BID vs. placebo.
- For the secondary objective comparing Foradil to Theophylline SR: the comparison of Foradil 24mcg BID vs. theophylline will be performed first, followed by the comparison of Foradil 12mcg BID vs. theophylline.
- An additional secondary objective will be to compare the two doses of Formoterol.
- The contrast of theophylline versus placebo will be used to test the sensitivity of the trial.

Analysis of covariance using a statistical fixed effects model was planned. The model was to include center, sex, reversibility, smoking status, and treatment as main effects and baseline FEV₁ as a covariate. Additional subgroup analyses were planned to compare reversible and non-reversible patients using the modified ITT population.

For FEV₁ AUC and FVC AUC, missing values within a visit were to be estimated by linear interpolation if no more than 3 values are missing and the values for baseline, 1, 2, 3, and 12 hours are given. (Otherwise, missing within-visit values were to be left as missing and the derived variables would not be calculated for that visit). The protocol states that "for all other variables, no missing value will be replaced by interpolation, extrapolation or last carried forward approach" [Protocol, Vol. 23: page 8:40].

All patients randomized who had received at least one dose of study medication were to be included in the safety analyses. Safety data was to be presented in listings, summary tables, and plots. Inferential statistics and plots were to be used to compare treatment groups. Descriptive summary statistics were also planned.

Additional pre-specified variables to be investigated are listed below, along with the planned analyses:

- SGRQ scores (symptoms, activity, impacts, and total)(6 and 12 months): analysis of covariance
- time to premature discontinuation due to AE or unsatisfactory therapeutic effect: Kaplan-Meier estimate
- percentage of "bad days" averaged 3-monthly over 12 months: analysis of covariance
- number of days on which additional therapy is required for COPD exacerbations: van Elteren test (In the Final Study Report this was changed to percentage of such days to adjust for the imbalance in the time to premature discontinuation in different treatment groups [Vol.20: page 8:41]).
- number of COPD-related hospitalizations: van Elteren test (protocol); no analysis was performed because of few such hospitalizations.
- the plan to analyze the time to first exacerbation requiring therapy was changed to the time to first bad day (change made prior to un-blinding [Vol. 20: page 8:41])

The 8/29/97 protocol amendment specified that the primary quality of life comparison between groups would be based upon the total SGRQ score, assuming that a difference of 4 points would be clinically significant.

4.2.2 Patient Disposition

The table below outlines the numbers of patients screened, randomized, and completed, by treatment group. Also provided in the table are the numbers of patients discontinuing the trial and the reasons given for discontinuation. A total of 1127 patients were screened and 854 patients were randomized. Of the four groups, the percentage of patients who discontinued the trial was highest in the theophylline group (39%) and lowest in the two Foradil groups (25% in the 12mcg BID group and 19% in the 24mcg BID group). Mean duration of exposure to study drug was similar among the two Foradil groups and the placebo group (297-317 days), but was shorter in the theophylline group (251 days) [Vol. 20: page 8-48]. The incidence of discontinuation due to COPD-related AE (cough, breathlessness, dyspnea, bronchospasm, or chronic obstructive airways disease exacerbated) was similar among the groups. Discontinuation due to non-COPD related AEs was much more frequent in the theophylline group (21%) than in the other groups (4-7%). *Four deaths occurred in the Foradil groups (collectively). None occurred in either the placebo or theophylline groups.*

Patient Disposition (Study 058) [number (%) of patients]					[Vol. 20: page 8:43]
	F12	F24	Placebo	Theo	Total
Total # of patients studied					1127
Screened					1127
Randomized	211	214	220	209	854
Completed	159 (75)	174 (81)	161 (73)	128 (61)	622 (73)
Discontinued in first 3 months	21 (10)	18 (8)	34 (15)	56 (27)	129 (15)
Discontinued					
Total	52 (25)	40 (19)	59 (27)	81 (39)	232 (27)
AE (COPD-related)	2 (1)	2 (1)	7 (3)	5 (2)	16 (2)
AE (Not COPD-related)	10 (5)	9 (4)	16 (7)	43 (21)	78 (9)
Abnormal test result(s)	1 (1)	0	0	2 (1)	3 (<1)
Unsatisfactory therapeutic effect	5 (2)	4 (2)	6 (3)	2 (1)	17 (2)
Protocol criteria not met	3 (1)	5 (2)	3 (1)	6 (3)	17 (2)
Non-compliance	10 (5)	5 (2)	7 (3)	11 (5)	33 (4)
Withdrawal of consent	11 (5)	5 (2)	15 (7)	9 (4)	40 (5)
Lost to follow-up	6 (3)	8 (4)	5 (2)	3 (1)	22 (3)
Administrative problems	1 (1)	1 (1)	0	0	2 (<1)
Death	3 (1)	1 (1)	0	0	4 (1)

As specified in the protocol, efficacy and safety analyses were carried out on all patients who were randomized and had received at least one dose of study medication (modified ITT population). No patient was excluded because of a protocol violation. Due primarily to a large discontinuation rate during the first three months of the study, only 725 of the total of 854 patients in the ITT population provided acceptable data for the calculation of an FEV₁ AUC for the primary efficacy analysis.

The Applicant also planned to do additional analyses on all randomized patients who had completed the 12-week treatment period and had not taken rescue medication in the six hours before the spirometry at Visit 3 (the "acceptable" patient population). **Reviewer's Comment: these analyses will not be discussed in this Review.** The protocol also called for subgroup analyses of reversible and non-reversible patients for various efficacy parameters in the ITT population. The table below provides the numbers of patients in these two subgroups, by treatment. **Reviewer's Comment: Interestingly, while the study enrolled approximately equal numbers of reversible and irreversible patients, the F24 group had a greater percent of reversible patients than did the F12 or Placebo groups.**

Number (%) of patients in the ITT subgroups					[Vol. 21: page 8:123]
	F12	F24	Placebo	Theo	Total
Subgroups:					
Reversible patients*	94 (45%)	117 (55%)	102 (46%)	103 (49%)	416 (49%)
Non-reversible patients	117	97	117	105	436

*FEV₁ increased by ≥15% after inhalation of albuterol at Visit 1

The table below summarizes selected baseline demographic variables by treatment group. The mean age of the patients was 63 years and 83% of the patients were men. There were no important differences between groups on the variables presented. A greater percentage of patients in the two Foradil groups had a history of cardiovascular disease, as compared with the placebo and theophylline groups. The Foradil 24mcg BID group had a slightly higher baseline symptom score than did the other groups.

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Demographic/Baseline Data, ITT population (Study 058)					
	[Vol. 20: page 8:46-7; Vol 21: page 8-125]				
	F12 (N=211)	F24 (N=214)	Placebo (N=220)	Theo (N=209)	Total (N=854)
Age (years)					
Mean	63	62	63	64	63
Range	37-80	40-82	44-84	34-88	34-88
Sex [n(%)]					
Male	184 (87)	178 (83)	175 (80)	172 (82)	709 (83)
Female	27 (13)	36 (17)	45 (21)	37 (18)	145 (17)
Baseline FEV ₁ (L) (Visit 2)					
Mean	1.36	1.39	1.40	1.33	1.37
Range	0.5-3.2	0.5-3.9	0.5-3.1	0.6-3.0	0.5-3.9
Morning pre-dose PEF (L/min)*					
Mean	259	251	252	247	253
Range	109-515	78-520	88-511	90-494	78-520
Total Daily Symptom Score (mean)	5.6	6.2	5.7	5.7	5.8
Daily puffs of rescue medication (mean)	3	2.9	3.1	2.6	2.9
Percentage reversibility					
Mean	16	19	16	17	17
Range	-25 - 84	-15 - 150	-45 - 88	-16 - 148	-45 - 150
Patients with concomitant diseases [n(%)]	131 (62)	136 (64)	132 (60)	132 (63)	531 (62)
Patients with history of cardiovascular (CV) disease [n(%)]					
CV disorders, general	73 (35)	75 (35)	55 (25)	53 (25)	
Rate and rhythm disorders	8 (4)	3 (1)	8 (4)	4 (2)	
Myo, endo, and pericardial & valve disorders	24 (11)	23 (11)	23 (11)	27 (13)	

*mean over the last 7 days of the run-in period

Regarding concomitant medications taken during the study period, slightly more patients in the placebo and Foradil 12mcg BID groups used corticosteroids (60% and 58%, respectively) than did patients in the Foradil 24mcg BID group (53%) [Vol.20: page 8:48]. Fewer patients in the Foradil 24mcg BID group took antibiotics (21%) than did patients in the Foradil 12mcg BID and placebo groups (29% for both) [Vol. 21: page 8-156].

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4.2.3 Efficacy Review

4.2.3.1 Primary Endpoint

The pre-specified primary efficacy endpoint was the normalized FEV₁ AUC over 12 hours after 12 weeks of treatment (Visit 3). *The primary efficacy analysis was conducted on 725 patients although the ITT population contained a total of 854 patients. The 129 ITT patients that were not considered in the primary analysis included 20, 17, 36, and 56 patients in the Foradil 12mcg BID, Foradil 24mcg BID, placebo, and theophylline groups, respectively.* The majority of these (119) were not included because the patients withdrew from the trial before Visit 3, without providing 12-hour spirometry. The others were not included because either reversibility data was missing (2 patients), or too few Visit 3 timepoints were collected to allow calculation of an AUC. A discussion of the impact of this rather high discontinuation rate during the first 3 months can be found in the "Reviewer's Comments on Efficacy" section below.

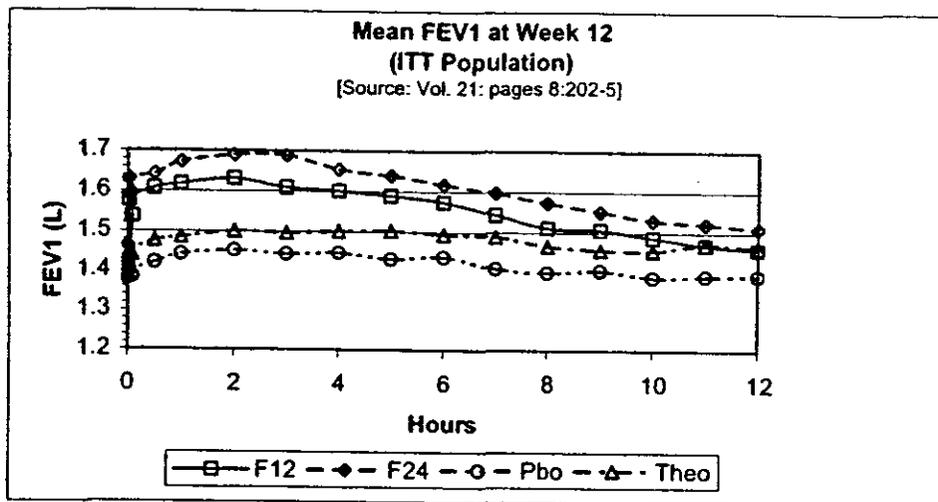
The table below summarizes the treatment group comparisons regarding FEV₁ AUC 0-12 hours at Week 12. In order to control for Type I error, the protocol specified that these comparisons were to be made in a hierarchical fashion, as described above.

Treatment Group Comparisons of FEV ₁ AUC 0-12 hours at 12 Weeks			[Vol. 20: page 8:50]
[ITT Population; NOTE: Analysis includes 725 of the 854 patients randomized]			
Comparison (n=725)	Estimate of Treatment Difference (L)	95% Confidence Interval	p-value
Foradil 24 v Placebo	0.208	0.152 - 0.264	<0.001
Foradil 12 v Placebo	0.200	0.144 - 0.257	<0.001
Foradil 24 v Theophylline	0.092	0.034 - 0.151	0.002
Foradil 12 v Theophylline	0.085	0.026 - 0.144	0.005
Foradil 24 v Foradil 12	0.008	-0.048 - 0.063	0.787
Theophylline v Placebo	0.116	0.056 - 0.176	<0.001

On this variable, both doses of Foradil were superior to placebo. However, there was no significant difference between Foradil 12mcg BID and Foradil 24mcg BID. The theophylline treatment arm was included in order to assess the sensitivity of this trial. Theophylline was demonstrated to be superior to placebo on FEV₁ AUC over 12 hours at Visit 3, but the difference was of borderline clinical significance (116 ml). Both doses of Foradil were statistically superior to theophylline, but the differences were not clinically significant (85 and 92 ml, in contrast to the pre-specified assumption of clinical significance of 120ml).

Factors that were found to be significantly related to outcome were baseline FEV₁, country, center within country and reversibility, whereas sex and smoking status were not.

The figure below shows the mean FEV₁ over 12 hours for each treatment group after 12 weeks of treatment (Visit 3).



4.2.3.2 Secondary Endpoints

4.2.3.2.1 Subgroup Analysis: Reversible vs. Non-reversible patients

The protocol indicated that an exploratory analysis of the primary efficacy variable would be performed using subgroups of the modified ITT population, based upon the baseline bronchodilator reversibility status of the patient [Vol. 23: page 8:88]. Reversibility was defined as an improvement in FEV₁ of $\geq 15\%$ 30 minutes after treatment with albuterol MDI (2 x 100mcg) [Vol. 23: page 8:23]. The tables below summarize the treatment group comparisons for the primary efficacy variable (FEV₁ AUC_{0-12 hours} at Week 12) for each subgroup.

Subgroup Analysis: Reversible Patients			[Vol. 23: page 8:52]
Treatment Group Comparisons of FEV ₁ AUC 0-12 hours at 12 Weeks			
[Modified ITT Population]			
Comparison (n=346)	Estimate of Treatment Difference (L)	95% Confidence Interval	p-value
Foradil 24 v Placebo	0.271	0.191 - 0.350	<0.001
Foradil 12 v Placebo	0.331	0.242 - 0.419	<0.001
Foradil 24 v Theophylline	0.049	- 0.036 - 0.133	0.259
Foradil 12 v Theophylline	0.109	0.017 - 0.200	0.020*
Foradil 24 v Foradil 12	- 0.060	- 0.143 - 0.023	0.156
Theophylline v Placebo	0.222	0.131 - 0.312	<0.001

Among the reversible subgroup of patients, both doses of Foradil were shown to be superior to placebo, and the estimated treatment differences were clinically significant (0.271L and 0.331L). Because of the hierarchical testing procedure and the failure to demonstrate a difference between Foradil 24 and theophylline, the comparison between

Foradil 12mcg BID and theophylline could not be considered (*). Although Foradil 12 was numerically superior to Foradil 24, this difference was not statistically significant.

Subgroup Analysis: Non-Reversible Patients			[Vol. 23: page 8:52]
Treatment Group Comparisons of FEV ₁ AUC 0-12 hours at 12 Weeks			
[Modified ITT Population]			
Comparison (n=379)	Estimate of Treatment Difference (L)	95% Confidence Interval	p-value
Foradil 24 v Placebo	0.166	0.085 - 0.248	<0.001
Foradil 12 v Placebo	0.109	0.030 - 0.187	0.007
Foradil 24 v Theophylline	0.125	0.037 - 0.213	0.006
Foradil 12 v Theophylline	0.067	- 0.016 - 0.150	0.114
Foradil 24 v Foradil 12	0.058	-0.023 - -0.138	0.158
Theophylline v Placebo	0.042	- 0.044 - 0.127	0.339

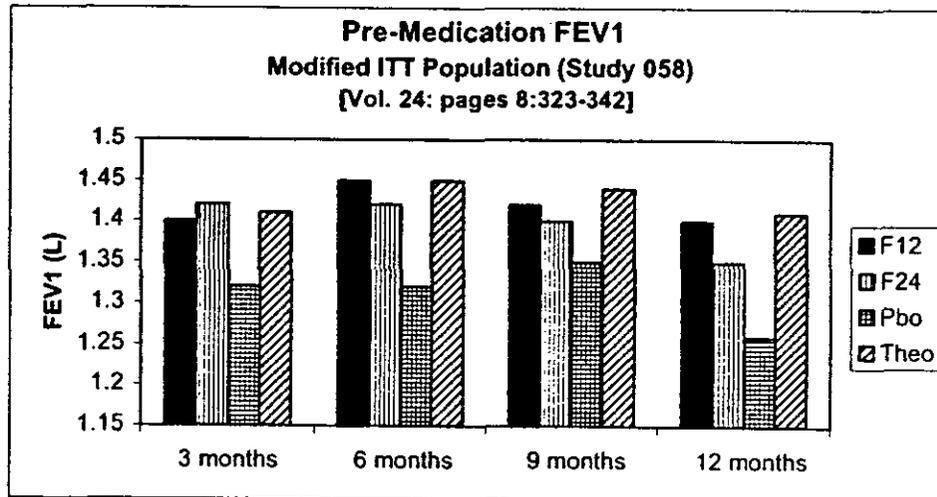
Among the non-reversible patients, both doses of Foradil were shown to be superior to placebo. However, the estimated difference between Foradil 12 and placebo (0.109L) did not reach the pre-specified threshold for clinical significance (0.120L). The two doses of Foradil were not significantly different. Foradil 24 was superior to theophylline, but Foradil 12 was not. Theophylline was not shown to be superior to placebo.

4.2.3.2.2 Secondary Spirometry Endpoints

The FEV₁ AUC_{0-12 hours} after 6 and 12 months of treatment were analyzed in the modified ITT population. After both 6 and 12 months of treatment, both doses of Foradil were statistically and clinically superior to placebo, with estimated treatment differences of 204mL (Foradil 24) and 237mL (Foradil 12) at 6 months, and 170mL (Foradil 24) and 207mL (Foradil 12) at 12 months. Thus, Foradil 12 was numerically, though not statistically, superior to Foradil 24 at both 6 and 12 months [Vol. 20: pages 8:53-4]. The table below outlines the data on FEV₁ AUC_{0-12 hours} after 12 months of treatment. This was the primary endpoint specified in the original protocol, which was subsequently amended.

Treatment Group Comparisons of FEV ₁ AUC 0-12 hours at 12 Months			[Vol. 20: page 8:54]
Comparison (n=616)	Estimate of Treatment Difference (L)	95% Confidence Interval	p-value
Foradil 24 v Placebo	0.170	0.107 - 0.233	<0.001
Foradil 12 v Placebo	0.207	0.143 - 0.272	<0.001
Foradil 24 v Theophylline	0.041	-0.026 - 0.107	0.233
Foradil 12 v Theophylline	0.077	0.009 - 0.146	0.026
Foradil 24 v Foradil 12	-0.037	-0.099 - 0.026	0.246
Theophylline v Placebo	0.130	0.061 - 0.198	<0.001

The pre-medication FEV₁ (12 hours after the last evening dose) after 3, 6, 9, and 12 months of treatment was analyzed. Foradil 24 was statistically superior to placebo at 3, 6, and 12 months, but not at 9 months ($p=0.099$). Foradil 12 was statistically superior to placebo at each time point. Although the two doses of Foradil were never statistically different, at three of the four time points (6, 9, and 12 months) Foradil 12 was numerically superior to Foradil 24. The data on pre-medication FEV₁ at each visit are illustrated below.



The pre-medication inspiratory vital capacity (IVC) after 3, 6, 9, and 12 months of treatment was analyzed. Foradil 24 was statistically superior to placebo at 3 and 6 months, but not at 9 or 12 months. Foradil 12 was statistically superior to placebo at each time point. Of note, "it is unknown in which patients FVC was measured instead of IVC." [Vol. 20: page 8:58]

The FVC AUC_{0-12 hours} after 3, 6, and 12 months of treatment was analyzed. Both doses of Foradil were statistically superior to placebo at all three visits. Although no significant differences were seen between the two doses of Foradil, at 6 and 12 months Foradil 12 was numerically superior to Foradil 24.

The mean pre-medication PEF (recorded daily on the patient diary card), averaged 3-monthly, was analyzed in the modified ITT population. The mean pre-medication PEF for the entire treatment period was also analyzed, although this was not planned in the protocol. Both doses of Foradil were statistically superior to placebo for each 3-month period analyzed and for the entire treatment period. No statistical difference was seen between the two doses of Foradil. Numerical differences between the two Foradil groups, all of which favored Foradil 24, were very small (4.9 – 12.5 L/min). The improvement in

PEF over placebo, averaged over all visits, was estimated at 28.9L/min for Foradil 24 and 22.2L/min for Foradil 12.

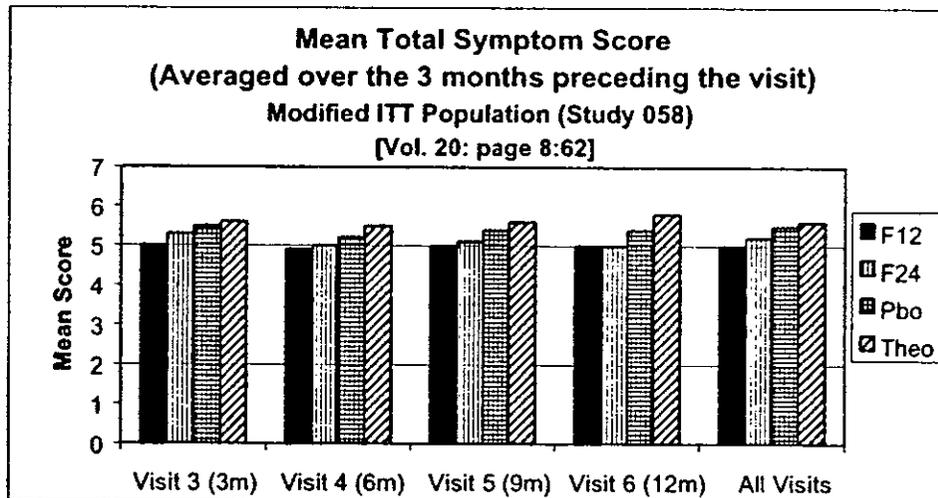
4.2.3.2.3 Rescue Medication Use

The protocol stated that the daily number of puffs of rescue medication would be averaged 3-monthly and compared between groups [Vol. 23: page 8:85]. Both doses of Foradil were statistically superior to placebo over each 3-month period of the study. There was no statistical difference between the two Foradil groups. [Vol. 20:page 8:64-5]

4.2.3.2.4 Patient Diary Scores

The total score on the daily patient diary, the components of which are described above, ranged from 0 (no symptoms) to 18 (worst symptoms). Total scores were averaged 3-monthly during the course of treatment. Comparisons between treatment groups were based upon ranking of patients' average 3-monthly diary scores at each visit.

There were no statistically significant results for any of the paired treatment contrasts at any visit. Data combined for the entire treatment period revealed that the Foradil 12 group was numerically slightly superior to the Foradil 24 group for mean symptom score (5.0 vs. 5.2) and mean percent of days with no symptoms (7.4 vs. 6.6) [Vol. 20: page 8:62]. However, as noted above, the Foradil 24 group reported a baseline symptom score that was slightly higher (worse) than the Foradil 12 group. The figure below illustrates the mean total symptom scores at each time point.

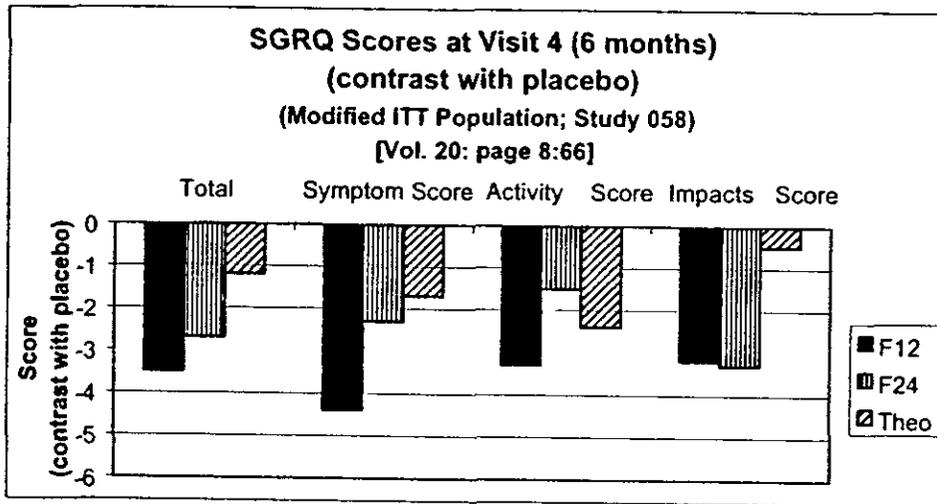


4.2.3.2.5 St. George's Respiratory Questionnaire

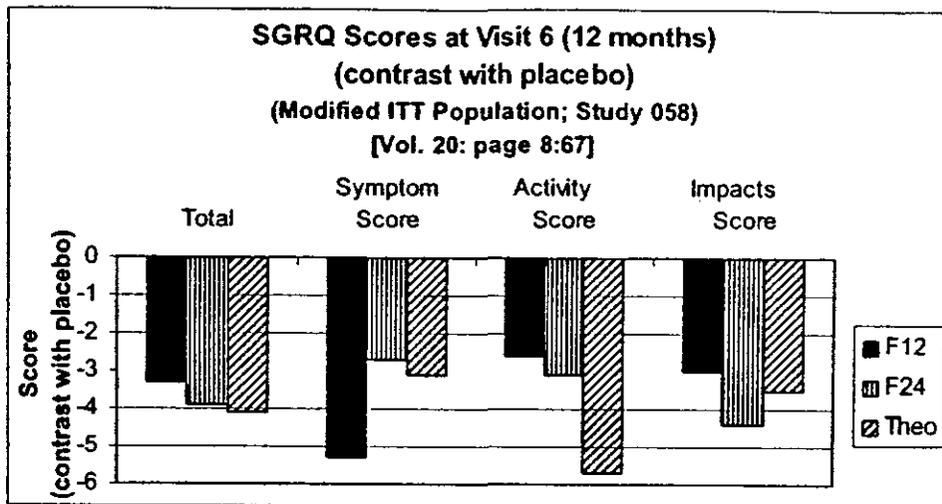
The protocol (as amended) specified that the St. George's Respiratory Questionnaire (SGRQ) would be administered at Visits 2, 4, and 6 (baseline, 6 months, and 12 months). Comparisons between groups were to be based on the total SGRQ score, with a difference

of 4 points pre-specified as representing a clinically meaningful difference [Vol. 23: page 8:81-2]. Both doses of Foradil were statistically superior to placebo for total SGRQ score at both visits, but neither group met the criteria for clinical significance at either visit. The Foradil 24 group showed an improvement in total score of 2.7 and 3.9 at 6 and 12 months, respectively. The Foradil 12 group showed an improvement of 3.5 and 3.3 at 6 and 12 months, respectively. The pre-specified clinically significant difference was 4.

The application also includes comparisons of the individual SGRQ domains; however, these were not planned in the protocol and, because neither dose was shown to be clinically superior to placebo at either time point, the individual domains will not be discussed. The figures below illustrate the comparisons of the Visit 4 (6 month) and Visit 6 (12 month) SGRQ scores (total, and for each domain) versus placebo, for each active treatment. Interpretation of the data from the theophylline group should include consideration of the high withdrawal rate in this group.



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4.2.3.2.6 Time to Withdrawal Due to Adverse Event or Unsatisfactory Therapeutic Effect

The protocol called for an analysis of time to withdrawal due to an adverse event or unsatisfactory therapeutic effect [Vol. 23: page 8:41]. A total of 115 patients discontinued the trial prematurely for these reasons or because of death. The table below provides the numbers of such events and the mean time to event, by group. Both Foradil groups had fewer such discontinuations than the placebo group.

Discontinuations due to AE, unsatisfactory therapeutic effect, or death [Vol. 20: page 8:68]				
	F12 (n=211)	F24 (n=214)	Pbo (n=220)	Theo (n=209)
Number (%) of discontinuations	20 (9)	16 (7)	29 (13)	50 (24)
Mean time to discontinuation (days)	115	135	116	65

4.2.3.2.7 Percentage of “Bad Days”

The protocol called for comparisons between treatment groups on the percentage of “bad days” averaged 3-monthly over the treatment period. Foradil 12 was statistically superior to placebo at Visits 3 and 6, and for the entire treatment period; however Foradil 12 was not statistically different from placebo for the 3-month periods prior to Visits 4 and 5. Foradil 24 was statistically superior to placebo at each visit, and for the entire treatment period. There was no statistically significant difference between the two Foradil doses.

4.2.3.2.8 COPD Exacerbations

The table below provides the number of patients having an exacerbation, and the percentage of days of additional therapy required for a COPD exacerbation.

COPD Exacerbations 8:72]		[Vol. 20: page			
	F12 (n=211)	F24 (n=214)	Placebo (n=220)	Theo (n=209)	
Patients having an exacerbation [number (%)]	189 (90%)	186 (87%)	202 (92%)	172 (82%)	
Percentage of days of additional therapy for COPD exacerbation [mean (range)]	7 (1-77)	4 (0-24)	8 (1-58)	5 (1-26)	

Because there were few COPD-related hospitalizations, no formal statistical analysis was performed. Forty-one patients had at least 1 COPD-related hospitalization. Of these, 5 patients had more than 1 (all in either the placebo or theophylline group). COPD-related hospitalizations occurred in 20 (9%) patients in the placebo group, 10 (5%) patients in the Foradil 12 group, 5 (2%) patients in the Foradil 24 group, and 6 (5%) patients in the theophylline group.

4.2.3.3 Reviewer's Comments on Efficacy

The four treatment groups were very similar at baseline. The only baseline differences of note relate to the Foradil 24mcg BID group, which had a higher percentage of patients with bronchodilator reversibility (55% vs. 45-49% in the other groups), and had a slightly higher symptom score (6.2 vs. 5.6-5.8 in the other groups). During the treatment period fewer patients in the Foradil 24mcg BID group used concomitant inhaled corticosteroids (53% vs. 58-60%) or antibiotics (21% vs. 29%). It is unlikely that these differences significantly affected the overall conclusions of the study.

Due to a large discontinuation rate during the first 3 months, many of the efficacy analyses (including the primary analysis) were performed on only 725 out of the 854 patients who were randomized. The medical reviewer (Dr. Sullivan) and the biometrics reviewer (Dr. Guo) discussed this issue and concluded that it is unlikely that this missing data significantly affected the overall study conclusions.

Based upon the pre-specified primary endpoint (FEV₁ AUC over 12 hours, after three weeks of treatment) as well as numerous secondary endpoints, both doses of Foradil were shown to be superior to placebo. Subgroup analyses of the primary endpoint demonstrated superiority of both doses of Foradil in both the reversible and non-reversible patients. The table below summarizes the findings on several important efficacy endpoints.

Results of Selected Efficacy Endpoints			
Endpoint		Superior to Placebo	Not Superior to Placebo
FEV ₁ AUC 0-12h, 3months (Primary)	F12	+	
	F24	+	
FEV ₁ AUC 0-12h, 6months	F12	+	
	F24	+	

Results of Selected Efficacy Endpoints		
Endpoint	Superior to Placebo	Not Superior to Placebo
FEV ₁ AUC 0-12h, 12months		
F12	+	
F24	+	
Pre-Medication FEV ₁ (at 3, 6, 9, and 12months)		
F12	+3m +6m +9m +12m	
F24	+3m +6m +12m	X9m
Rescue Medication Use		
F12	+	
F24	+	
Diary Scores		
F12		X
F24		X
SGRQ		
F12		X ^a
F24		X ^a
Percentage of "bad days" (at each visit and for entire period)		
F12	+v3 +v6 +entire	Xv4 Xv5
F24	+Visits 3, 4, 5, 6 and entire	

^aStatistically superior, but difference did not reach pre-specified criteria for minimal meaningful difference.

Another important comparison is that of the relative efficacy of Foradil 12mcg BID versus Foradil 24mcg BID. The data do not suggest that 24mcg BID offers any important benefit over 12mcg BID. For instance, there was no difference between these two groups on the primary endpoint (difference=0.008L, p=0.787). In addition, Foradil 12mcg BID was numerically, though not statistically, superior to Foradil 24mcg BID for FEV₁ AUC 0-12 hours at both 6 and 12 months (ITT population). A similar pattern was seen for both pre-medication FEV₁ and FVC AUC 0-12 hours. There was no statistical difference between the two groups regarding rescue medication use. The Foradil 24mcg BID group was numerically superior to the Foradil 12mcg BID group, but the difference between groups was small (0.2 puffs per day [mean] over the entire study period) [Vol. 20: page 8:64]. Patient diary symptom scores (mean as well as mean number of days with no symptoms) were slightly superior in the Foradil 12mcg BID group. Quality of life scores (SGRQ total score) were not significantly different, with small numerical differences favoring Foradil 12mcg BID after 6 months and Foradil 24mcg BID after 12months [Vol. 20: pages 8:66-7]. Interestingly, when the primary variable (FEV₁ AUC 0-12 hours after 3 months of treatment) was analyzed in the subset of patients with bronchodilator reversibility, the Foradil 12mcg BID group was numerically superior to the Foradil 24mcg BID group (difference=0.06L, p=0.156). In contrast, when this variable was analyzed in the subset of patients without bronchodilator reversibility, the Foradil 24mcg BID group was numerically superior to the Foradil 12mcg BID group (difference = 0.58L, p= 0.158)

4.2.4 Safety Review

Because this study was so similar in design to Study 056, the safety data from the two studies will be examined collectively in the Integrated Summary of Safety. No gross safety concerns were noted in this study.

4.2.5 Summary of Study

This was a 12-month, multicenter, randomized, placebo-controlled study comparing Foradil 12mcg BID, Foradil 24mcg BID, and placebo in adults with COPD. In addition, theophylline was used as an open-label active comparator. The primary endpoint was FEV₁ AUC 0-12hours, measured after 3 months of treatment. The results demonstrated the superiority of both doses of Foradil over placebo for the pre-specified primary endpoint, as well as numerous secondary endpoints including other spirometric variables and rescue medication use. Patient diary symptom scores and quality of life questionnaires did not demonstrate a significant difference between active treatment and placebo. Comparisons of the relative efficacy of the two doses of Foradil did not suggest an important incremental benefit of the higher dose.

Safety data from this study will be discussed in the Integrated Summary of Safety. Of possible significance, there were four deaths in this study, all of which were in the Foradil groups.

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4.3 STUDY FOR-INT-03: A RANDOMIZED, DOUBLE-BLIND, WITHIN-PATIENT, COMPARISON OF FORDIL 12MCG BID AND SALBUTAMOL 200MCG QID WHEN ADDED TO REGULAR TREATMENT WITH IPRATROPIUM BROMIDE 40MCG QID IN PATIENTS WITH COPD

4.3.1 Study Description

This study was submitted as a supportive study. It does not involve a placebo control, and no data from this study is proposed to be included in the label. The study was not subjected to in-depth review. It will be summarized briefly below.

4.3.1.1 Design

This was a multicenter, randomized, double-blind, double-dummy, two-period crossover study of Foradil 12mcg BID versus salbutamol 200mcg QID, when added to regular treatment with ipratropium bromide 40mcg QID in patients with COPD.

4.3.1.2 Duration

This crossover study included a 2-week run-in period, followed by two 3-week treatment periods. There was no washout period between the treatment periods. However, for the analyses the first two weeks of each treatment period were not considered. The study was conducted between February 22, 1999, and October 29, 2000.

4.3.1.3 Study Centers

The study was performed at 24 centers in nine countries (Argentina, Canada, Greece, Italy, Mexico, Norway, Poland, Portugal, and Spain). There were no US study centers.

4.3.1.4 Population

The study was performed in male and female patients with "partially reversible"¹ chronic obstructive pulmonary disease, a history of more than 10 pack-years of cigarette smoking, and bronchodilator reversibility $\geq 5\%$ but not more than 12% of the predicted FEV₁ value. Of the 252 patients who were screened, 172 were randomized to treatment.

Power calculations were performed based upon an estimated standard deviation of 40L/min for the primary efficacy variable. It was determined that 130 patients would be necessary in order to demonstrate a treatment difference of 10L/min, with 80% power and a significance level of 0.05% (two-tailed). In order to account for non-evaluable patients due to early dropouts and missing data, the Sponsor intended to randomize a minimum of 160 patients. The actual number of randomized patients was 172.

¹ Defined as an improvement in FEV₁ $\geq 5\%$ from baseline, and not more than 12% of the predicted FEV₁, 30 minutes following inhalation of 400mcg of salbutamol.

4.3.1.5 Investigational and Reference Therapy

Investigational and reference therapy used in Study FOR-INT-03 [Vol. 27: page 8:12]	
Drug	Batch Number
Formoterol	B970097
Formoterol Placebo	B970110 DPC 11055
Salbutamol pMDI	M85
Salbutamol Placebo pMDI	17/301/52
Ipratropium pMDI	97122

4.3.1.6 Objective

The primary objective was to investigate the effect of the study treatments on lung function, by comparing morning pre-medication PEFr averaged over the last 7 days of each 3-week treatment period. Secondary objectives included comparisons of other efficacy evaluations, quality of life, and safety/tolerability parameters.

4.3.1.7 Inclusion Criteria

The main criteria for inclusion were: diagnosis of COPD according to ATS criteria; age >40 years; >10 pack-year smoking history; baseline FEV₁ ≤ 65% of predicted (and ≥ 1.0L) and FEV₁/FVC ≤ 0.70; an increase in FEV₁, 30 minutes following inhalation of 400mcg salbutamol, of at least 5% from baseline value and not more than 12% of the predicted FEV₁²; total symptom score >1 on at least 3 of the last 7 days prior to Visit 2; use of ipratropium bromide for at least 1 month prior to Visit 1.

4.3.1.8 Exclusion Criteria

Exclusion criteria included: current or childhood asthma according to ATS criteria, recent respiratory tract infection, hospitalization, or ER visit for COPD, the need for long-term oxygen therapy, and any recent change in, or initiation of, inhaled corticosteroids. Parenteral or oral corticosteroids were prohibited during the study or within 1 month of Visit 1.

4.3.1.9 Conduct

Patients were screened and entered into a two-week run-in period, during which ipratropium bromide was administered. At the end of the run-in period, patients satisfying the inclusion and exclusion criteria were entered into the first of the two treatment periods. After three weeks of treatment the patients then entered the remaining treatment arm. The treatments were Foradil plus ipratropium bromide (Foradil/IB) and salbutamol plus ipratropium bromide (salbutamol/IB). The diagram below illustrates the design of the study.

² This was changed from "not more than 12% of baseline" after 169 patients had been screened. The new text was applied to 83 patients

Part:	I (run-in period)	II (Treatment Periods)		III
Visit:	1	2	3	4
Treatment Sequence 1	Ipratropium Bromide	Foradil + IB		Salbutamol + IB
Treatment Sequence 2	Ipratropium Bromide	Salbutamol + IB		Foradil + IB
Day:	-14	1	21	42

Ipratropium bromide was used as the rescue medication throughout the study. Short courses of antibiotics, oral corticosteroids, and/or oxygen were allowed. If the addition of a concomitant medication for COPD was required, the patient was withdrawn from the study.

Efficacy measures included pre-dose spirometry (Visits 2, 3, and 4), six-hour serial spirometry (Visits 3 and 4)³, quality of life questionnaire (Visits 3 and 4), asthma symptom scores (patient diary), and morning pre-dose PEFR performed and recorded by the patient for the last 7 days before Visits 3 and 4. All patients used _____ Flow Meters for PEFR measurements. The study report did not describe any measures taken to ensure the accuracy of these peak flow meters throughout the trial.

The asthma symptom questionnaire consisted of the following six individual topics: ability to perform usual daily activity, breathlessness, waking at night due to respiratory symptoms, cough, amount of sputum, and breathlessness on rising. The diary was to be completed each morning, prior to taking study medication. **Reviewer's Note: This symptom questionnaire seems to add emphasis to nocturnal symptoms because it is filled out upon rising in the morning, and it contains two questions related to nocturnal/ early AM symptoms. This would likely favor the longer-acting medication, Foradil.** The Saint George's Respiratory Questionnaire, used for assessment of quality of life, was modified to reflect the treatment period of 3 weeks, rather than the 1-month reporting period of the original instrument.

Safety measures included adverse event data, physical examination, and vital signs.

4.3.1.10 Data Analysis

The primary efficacy parameter was the mean morning pre-medication PEFR for the last week of each treatment period. Secondary efficacy parameters were: pre-dose FEV₁ and FVC at Visits 3 and 4, peak post-dose FEV₁ and FVC at Visits 3 and 4, post-dose FEV₁ and FVC at each time point, FEV₁ AUC 0-6 hours and FVC AUC 0-6 hours at Visits 3 and 4, and total score of the asthma symptoms derived from the patient's diary averaged for the last week of each treatment period.

³ 5, 15, 30 minutes, 1 hour, and hourly up to 6 hours after dosing

Three different intent-to-treat populations were defined. **None of these represent a true ITT population.** The first population (ITT1) consisted of all randomized patients who received study medication and from whom at least one efficacy measurement during baseline and one for *each* treatment period was obtained. For certain variables (e.g. morning pre-medication PEFR) the mean value of a 7 day period was used. This value was only calculated if at least 5 days with measurements were available. The second population (ITT2) included ITT1 patients without COPD exacerbation during treatment periods. The third population (ITT3) was not described in the protocol. It consisted of all ITT1 patients with at least one COPD exacerbation during treatment periods. The protocol stated that the “major conclusions” from the study would be based upon the analysis of the primary efficacy parameter in the ITT1 population [Vol. 28: page 8:33].

For the primary efficacy analysis, an analysis of variance was performed using a model that included treatment, treatment period, treatment sequence and patient within treatment sequence as effects.

4.3.2 Patient Disposition

A total of 252 patients were screened, of which 172 were randomized (88 to the treatment sequence Foradil-IB/salbutamol-IB, and 84 to the sequence salbutamol-IB/Foradil-IB). Of these, 159 patients completed the study and 13 withdrew prematurely, all during the first treatment period (4 who had taken Foradil, and 9 who had taken salbutamol). All four patients who discontinued due to AEs did so after treatment with salbutamol. One patient withdrew due to unsatisfactory therapeutic effect, after treatment with Foradil.

The ITT1 population consisted of the 159 patients who completed the study. The table below summarizes the demographic/baseline characteristics of the ITT1 population.

Demographic and Baseline Characteristics (Study FOR-INT-03) (N=159)		[Vol. 27: page 8:42]
Variable		
Age (years)	Mean (SD), Range	65 (9.4), 40-91
Sex [N(%)]	Male/Female	128 (80.5)/31 (19.5)
Race [N(%)]	Caucasian/ Black/ Oriental/ Other	142 (89.3) / 1 (0.6) / 0 / 16 (10.1)
FEV ₁ before salbutamol (L)	Mean (SD), Range	1.4 (0.36), 0.7 – 2.6
FEV ₁ before salbutamol (% pred)	Mean (SD), Range	51.3 (10.48), 28.7 – 75.4
FEV ₁ /FVC before salbutamol	Mean (SD), Range	.53 (.09), .29 - .72
Mean AM pre-dose PEFR (L/min)	Mean (SD), Range	259 (80.8), 67 - 600

4.3.3 Efficacy Review

4.3.3.1 Primary Endpoint

Although the ITT1 population consisted of 159 patients, only 144 patients had values for the primary efficacy parameter. Thus, the primary analysis was performed on 84% of the patients who were randomized (144 out of 172 patients randomized).

The mean morning PEFr increased under both treatments, but the increase was statistically higher in the Foradil/IB group. The difference between groups was estimated to be 12.1L/min, with 95% confidence interval of 5.6 – 18.6L/min (p=0.0003). **Note that this endpoint would be expected to favor Foradil, which is longer acting, over salbutamol.**

4.3.3.2 Secondary Endpoints

4.3.3.2.1 Spirometry Endpoints

The table below shows the results of the pre-specified secondary spirometric comparisons. *Foradil/IB was superior to salbutamol/IB on all parameters.* For these comparisons, the Visit 2 pre-dose spirometry values were used as baseline. Notice that, for FEV₁, the difference between treatment groups was larger pre-dose than it was at the post-dose measures up to 2 hours. This is because between 5 minutes and 2 hours the change from *test day* baseline was greater with salbutamol/IB (this difference was statistically significant at 15 minutes and 1 hour). However, Foradil/IB was still superior at all time-points in the pre-specified analyses, which used the Visit 2 pre-dose values as the baseline.

Secondary Spirometry Variables Estimates of Treatment Differences (Foradil/IB – Salbutamol/IB) (ITT1 population)				
Variable	FEV ₁		FVC	
	Estimate	p-value	Estimate	p-value
Pre-dose FEV ₁	0.116	<0.001	0.159	<0.001
FEV ₁ 5 minutes after study drug	0.097	<0.001	0.109	<0.001
FEV ₁ 15 minutes after study drug	0.083	<0.001	0.079	0.0088
FEV ₁ 30 minutes after study drug	0.094	<0.001	0.118	0.001
FEV ₁ 1 hour after study drug	0.087	<0.001	0.122	<0.001
FEV ₁ 2 hours after study drug	0.104	<0.001	0.138	<0.001
FEV ₁ 3 hours after study drug	0.119	<0.001	0.161	<0.001
FEV ₁ 4 hours after study drug	0.159	<0.001	0.209	<0.001
FEV ₁ 5 hours after study drug	0.161	<0.001	0.217	<0.001
FEV ₁ 6 hours after study drug	0.137	<0.001	0.188	<0.001
Peak post-dose FEV ₁	0.105	<0.001	0.117	<0.001
AUC (L·min)	44.5	<0.001	58.7	<0.001

4.3.3.2.2 Symptom Scores

The total symptom score was the total of six individual scores, which ranged from 0-3. Thus the total symptom score could range from 0 (best score) to 18 (worst score). The mean total symptom score was 0.6 points lower under Foradil/IB than under salbutamol/IB. This difference was statistically significant (p=0.0042) [Vol. 27: page 8:52]. **The clinical significance of this difference is unknown.**

The Foradil/IB treatment was numerically superior for each of the individual symptoms, with differences between groups ranging from 0.08 to 0.16. The greatest differences were

seen in the categories of “breathlessness during the last 24 hours” (0.16), and “breathlessness on rising” (0.14).

4.3.3.2.3 St. George’s Respiratory Questionnaire (SGRQ)

The SGRQ was administered at the end of the run-in period and at the end of each treatment period. As specified in the protocol, the two treatment groups were compared based on the total SGRQ score and based on each of the three domains within the SGRQ (symptoms, activity, and impacts). The protocol did not specify a minimum difference that would be considered clinically significant. The only statistically significant difference between the treatments was seen for the symptoms domain ($p=0.04$). This difference, which favored the Foradil/IB treatment, was numerically small (2.64). **The clinical significance of this difference is not known.**

4.3.3.2.4 COPD Exacerbations

Statistical analysis of the COPD exacerbation data was not planned or performed. COPD exacerbations occurred in 34.6% of the patients during treatment with Foradil/IB, as compared with 30.8% of the patients during treatment with salbutamol/IB. **This frequency of COPD exacerbation seems high, given that each treatment period lasted only 3 weeks.**

4.3.3.2.5 Rescue Medication Use

Patients were instructed to record in their diaries the number of puffs of rescue medication (ipratropium bromide) that they used each day. The Sponsor states that some patients evidently recorded the total number of puffs of ipratropium bromide, rather than only the rescue use of ipratropium bromide. In some instances, but not all, this error was corrected. Because of this complication, the rescue medication data will not be discussed.

4.3.3.3 Reviewer’s Comments on Efficacy

This study demonstrated that patients with “partially reversible” COPD who were treated with Foradil plus IB had a higher AM pre-medication PEFR than did patients treated with salbutamol plus IB. The choice of the primary efficacy parameter, pre-dose PEFR averaged over the last week of treatment, would tend to favor the longer-acting Foradil over salbutamol. Several of the secondary endpoints (pre-dose FEV₁ and FVC, and components of the symptom score) might also be expected to favor Foradil, based on its longer duration of action. The study did suggest that the acute effects of salbutamol/IB (5 minutes to 2 hours) were superior to Foradil/IB, when assessed as change from *test day* baseline. However, this difference may not be relevant, given that the actual test day baseline was higher in the Foradil/IB group. The results of this study do not substantially inform the regulatory decision regarding the approval of Foradil for the COPD indication. It is also not clear that the results

4.3.4 Safety Review

4.3.4.1 Overall Clinical Adverse Events

Sixteen patients (9.8%) had 19 AEs under treatment with Foradil/IB, and 22 patients (13.1%) had 34 AEs under treatment with salbutamol/IB. The most frequently affected body system was the respiratory system, for which six patients (3.7%) reported symptoms under treatment with Foradil/IB and 14 patients (8.3%) reported symptoms under treatment with salbutamol/IB. The table below summarizes the most common AEs by WHO preferred term.

AEs Occurring in ≥ 2 Patients in Either Treatment (Study FOR-INT-03)		[Vol. 27: page 8-57]	
	Foradil/IB N (%)	Salbutamol/IB N (%)	
Patients studied:			
Total # of patients studied	163	168	
Total # of patients with an AE	16 (9.8)	22 (13.1)	
Dyspnea	2 (1.2)	5 (3.0)	
Headache	2 (1.2)	1 (0.6)	
Infection, viral	2 (1.2)	1 (0.6)	
Pharyngitis	1 (0.6)	3 (1.8)	
Coughing	0 (0)	2 (1.2)	
Nausea	0 (0)	2 (1.2)	
Obstructive Airways Disease	0 (0)	5 (3)	

4.3.4.2 Drug-related Adverse Events

Drug-related AEs were reported in three patients (3 AEs) under treatment with Foradil/IB and in seven patients (10 AEs) under treatment with salbutamol/IB. In the Foradil/IB treatment these AEs were hypertension, dry mouth, and cramps in the leg. In the salbutamol/IB treatment the AEs were pharyngitis (3 patients), dyspnea (2 patients), dizziness, tremor, cramps in the leg, coughing, and obstructive airways disease (1 patient each).

4.3.4.3 Withdrawals, Severe Adverse Events, Serious Adverse Events, and Deaths

Four patients, all under treatment with salbutamol/IB, withdrew because of AEs. These events were: fever/dyspnea/respiratory disorder, pharyngitis, dyspnea/coughing/pharyngitis, and COPD exacerbation.

Severe AEs occurred in one patient under treatment with Foradil/IB (dyspnea) and in four patients under treatment with salbutamol/IB (dyspnea, infection, obstructive airway disease, and aggravation of diabetes mellitus). There were 4 moderate AEs in the Foradil/IB treatment period and 15 moderate AEs in the salbutamol/IB treatment period.

One serious adverse event occurred in the study. This patient was under treatment with salbutamol/IB and was hospitalized with a COPD exacerbation.

No patient died during the study.

4.3.4.4 Labs and EKG Reports

No laboratory or EKG testing was done.

4.3.4.5 Other Safety Endpoints

No important change was noted in blood pressure or heart rate measurements and no important difference between groups was seen.

4.3.4.6 Reviewer's Comments on Safety

This study allows comparison of the safety profiles of Foradil versus salbutamol, when added to a regimen of ipratropium bromide, in patients with "partially reversible" COPD. In the study, there was a suggestion that Foradil was better tolerated than salbutamol. Under treatment with salbutamol there were more overall AEs (mostly involving the respiratory system), more drug-related AEs, and more moderate AEs, more withdrawals due to AEs. There was no significant signal that Foradil was associated with adverse events that would not be expected based upon the underlying disease or the drug class (β -adrenergic agonist). As noted in the discussion of the efficacy findings, the occurrence of COPD exacerbations during this study was more frequent than might be expected in a study of this duration.

4.3.5 Summary of Study

This was a multicenter, randomized, double blind, double-dummy, two-period crossover study of Foradil 12mcg BID versus salbutamol 200mcg QID, when added to regular treatment with ipratropium bromide 40mcg QID in patients with "partially reversible" COPD. Foradil is a long-acting β -adrenergic agonist and, as expected, it was shown to be superior to salbutamol for morning, pre-dose PEFr (the primary efficacy parameter), FEV₁, and FVC, as well as post-dose spirometry and daily symptom score. The safety profile of Foradil in this setting was no worse, and possibly better than that of salbutamol. However, the results of this study offer little relevant efficacy information regarding the regulatory approval decision of Foradil for the COPD indication.

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5 Overview of Efficacy

The Applicant has submitted two adequate and well controlled Phase 3 studies and one supportive study intended to support the following proposed indication: "Foradil is indicated for the treatment of Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.

The two Phase 3 studies (Study 056 and Study 058) were four-arm studies comparing the efficacy of Foradil 12mcg BID, Foradil 24mcg BID, an active comparator, and placebo in adults with chronic obstructive pulmonary disease (COPD). These two studies demonstrated that Foradil 12mcg BID and Foradil 24mcg BID are effective in the treatment of bronchospasm in patients with COPD. However, the studies did not demonstrate that Foradil 24mcg BID offers any advantage over Foradil 12mcg BID. Further, the data submitted do not justify

Adequate and well-controlled trials submitted in support of NDA				
Study	Design/ Duration/ Purpose	Control	Number of Patients	Primary Efficacy Measure
056	Randomized, double-blind, controlled 3 months Study of: efficacy, dose response, QOL, safety, PK, pharmacogenomics	5. Placebo 6. Ipratropium bromide MDI 40mcg QID	ITT=780 12mcg=194 24mcg=192 Pbo=200 IB=194	FEV ₁ AUC _{0-12hours} after 3 months of treatment
058	Randomized, double-blind, controlled 12 months Study of: efficacy, dose response, QOL, safety, pharmacogenomics	5. Placebo 6. Theophylline 200-400mg po BID	ITT=854 12mcg=211 24mcg=214 Pbo=220 Theo=209	FEV ₁ AUC _{0-12hours} after 3 months of treatment

The supportive study (FOR-INT-03) was a non-US, multicenter, randomized, double-blind, double-dummy, two-period crossover study of Foradil 12mcg BID versus salbutamol 200mcg QID, when added to regular treatment with ipratropium bromide 40mcg QID in patients with "partially reversible" COPD. This study offered little relevant efficacy information regarding the regulatory approval decision of Foradil for COPD and will not be further discussed in this section. The study is reviewed in Section 4.4 of this document.

5.1 DESIGN FEATURES OF THE PIVOTAL STUDIES

The two pivotal studies (Study 056 and Study 058) were large, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled studies comparing Foradil 12mcg BID, Foradil 24mcg BID, placebo, and an active comparator in patients with COPD. To qualify for inclusion in the studies, patients were required to: 1) meet American Thoracic Society criteria for the diagnosis of COPD; 2) meet specified spirometry criteria⁴; 3) have a history of at least 10 pack-years of smoking; and 4) experience symptoms during the run-in period. The studies included patients with and without a documented response to bronchodilator treatment. The active comparators were ipratropium bromide MDI (blinded) in Study 056 and slow-release theophylline (open-label) in study 058. In both studies, patients were randomized after a 10-21 day single-blind placebo run-in period, then were evaluated at regular intervals for the duration of the studies. The treatment periods were 12 weeks and 12 months for Studies 056 and 058, respectively.

In both studies the primary endpoint was FEV₁ AUC_{0-12 hours} after 12 weeks of treatment. Secondary endpoints included other spirometric variables (pre-dose FEV₁, post-dose FEV₁ at various timepoints, FVC AUC_{0-12 hours}), daily diary symptom scores, rescue medication use (recorded daily in a diary), COPD exacerbations, and St. Georges Respiratory Questionnaire (SGRQ) scores.

5.2 STATISTICAL CONSIDERATIONS

Both pivotal studies were designed to have a power of 80% to detect a difference of 120ml between active drug and placebo on the primary endpoint (FEV₁ AUC_{0-12 hours}). This magnitude of difference was pre-specified as representing a clinically meaningful effect size. The enrollment goal for both studies, allowing for an expected dropout rate of 15%, was 824 randomized patients. Due to a lower than expected dropout rate in Study 056, the target was subsequently reduced to 770 randomized patients. Actual enrollments were 780 patients in Study 056 and 854 patients in Study 058.

In both studies, the pre-specified population for statistical analysis was the modified intention-to-treat population, defined as all randomized patients who received at least one dose of trial medication. The primary endpoint was analyzed using analysis of covariance. In order to control for Type I error due to multiple testing, the protocols, as amended, dictated that the comparison of Foradil 12 vs. placebo would only be considered if comparison of Foradil 24 vs. placebo was first shown to be significant.

5.3 STUDY PATIENTS

The demographic and baseline features of the randomized patients are provided with the individual study reviews in Section 4 of this document. The mean age of the patients was 63-64 years. In both studies the majority of patients (75% in Study 056, 83% in Study

⁴Pre-bronchodilator FEV₁ <70% of predicted and at least 0.75 liters, with an FEV₁/VC <88% of predicted (men) or <89% of predicted (women).

058) were men. The mean baseline FEV₁ was 1.28L in Study 056 and 1.37L in Study 058. Approximately half of the patients in each study demonstrated reversibility (≥15% increase in FEV₁) after albuterol administration.

As expected, the number of withdrawals was greater in Study 058 (27%) than in Study 056 (11%). This was likely due to the difference in study duration, as the withdrawal rate in Study 058 after 3 months (15%) was similar to the withdrawal rate reported in Study 056. As mentioned elsewhere, the primary analysis for Study 058 was carried out after 3 months.

5.4 EFFICACY RESULTS

5.4.1 Primary Endpoint

Both studies demonstrated that both doses of Foradil were statistically superior to placebo on the pre-specified primary endpoint, FEV₁ AUC_{0-12 hours} after 12 weeks of treatment, and that the treatment effects were greater than the minimally meaningful effect size that was pre-specified by the Applicant. This endpoint is a reasonable and accepted endpoint for studies intended to demonstrate meaningful benefit in patients with COPD. The estimated effect sizes in the two studies were 0.223L and 0.200L for F12, and 0.194L and 0.208L for F24 and all of these comparisons were highly statistically significant (p<0.001). The table below summarizes the comparisons for both doses of Foradil for each study.

Primary Endpoint: Treatment Group Comparisons of FEV ₁ AUC 0-12 hours at 12 Weeks			
Comparison	Estimate of Treatment Difference (L)	95% Confidence Interval	p-value
Study 056			
Foradil 24 v Placebo	0.194	0.145 - 0.243	<0.001
Foradil 12 v Placebo	0.223	0.174 - 0.273	<0.001
Study 058			
Foradil 24 v Placebo	0.208	0.152 - 0.264	<0.001
Foradil 12 v Placebo	0.200	0.144 - 0.257	<0.001

5.4.2 Secondary Endpoints

The primary variable, FEV₁ AUC_{0-12 hours}, was also evaluated after the first dose (Study 056) and after 6 and 12 months of treatment (Study 058). Both doses of Foradil were statistically superior to placebo at each of these time points, with effect sizes greater than the pre-specified minimally meaningful difference. Pre-medication FEV₁, an indication of end-of-dosing-interval efficacy, was examined after 4, 8, and 12 weeks of treatment in Study 056, and after 3, 6, 9, and 12 months of treatment in Study 058. With one exception (F24 vs. placebo after 9 months of treatment), both doses were superior to placebo on pre-medication FEV₁ at each time point. Several other secondary spirometric

endpoints also demonstrated the superiority of both F12 and F24 over placebo. The table below provides data on selected secondary spirometry endpoints.

Selected Secondary Spirometry Endpoints				
Endpoint	Comparison	Estimate of Treatment Difference (L)	95% Confidence Interval	p-value
Study 056				
FEV ₁ AUC _{0-12hours} (1 st Dose) ¹	F24 v Pbo	0.223	0.187 – 0.258	<0.001
	F12 v Pbo	0.217	0.181 – 0.253	<0.001
Pre-dose FEV ₁ ²	-----			
	4 weeks	F24 v Pbo	0.093	0.042 – 0.145
	F12 v Pbo	0.085	0.033 – 0.138	0.001
8 weeks	F24 v Pbo	0.105	0.052 – 0.158	<0.001
	F12 v Pbo	0.134	0.081 – 0.187	<0.001
12 weeks	F24 v Pbo	0.105	0.051 – 0.159	<0.001
	F12 v Pbo	0.155	0.101 – 0.208	<0.001
Study 058				
FEV ₁ AUC _{0-12hours} (12 months) ³	F24 v Pbo	0.170	0.107 – 0.233	<0.001
	F12 v Pbo	0.207	0.143 – 0.272	<0.001
Pre-dose FEV ₁ ⁴	-----			
	3 months	F24 v Pbo	0.101	0.046 – 0.155
	F12 v Pbo	0.079	0.024 – 0.134	0.005
6 months	F24 v Pbo	0.107	0.045 – 0.169	0.001
	F12 v Pbo	0.134	0.071 – 0.198	<0.001
9 months	F24 v Pbo	0.053	-0.010 – 0.116	0.099
	F12 v Pbo	0.073	0.009 – 0.138	0.026
12 months	F24 v Pbo	0.093	0.029 – 0.158	0.005
	F12 v Pbo	0.142	0.076 – 0.208	<0.001

¹Vol 17: page 8:270 ²Vol 14: pages 8:50 ³Vol 20: page 8:54 ⁴Vol 20: page 8:56

Both studies demonstrated that the daily use of rescue medication was significantly less in both Foradil groups, as compared to placebo. The results of the patient diary symptom scores differed somewhat between studies, perhaps because the two studies did not assess symptoms at the same time points. In Study 056 patient diary symptom scores were compared at 4, 8, and 12 weeks, while in Study 058 these comparisons were made at 3, 6, 9, and 12 months. In Study 056, both doses of Foradil were superior to placebo at 4 and 8 weeks, and one dose (12mcg BID) was superior at 12 weeks. In Study 058 neither of the Foradil groups were superior to placebo at any of the time points (3, 6, 9, and 12 months). **One explanation for this observation may be that patient symptom scores detect a benefit of treatment with Foradil early (i.e. for the first 8-12 weeks), but this benefit is not evident with more long-term use.**

5.4.3 Active Comparator Data

Both studies involved the use of an active comparator, ipratropium bromide MDI in Study 056 and theophylline in Study 058. Of the two comparators, the ipratropium bromide comparison is the more informative. Although both drugs are indicated for

COPD, ipratropium bromide is used more commonly than theophylline in this patient population. Also, because of differences in dosage forms and the need for dosage adjustment (based on blood levels) with theophylline, the theophylline arm was not blinded. Finally, conclusions based on the theophylline comparison are limited because of a disproportionately high rate of withdrawal in the theophylline group.

The data from Study 056 suggest that both doses of Foradil are marginally superior to ipratropium bromide when used at the labeled dose. Both doses were statistically superior to ipratropium bromide on the primary variable, FEV₁ AUC_{0-12 hours}. However, the absolute differences, 0.086L and 0.057L for F12 and F24, respectively, did not reach the pre-specified criteria for clinical relevance (0.120L).

No comparisons are justified. The limitations of the theophylline comparison and the magnitude of the benefit over ipratropium are discussed above. Also, neither comparison was independently substantiated (replicated) in a separate study.

5.4.4 Subset Efficacy Analyses

The section of the NDA entitled Integrated Summary of Efficacy briefly discusses the influence of demographic factors on the efficacy of Foradil [Vol 30: pages 8:59-61].

The majority of patients (65%) were over 65 years of age. Seventy-five percent of the patients were between the ages of 55 and 74 years. The primary variable, FEV₁ AUC_{0-12 hours}, was analyzed by age category (≥ 65 < 65 years). For both age categories Foradil 12 and Foradil 24 were statistically superior ($p < 0.001$) to placebo, with effect sizes greater than the pre-specified minimally meaningful difference. There was no observable difference in the estimated treatment effect size between the two age categories. An assessment of mean 12-hour urinary recovery of unchanged formoterol after 12 weeks of repeated dosing (Foradil 12mcg BID) raised the possibility of an age effect on the pharmacokinetics of Foradil in COPD patients (Study 056). The mean recovery was 1.92nmol for the <65y age group (n=5), as compared with 2.01 nmol for the ≥ 65 y age group.

The majority of patients (80%) were male. The primary variable, FEV₁ AUC_{0-12 hours} after 3 months of treatment, was analyzed by gender. Both doses of Foradil were statistically superior to placebo for both male and female patients, with treatment effect sizes greater than the pre-specified minimally meaningful difference. For Foradil 24mcg BID there was no difference in treatment effect size between males and females. However, for Foradil 12mcg BID, the estimated treatment effect size was substantially greater in men than in women (0.230L vs. 0.138L) [Vol. 30: page 8:61].

Because the majority (98%) of patients in both studies were Caucasians, subgroup analyses based on race were not possible.

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5.5 EFFICACY DETERMINATION

5.5.1 Overall Assessment

The benefit of treatment with Foradil, as demonstrated in the primary and secondary endpoints of the two pivotal studies, is sufficiently consistent and clinically important to support approval of Foradil for the chronic treatment of COPD. The studies included patients with and without bronchodilator responsiveness. In both studies, benefit was demonstrated statistically in both of these subgroups, although the benefit of F12 over placebo in the non-reversible group (0.109L) did not reach the predefined definition of clinical significance (0.120L) in Study 058.

The Applicant has also proposed

5.5.2 Individual Doses

As discussed above, the data submitted support the Applicant's contention that Foradil is effective in patients with COPD. The Applicant has proposed to market Foradil, 12mcg BID. The data from both studies suggest that the higher dose does not provide any added benefit. F24 was not statistically superior to F12 on any endpoint, and for many endpoints F12 was actually numerically superior to F24. For instance, on the primary endpoint, FEV₁ AUC_{0-12 hours} after 3 months of treatment, F12 was numerically superior to F24 in Study 056. In Study 058 the two doses of Foradil were virtually identical on this endpoint. In Study 058, where this variable was examined after longer treatment periods, F12 was numerically superior to F24 after 6 and 12 months of treatment.

Other secondary endpoints also suggested that F24 was not superior to F12. In regard to the pre-medication FEV₁, an indicator of end-of-dosing-interval efficacy, F12 was numerically superior to F24 after 8 and 12 weeks (Study 056) and after 3, 6, and 12 months (Study 058) [see table entitled Selected Secondary Spirometry Endpoints above]. F12 was numerically superior to F24 in regard to rescue medication use in Study 056, although it must be noted that in that study the F24 group required more rescue

medication in the baseline period than did the F12 group. In regard to diary symptom scores, F12 was numerically superior to F24 at 8 and 12 weeks in Study 056 and for the treatment period overall in Study 058. (However, the F24 group reported a baseline symptom score that was slightly worse than the F12 group).

5.5.3 Quality of Life Issues

The SGRQ was administered to patients in both pivotal studies. In Study 056 it was administered at baseline and at 12 weeks. In Study 058 it was administered at baseline and at 6 and 12 months. The protocol, as amended, stated that comparisons between groups would be based upon the total SGRQ score, with a difference of 4 points pre-specified as the minimal clinically meaningful difference. In Study 056, at 12 weeks both doses of Foradil were statistically superior to placebo for total SGRQ, but only Foradil 12mcg BID met the pre-specified criteria for clinical significance (Foradil 12 vs. placebo = -5.06; Foradil 24 vs. placebo = -3.34). In Study 058, while both doses of Foradil were statistically superior to placebo at 6 and 12 months, the differences did not reach the pre-specified criteria for clinical significance for either drug at either timepoint. The table below provides the placebo comparisons for total SGRQ scores for both studies. The highlighted cell indicates the only comparison that was both statistically significant ($p < 0.05$) and clinically meaningful (difference of 4).

Total SGRQ Score: Comparisons with placebo					
		Foradil 12mcg vs. Pbo		Foradil 24mcg vs. Pbo	
		Difference	p-value	Difference	p-value
Study 056	12 weeks	-5.06	<0.001	-3.34	0.009
	6 months	-3.5	0.011	-2.7	0.042
Study 058	12 months	-3.3	0.030	-3.9	0.009

6 Overview of Safety

The Integrated Summary of Safety (ISS) compiled by the Applicant combines safety data from 1634 patients with COPD who participated in the two pivotal Phase 3 studies (Studies 056 and 058) [Vol. 33: pages 8:1-72]. Among these patients, 811 received formoterol, 420 received placebo, 194 received ipratropium bromide, and 209 received theophylline. The Applicant refers to this group of patients as the “key population,” [Vol. 33: page 8:12] or the “key safety population.” [Vol. 33: page 8:13] The ISS also includes safety data from 172 patients who participated in the supportive study FOR-INT-03. However, this data is not integrated with the “key population” data. Note: As agreed upon at the pre-NDA meeting, the Applicant subsequently submitted an integrated summary of safety that combined the safety data from the placebo controlled studies involving both COPD patients and asthma patients. This integration was submitted with the 120-Day Safety Update and is reviewed in the section of this review entitled “120-Day Safety Update.”

6.1 EXTENT OF EXPOSURE

6.1.1 Patient Exposure

Patients were exposed to either 3 months (Study 056) or 12 months (Study 058) of treatment. A total of 316 patients were exposed to Foradil for more than 48 weeks. Patients treated with Foradil received either 12mcg BID (F12) or 24mcg BID (F24). The table below summarizes the overall exposures to the two doses of Foradil, placebo, and the two active comparators, ipratropium bromide (IB) and theophylline (Theo).

Overall Exposures in the ISS Population				[Vol. 33: page 8:16]		
	Foradil, N (%)			Pbo N=420 N (%)	IB N=194 N (%)	Theo N=209 N (%)
	F12 BID N=405	F24 BID N=406	All Foradil N=811			
=1 day	2 (1)	6 (2)	8 (1)	5 (1)	0	4 (2)
2-7 days	3 (1)	3 (1)	6 (1)	9 (2)	1 (1)	21 (10)
>1wk-4 wks	7 (2)	10 (3)	17 (2)	12 (3)	7 (4)	13 (6)
>4wks-12 wks	76 (19)	59 (15)	135 (17)	82 (20)	53 (27)	13 (6)
>12wks-24wks	137 (34)	139 (34)	276 (34)	132 (31)	133 (69)	15 (7)
>24wks-36wks	13 (3)	10 (3)	23 (3)	9 (2)	0	9 (4)
>36wks-48wks	15 (4)	15 (4)	30 (4)	19 (5)	0	15 (7)
>48wks	152 (38)	164 (40)	316 (39)	152 (36)	0	119 (57)

6.1.2 Demographic and Baseline Features

The table below summarizes the demographic features of the population included in the Applicant’s Integrated Summary of Safety. The majority of patients in all groups were white men. The treatment groups were comparable in regard to these demographic features (age, sex, race, and smoking habits).

Demographic Features of ISS Population						
	Foradil, N (%)			Pbo N=420 N (%)	IB N=194 N (%)	Theo N=209 N (%)
	F12 BID N=405	F24 BID N=406	All Foradil N=811			
Age, N(%)						
<40	1 (0.2)	0	1 (0.1)	1 (0.2)	0	1 (0.5)
40-54	61 (15)	73 (18)	134 (17)	71 (17)	27 (14)	32 (15)
55-64	140 (35)	141 (35)	281 (35)	145 (35)	74 (38)	76 (36)
65-74	168 (42)	165 (41)	333 (41)	168 (40)	72 (37)	80 (38)
>74	35 (9)	27 (7)	62 (8)	35 (8)	21 (11)	20 (10)
Sex, N(%)						
male	328 (81)	323 (80)	651 (80)	332 (79)	136 (70)	172 (82)
female	77 (19)	83 (20)	160 (20)	88 (21)	58 (30)	37 (18)
Race, N(%)						
white	399 (99)	398 (98)	797 (98)	408 (97)	193 (100)	203 (97)
black	3 (1)	1 (0.2)	4 (0.5)	2 (0.5)	0	2 (1)
other	3 (1)	7 (2)	10 (1)	10 (2)	1 (1)	4 (2)
Smoking, N(%)						
current (>10 pack yrs)	171 (42)	178 (44)	349 (43)	177 (42)	82 (42)	78 (37)
previous (>10 pack yrs)	234 (58)	228 (56)	462 (57)	243 (58)	112 (58)	131 (63)

The table below summarizes various characteristics of the patients' COPD at baseline. The patients had a mean 8-year history of COPD and a mean baseline FEV₁ of 46% of predicted. The treatment groups were similar regarding the characteristics of their COPD. There were slightly more patients in the F24 group than the F12 or placebo groups who had bronchodilator reversibility.

Baseline COPD Characteristics (ISS Population)							[Vol. 33: page 8:19]
	Foradil			Pbo N=420	IB N=194	Theo N=209	
	F12 BID N=405	F24 BID N=406	All Foradil N=811				
Duration of COPD (years)							
mean	8.4	7.5	7.9	8.2	7.2	8.5	
SD	8.7	7.5	8.1	8.3	6.8	8.4	
median	5.2	5.1	5.1	5.5	5.0	6.0	
range	0-50	0-41	0-50	0-47	0-38	0-50	
% predicted FEV ₁							
≤40%	145 (36)	158 (39)	303 (37)	155 (37)	86 (44)	74 (35)	
>40%	260 (64)	248 (61)	508 (63)	265 (63)	108 (56)	135 (65)	
mean	46.7	46.0	46.3	46.3	44.9	46.3	
SD	12.9	13.2	13.0	13.0	13.4	12.3	
median	46.0	46.0	46.0	46.0	43.5	45.0	
range	22-83	18-70	18-83	19-74	17-82	21-69	
Reversibility, N(%)							
non-reversible	213 (53)	189 (47)	402 (50)	218 (52)	100 (52)	105 (51)	
reversible	192 (47)	216 (53)	408 (50)	201 (48)	93 (48)	103 (50)	
not known	0	1	1	1	1	1	

The table below summarizes the most common concomitant medications taken at baseline. Patients who were using inhaled corticosteroids were to remain on a stable dose throughout the study.

Concomitant Medications (ISS population)				[Vol. 33: page 8:19]		
	Foradil, N(%)			Pbo N=420 N (%)	IB N=194 N (%)	Theo N=209 N (%)
	F12 BID N=405	F24 BID N=406	All Foradil N=811			
Salbutamol	106 (26)	106 (26)	212 (26)	107 (26)	43 (22)	71 (34)
Budesonide	93 (23)	91 (22)	184 (23)	102 (24)	46 (24)	32 (15)
Acetylsalicylic acid	47 (12)	61 (15)	108 (13)	45 (11)	17 (9)	29 (14)
Beclomethasone	58 (14)	49 (12)	107 (13)	60 (14)	26 (13)	43 (21)
Paracetamol	57 (14)	35 (9)	92 (11)	47 (11)	28 (14)	13 (6)
Fluticasone	33 (8)	45 (11)	78 (10)	51 (12)	32 (17)	16 (8)

6.1.3 Disposition

The table below summarizes the patient dispositions by treatment group. The percentage of patients discontinuing for any reason was highest in the theophylline treatment group, primarily because of discontinuations due to adverse event. The percentage of patients discontinuing treatment was slightly greater in the placebo group (21%) than in the two Foradil groups (16%), and was lowest in the ipratropium bromide group (9%). There were 4 discontinuations due to death. All of these occurred in the Foradil treatment groups (3 in the F12 group and 1 in the F24 group).

Patient Disposition by Treatment Group (ISS population)				[Vol. 33: page 8:21]		
	Foradil, N (%)			Pbo N=420 N (%)	IB N=194 N (%)	Theo N=209 N (%)
	F12 BID N=405	F24 BID N=406	All Foradil N=811			
Total no. of patients	405 (100)	406 (100)	811 (100)	420 (100)	194 (100)	209 (100)
Total no. completed	340 (84)	343 (85)	683 (84)	332 (79)	177 (91)	128 (61)
Total no. discontinued	65 (16)	63 (16)	128 (16)	88 (21)	17 (9)	81 (39)
Reason for Discontinuation						
Adverse event	18 (4)	25 (6)	43 (5)	34 (8)	9 (5)	48 (23)
Noncompliance	12 (3)	7 (2)	19 (2)	11 (3)	2 (1)	11 (5)
Protocol criteria not met	6 (2)	11 (3)	17 (2)	5 (1)	2 (1)	6 (3)
Withdrew consent	11 (3)	5 (1)	16 (2)	22 (5)	2 (1)	9 (4)
Lost to follow-up	7 (2)	8 (2)	15 (2)	5 (1)	0	3 (1)
Unsatisf. therapeutic effect	6 (2)	4 (1)	10 (1)	9 (2)	1 (1)	2 (1)
Death	3 (1)	1 (0.2)	4 (0.5)	0	0	0
Administrative problem	1 (0.2)	2 (0.5)	3 (0.4)	1 (0.2)	0	0
Abnormal lab value	1 (0.2)	0	1 (0.1)	0	0	2 (1)
Abnormal test result	0	0	0	1 (0.2)	1 (1)	0

6.2 SIGNIFICANT/POTENTIALLY SIGNIFICANT EVENTS

6.2.1 Deaths

Four of the 811 formoterol-treated patients died during the studies. No deaths were reported during the study period in the other treatment groups. All four of the deaths were in patients enrolled in Study 058. Three of the deaths were in patients receiving Foradil 12mcg BID and one was in a patient receiving Foradil 24mcg BID. One of the deaths in the Foradil 12mcg BID group was due to suicide. The table below provides further information regarding these patients.

Deaths occurring during the clinical studies				[Vol. 33: page 8:34]
Center/Patient	Age/Sex	Treatment and Duration	Event(s)	Investigator Attribution
7685/2064	67/M	F12 BID x 158 days	Coronary sclerosis; asthma; cardiac failure	Not related
6960/1557	53/M	F12 BID x 40 days	Suicide by strangulation/hanging	Not related
5502/0402	61/M	F12 BID x 19 days	Acute myocardial infarction; interventricular cardiac septum rupture	Possibly related
7875/2253	60/M	F24 BID x 110 days	Swelling brain (post-traumatic fall)	Not related

Dr. Sullivan reviewed narrative summaries [Vol. 36: pages 8:207, 208, 214, 216, 222], and patient profiles [submitted electronically Nov. 15, 2000: path: Crt/profile/e0001/ PID 058-E0001-5502.pdf, Crt/profile/ZA0086/ PID 058-ZA0086-7685.pdf, Crt/profile/CZ0003/ PID 058-CZ0003-7875.pdf, and Crt/profile/SK0052/ PID 058-SK0052-6960.pdf] for all of the deaths during the clinical trials. Patient 5502/0402, who was treated at a study center in Spain, developed acute chest pain on day 19 of treatment with Foradil 12mcg BID. He was admitted to the hospital and treated with thrombolytics but developed recurrent chest pain, a new murmur, and documented left-to-right shunt. He was transferred to another hospital for cardiac surgery but died two days later. At his screening visit, this patient had an FEV₁ of 1.49L (48% of predicted), and a right bundle branch block on his ECG. Patient 7685/2064, who was treated at a study center in South Africa, developed acute chest pain on day 158 of treatment with Foradil 12mcg BID. He was dead when he arrived at the hospital. The event terms used in the table above are derived from the death certificate. Patient 7875/2253, who was treated at a study center in the Czech Republic, suffered a fall on day 110 of treatment with Foradil 24mc BID. He died of traumatic brain swelling resulting from the fall. In summary, two of these deaths are unlikely to be related to the study drug (6960/1557, and 7875/2253) and two deaths, both cardiac in nature, could be related to the study drug (7685/2064, and 5502/0402).

In addition to the four deaths that occurred during the study, there were four deaths that occurred during the post-study period. All four had participated in Study 058 and these

deaths included one patient in each treatment group (F12, F24, theophylline, and placebo). The table below provides additional information on these four patients.

Deaths occurring during the post-study period [Vol. 33: page 8:34]					
Center/Patient	Age/Sex	Cause of Death	Days following last day in the study	Treatment Received	Investigator Attribution
6433/1038	72/M	Acute pulmonary edema/ progression of cancer	273	Placebo	Not related
5044/5044	53/M	Pulmonary cancer	-49	Theophylline	Not related
7627/2020	54/M	Myocardial infarction	52	F12	Not related
6464/1056	65/M	Malignant GI neoplasm	312	F24	Not related

Dr. Sullivan reviewed narrative summaries for all of the deaths occurring during the post-study period. [Vol. 36: pages 8:216, 218, 219, 228, 229, 237] Patient 7627/2020, who was treated with Foradil 12mcg BID at a study center in South Africa, was admitted to the hospital for acute vascular occlusion of the right leg on treatment day 317. Six days later he underwent above-the-knee amputation. He discontinued study medication on that day. Approximately 7 weeks later he was reported to have died of a myocardial infarction. Patient 6464/1056, who was treated with Foradil 24mcg BID at a study center in Italy, developed epigastric pain and weight loss on treatment day 86. He was diagnosed with gastric carcinoma and was withdrawn from the study. He died 312 days after withdrawal. Patient 6433/1038, who was treated with placebo at a study center in Italy, was diagnosed with gastric carcinoma while in the study. He was withdrawn from the study, subsequently diagnosed with carcinoma of the colon, and eventually died, 273 days after withdrawal. Patient 5044/5044, who was treated with theophylline at a study site in Austria, was diagnosed with lung cancer on treatment day 330. He was withdrawn from the study on that day and subsequently died, approximately 49 days after withdrawal.

One additional event of note is a patient who was successfully resuscitated from an episode of ventricular fibrillation, which occurred on Day 98 of treatment with Foradil 12mcg BID. This was a 71 year old man who was participating in Study 058 at a study center in Italy (Center 35, Patient number 6267). Following this event, he withdrew from the study because of possible relationship to the study drug. [electronic submission dated 11/15/00: crt/profile/058/ I0035/PID 058-10035-6267]

6.2.2 Serious Adverse Events

The table below shows the serious adverse events, by most frequently affected body system. The Foradil groups had a lower incidence of SAEs compared with placebo, primarily due to fewer respiratory events. The incidence of respiratory SAEs might be interpreted to support dose-ordered efficacy of Foradil. The incidence of respiratory SAEs was 6% in the placebo group, 4% in the Foradil 12mcg BID group, and 2% in the Foradil 24mcg BID group. Also of note, cardiovascular SAEs were slightly less frequent

in the F24 group (0.5%), as compared with the F12 group (2%), and both were similar to placebo (1%). The cardiovascular SAEs experienced by subjects in the Foradil treatment groups were: ventricular fibrillation, myocardial infarction (2 events), cerebrovascular disorders (2 events), embolism nos, arterial thrombosis, and aneurysm. Cardiovascular SAEs in the placebo group were: hypertension, cardiac failure (2 events), syncope, ventricular extrasystoles, angina pectoris, myocardial ischemia, and deep thrombophlebitis.

Serious Adverse Events							[Vol. 33: page
	F12 n (%)	F24 n (%)	All Foradil n (%) ¹	Pbo n (%)	IB n (%)	Theo n (%)	
Total Patients	405 (100)	406 (100)	811 (100)	420 (100)	194 (100)	209 (100)	
Total Patients with SAE	31 (8)	18 (4)	49 (6)	40 (10)	7 (4)	21 (10)	
Maximum Duration of Treatment	1 year	1 year	1 year	1 year	3 months	1 year	
Body System:							
Respiratory	16 (4)	7 (2)	23 (3)	27 (6)	6 (3)	10 (5)	
Cardiovascular	6 (2)	2 (0.5)	8 (1)	7 (2)	0	5 (2)	
Digestive	3 (1)	3 (1)	6 (1)	6 (1)	0	2 (1)	
Musculoskeletal	3 (1)	1 (0.2)	4 (0.5)	0	1 (1)	1 (0.5)	
Body as a Whole	3 (1)	0	3 (0.4)	3 (1)	0	1 (0.5)	
Urogenital/Reprod	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.2)	0	1 (0.5)	
Special Senses	1 (0.2)	1 (0.2)	2 (0.2)	0	0	1 (0.5)	
Nervous		1 (0.2)	1 (0.1)	1 (0.2)	0	2 (1)	
Infections/Infestations	2 (0.5)	1 (0.2)	3 (0.4)	1 (0.2)	0	0	
Lab Abnormality	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.2)	0	0	
Metabolic/Nutritional	0	1 (0.2)	1 (0.1)	0	0	0	
Hemic/Lymphatic	0	0	0	1 (0.2)	0	0	

¹both Foradil 12mcg BID and 24mcg BID dose groups

6.2.3 Withdrawals Due to Adverse Events

The table below shows the adverse events that lead to discontinuation, by treatment group. All but 8 of the discontinuations due to adverse events occurred during the first 3 months of treatment. Of the 8 patients who withdrew due to AE after 3 months, 3 were in the theophylline group and 5 were in the Foradil groups. Overall, the theophylline group had the most withdrawals due to AEs. This was primarily due to an increased frequency of digestive and nervous system events in the theophylline group. There were more withdrawals due to AEs in the placebo group than in either of the Foradil groups. There were minimally more such events in the Foradil 24mcg BID group as compared to the Foradil 12mcg BID group (6% vs. 5%).

Withdrawals due to Adverse Events						
8:28]	[Vol. 33: page					
	F12 n (%)	F24 n (%)	All Foradil n (%) ¹	Pbo n (%)	IB n (%)	Theo n (%)
Total Patients	405 (100)	406 (100)	811 (100)	420 (100)	194 (100)	209 (100)
Total Patients Who Discontinued due to AE	19 (5)	25 (6)	44 (5)	34 (8)	9 (5)	50 (24)
Maximum Duration of Treatment	1 year	1 year	1 year	1 year	3 months	1 year
Body System:						
Respiratory	6 (2)	12 (3)	18 (2)	19 (5)	6 (3)	7 (3)
Cardiovascular	6 (2)	2 (0.5)	8 (1)	3 (1)	0	6 (3)
Musculoskeletal	3 (1)	4 (1)	7 (1)	3 (1)	0	2 (1)
Nervous	3 (1)	4 (1)	7 (1)	1 (0.2)	0	23 (11)
Digestive	2 (0.5)	3 (1)	5 (1)	3 (1)	0	28 (13)
Body as a Whole	2 (0.5)	2 (0.5)	4 (0.5)	2 (0.5)	1 (1)	5 (2)
Special Senses	0	2 (0.5)	2 (0.2)	1 (0.2)	0	1 (0.5)
Infections/Infestations	0	0	0	0	0	2 (1)
Skin/Appendages	0	0	0	1 (0.2)	0	0
Urogenital/Repro	0	0	0	1 (0.2)	0	1 (0.5)
Heme/Lymphatic	0	0	0	1 (0.2)	0	0

6.3 OTHER SAFETY FINDINGS

6.3.1 Overall Adverse Events

The table below provides data on the body systems that were most frequently affected by adverse events ($\geq 2\%$ in any treatment group). The most frequent body system affected was the respiratory system. The frequency of adverse events was similar in the Foradil groups and the placebo group, slightly less in the ipratropium bromide (IB) group, and slightly greater in the theophylline group. Of note, the maximum duration of treatment in the IB group was only 3 months, as compared with 1 year in each of the other groups. When the analysis is limited to the first 3 months of treatment, the frequency of adverse events was similar in the Foradil groups (combined and individual), the placebo group, and the IB group. The incidence of cardiovascular AEs was similar among the two Foradil groups and placebo. The Applicant provided additional data regarding the incidences of moderate/severe cardiovascular AEs, which are not shown in the table [Vol. 33: page 52]. The incidence of moderate/severe cardiovascular AEs was 3.2% in the F12 group, 3.4% in the F24 group, and 4% in the placebo group.

Body Systems Most Frequently Affected by Adverse Events ($\geq 2\%$ in any group) [Vol. 33: page 8:23]						
	F12 n (%)	F24 n (%)	All Foradil n (%) ¹	Pbo n (%)	IB n (%)	Theo n (%)
Total Patients	405 (100)	406 (100)	811 (100)	420 (100)	194 (100)	209 (100)
Total Patients with AE	254 (63)	255 (63)	509 (63)	266 (63)	110 (57)	142 (68)
Maximum Duration of Treatment	1 year	1 year	1 year	1 year	3 months	1 year
Body System:						
Respiratory	153 (38)	150 (37)	303 (37)	155 (37)	57 (29)	63 (30)
Infections/Infestations	64 (16)	55 (14)	119 (15)	77 (18)	27 (14)	27 (13)
Musculoskeletal	52 (13)	61 (15)	113 (14)	45 (11)	14 (7)	27 (13)
Nervous	41 (10)	49 (12)	90 (11)	58 (14)	23 (12)	55 (26)
Body as a Whole	41 (10)	45 (11)	86 (11)	47 (11)	15 (8)	20 (10)
Digestive	40 (10)	41 (10)	81 (10)	52 (12)	14 (7)	73 (35)
Cardiovascular	26 (6)	29 (7)	55 (7)	25 (6)	9 (5)	23 (11)
Skin/Appendages	18 (4)	13 (3)	31 (4)	24 (6)	6 (3)	6 (3)
Special Senses	13 (3)	20 (5)	33 (4)	7 (2)	5 (3)	9 (4)
Urogenital/Reprod	11 (3)	12 (3)	23 (3)	18 (4)	3 (2)	7 (3)
Lab Abnormality	1 (0.2)	6 (2)	7 (1)	3 (1)	4 (2)	5 (2)
Total Patients with AE First 3 months ²	190 (47)	193 (48)	383 (47)	206 (49)	101 (52)	112 (54)

¹both Foradil 12mcg BID and 24mcg BID dose groups

²Source: Vol. 34: pages 8:52, 67, 75, 81, 160, 170

The table below shows the most frequent adverse events. The table includes AEs that 1) occurred in $\geq 1\%$ of patients in any group, and 2) occurred more frequently in a Foradil group (12mcg BID, 24mcg BID, or combined) than in the placebo group. AEs that showed dose ordering for Foradil are shaded. The frequencies of AEs in the Foradil groups and placebo group were similar. Dose ordering was noted in several categories, most notably muscle cramps and tremor. Muscle cramps were not reported in any patients in the placebo group but were reported in 2% of the F12 group and 4% of the F24 group. Tremor was reported in 0.5% of the placebo group, as compared with 1% in the F12 group and 3% in the F24 group. Although the differences between groups was small, the observations are likely valid because these AEs are expected with this class of drug (beta-agonists). The Applicant has proposed to include a slightly different table in the draft label [Submission dated 5/4/01, proposed USPI, page 22]. In the Applicant's proposed table

Frequently Occurring AEs: that were both more frequent in a Foradil group as compared with the placebo group, and occurred in ≥1% in either F12, F24, All Foradil, or Placebo [Vol. 33: page 8:24-5 and Vol. 34: pages8:1-196]						
	F12 n (%)	F24 n (%)	All Foradil n (%) ¹	Pbo n (%)	IB n (%)	Theo n (%)
Total Patients	405 (100)	406 (100)	811 (100)	420 (100)	194 (100)	209 (100)
Total Patients with AE	254 (63)	255 (63)	509 (63)	266 (63)	110 (57)	142 (68)
Maximum Duration of Treatment	1 year	1 year	1 year	1 year	3 months	1 year
Body System:						
Respiratory System						
upper resp tract inf	30 (7.4)	24 (5.9)	54 (6.7)	24 (5.7)	5 (3)	12 (6)
coughing	15 (3.7)	22 (5.4)	37 (4.6)	19 (4.5)		
pharyngitis	14 (3.5)	16 (3.9)	30 (3.7)	10 (2.4)	4 (2)	7 (3)
sinusitis	11 (2.7)	7 (1.1)	18 (2.2)	7 (1.7)	2 (1)	4 (2)
sputum increased	6 (1.5)	8 (2.0)	14 (1.7)	5 (1.2)		
epistaxis	4 (1.0)	4 (1.0)	8 (1.0)	0		
dyspnea	19 (4.7)	26 (6.4)	45 (5.5)	24 (5.7)		
sputum abnormal	2 (0.5)	5 (1.2)	7 (0.9)	3 (0.7)		
respiratory disorder	3 (0.7)	4 (1.0)	7 (0.9)	2 (0.5)		
Musculoskeletal System						
cramps muscle	7 (1.7)	15 (3.7)	22 (2.7)	0	2 (1)	1 (0.5)
cramps leg	7 (1.7)	6 (1.5)	13 (1.6)	2 (0.5)		
arthralgia	5 (1.2)	10 (2.5)	15 (1.8)	9 (2.1)	4 (2)	4 (2)
myalgia	4 (1.0)	9 (2.2)	13 (1.6)	2 (0.5)	1 (1)	2 (1)
pain back	17 (4.2)		30 (3.7)	17 (4.0)		
sprains and strains	0	6 (1.5)	6 (0.7)	1 (0.2)		
arthritis	1 (0.2)	5 (1.2)	6 (0.7)	4 (1.0)		
Nervous System						
tremor	4 (1.0)	10 (2.5)	14 (1.7)	2 (0.5)	0	12 (6)
dysphonia	4 (1.0)	6 (1.5)	10 (1.2)	1 (0.2)		
anxiety	6 (1.5)	3 (0.7)	9 (1.1)	5 (1.2)	1 (1)	5 (2)
Body as a Whole						
pain chest	13 (3.2)	9 (2.2)	22 (2.7)	9 (2.1)	3 (2)	4 (2)
fever	9 (2.2)	10 (2.5)	19 (2.3)	6 (1.4)	3 (2)	3 (1)
edema dependent	2 (0.5)	6 (1.5)	8 (1.0)	1 (0.2)		
trauma	5 (1.2)	1 (0.2)	6 (0.7)	0		
pain	1 (0.2)	5 (1.2)	6 (0.7)	4 (1.0)		
allergy	0	4 (1.0)	4 (0.5)	0		
edema legs	1 (0.2)	4 (1.0)	5 (0.6)	3 (0.7)		
Cardiovascular System						
Palpitation	3 (0.7)	4 (1.0)	7 (0.9)	1 (0.2)		
Digestive System						
Mouth dry	5 (1.2)	3 (0.7)	8 (1.0)	4 (1.0)		
Stomatitis	4 (1.0)	0	4 (0.5)	0		
Tooth ache	4 (1.0)	0	4 (0.5)	2 (0.5)		
Pain abdominal	4 (1.0)	11 (2.7)	15 (1.8)	9 (2.1)	3 (2)	14 (7)
Infections/Infestations						
Herpes zoster	4 (1.0)	1 (0.2)	5 (0.6)	2 (0.5)		
Skin and Appendages						
Pruritis	6 (1.5)	0	6 (0.7)	4 (1.0)		

Frequently Occurring AEs: that were both more frequent in a Foradil group as compared with the placebo group, and occurred in $\geq 1\%$ in either F12, F24, All Foradil, or Placebo [Vol. 33: page 8:24-5 and Vol. 34: pages8:1-196]						
	F12 n (%)	F24 n (%)	All Foradil n (%) ¹	Pbo n (%)	IB n (%)	Theo n (%)
Urogenital and Repro Urinary tract infection	4 (1.0)	2 (0.5)	6 (0.7)	3 (0.7)		
Special Senses conjunctivitis	2 (0.5)	5 (1.2)	7 (0.9)	2 (0.5)		

¹both Foradil 12mcg BID and 24mcg BID dose groups

Beta-adrenergic receptor agonists might potentially be associated with an increased risk of cardiovascular AEs. However, the frequency of all specific cardiovascular events was similar among the Foradil and placebo groups [Vol. 33: page 8:53]. The table below compares the frequencies of selected cardiovascular events among the treatment groups.

Number (%) of patients with selected cardiovascular adverse events [Vol. 33: page 8:53]					
	F12 n (%)	F24 n (%)	Pbo n (%)	IB n (%)	Theo n (%)
Total Patients	405 (100)	406 (100)	420 (100)	194 (100)	209 (100)
Total Patients with AE	254 (63)	255 (63)	266 (63)	110 (57)	142 (68)
Maximum Duration of Treatment	1 year	1 year	1 year	3 months	1 year
Hypertension	4 (1.0)	7 (1.7)	8 (1.9)	2 (1.0)	6 (2.9)
Palpitation	3 (0.7)	4 (1.0)	1 (0.2)	1 (0.5)	3 (1.4)
Tachycardia	2 (0.5)	2 (0.5)	1 (0.2)	2 (1.0)	3 (1.4)
Atrial fibrillation	1 (0.2)	1 (0.2)	3 (0.7)	0	3 (1.4)
Supraventricular tachycardia	1 (0.2)	0	1 (0.2)	0	0
Myocardial infarction	3 (0.7)	0	0	0	1 (0.5)
Angina pectoris	1 (0.2)	2 (0.5)	3 (0.7)	1 (0.5)	3 (1.4)
Myocardial ischemia	0	1 (0.2)	1 (0.2)	0	0

The table below summarizes the adverse events by severity. The theophylline group, which was open-label, reported severe AEs more frequently than did the other treatment groups. The percentage of patients reporting severe adverse events was slightly lower in the Foradil groups as compared with the placebo group.

Severity of Adverse Events 8:26]		[Vol. 33: page				
	F12 n (%)	F24 n (%)	All Foradil n (%) ¹	Pbo n (%)	IB n (%)	Theo n (%)
Total Patients	405 (100)	406 (100)	811 (100)	420 (100)	194 (100)	209 (100)
Total Patients with AE	254 (63)	255 (63)	509 (63)	266 (63)	110 (57)	142 (68)
Maximum Duration of Treatment	1 year	1 year	1 year	1 year	3 months	1 year
Severity Grade:						
Mild						
no. of events	315	325	640	337	109	199
no. of patients	100 (25)	99 (25)	199 (25)	97 (23)	44 (23)	43 (21)
Moderate						
no. of events	212	241	453	275	95	177
no. of patients	111 (27)	116 (29)	227 (28)	116 (28)	51 (26)	65 (31)
Severe						
no. of events	56 43 (11)	60	116	79	20	56
no. of patients		40 (10)	83 (10)	53 (13)	15 (8)	34 (16)

¹both Foradil 12mcg BID and 24mcg BID dose groups

6.3.2 Drug-related Adverse Events

The table lists the incidence of AEs that were considered to be drug-related by the investigator. The table includes the drug-related AEs that both 1) occurred in $\geq 1\%$ of patients in any group, and 2) occurred more frequently in a Foradil group (12mcg BID, 24mcg BID, or combined) than in the placebo group. AEs that showed dose-ordering for Foradil are shaded. These were: muscle cramps, tremor, dysphonia, dyspnea, and abdominal pain. Although dose-ordered, the differences between the two Foradil groups were small.

Drug-related AEs: that were both more frequent in a Foradil group as compared with the placebo group, and occurred in $\geq 1\%$ in any group		[Vol. 33: page 8:27]				
	F12 n (%)	F24 n (%)	All Foradil n (%) ¹	Pbo n (%)	IB n (%)	Theo n (%)
Total Patients	405 (100)	406 (100)	811 (100)	420 (100)	194 (100)	209 (100)
Total Patients with AE	254 (63)	255 (63)	509 (63)	266 (63)	110 (57)	142 (68)
Patients with drug-related AE	40 (10)	55 (14)	95 (12)	40 (10)	23 (12)	66 (32)
Maximum Duration of Treatment	1 year	1 year	1 year	1 year	3 months	1 year
Adverse Events:						
cramps muscle	4 (1)	9 (2)	16 (2)	0	2 (1)	1 (0.5)
tremor	4 (1)	10 (3)	13 (2)	1 (0.2)	0	10 (5)
anxiety	4 (1)	1 (0.2)	5 (1)	0	0	2 (1)
insomnia	4 (1)	0	4 (0.5)	2 (0.5)	2 (1)	7 (3)
pruritis	4 (1)	0	4 (0.5)	1 (0.2)	0	1 (0.5)
dry mouth	4 (1)	3 (1)	7 (1)	2 (0.5)	2 (1)	0
tachycardia	2 (0.5)	0	2 (0.2)	0	1 (1)	3 (1)
dysphonia	1 (0.2)	4 (1)	5 (1)	0	2 (1)	0
nervousness	1 (0.2)	0	1 (0.1)	0	1 (1)	5 (2)
dyspnea	0	5 (1)	5 (1)	2 (0.5)	5 (3)	0
pain abdominal	0	1 (0.2)	1 (0.1)	0	1 (1)	11 (5)

¹both Foradil 12mcg BID and 24mcg BID dose groups

6.3.3 Lab Findings, Vital Signs, ECGs

6.3.3.1 Laboratory Studies

The laboratory data presented does not raise a significant safety concern.

The Applicant presented the biochemistry and hematology laboratory values in a shift table that compares the occurrence of a shift from the normal range to low or high values, according to treatment groups [Vol. 33: page 8:43]. According to this analysis there were few noteworthy differences between groups. The Foradil 24mg group had a slightly higher incidence of elevated SGOT (7%) and SGPT (11%) than the placebo group (4% and 7%, respectively). The Foradil 24mcg BID group also had a higher incidence of decreased RBC (22%) than the placebo group (12%). The incidences of decreasing hemoglobin were less different, with this occurring in 10% of patients in the Foradil 24mcg BID group and 7% in the placebo group. The Applicant states that there was no indication of reduced RBC in the asthmatic patient safety database or in a recent large pediatric trial.

Because of known effects of beta-adrenergic receptor agonists on serum potassium and glucose, these laboratory values were presented in greater detail [Vol. 33: page 8:44-45]. Eight patients had a potassium value lower than normal and greater than 3.2 during the course of the studies, 3 in the F12 group, 3 in the F24 group, and 5 in the placebo group. Three patients had potassium values below 3.2 during the course of the study, 2 in the F24 group and 1 in the placebo group. The Applicant did not present the glucose data for both studies together [Vol. 33: page 8:44-45]. Interpreting the data provided, the numbers of patients with post-treatment glucose values >7.8 mmol/L were: 15 in the F12 group, 17 in the F24 group, and 24 in the placebo group. At 12 months the F24 group had a statistically lower glucose level than the placebo group (estimated difference: 0.41mmol/L) (Study 058).

6.3.3.2 Vital Signs

The Applicant did not integrate the vital sign data from the two pivotal studies [Vol. 33: page 8:48-50]. The data provided suggest minimal effect of Foradil at the 24mcg BID dose on pulse and blood pressure.

The Applicant states that there were no statistically significant differences between either of the Foradil doses and placebo in regard to pulse rate or blood pressure measurements in Study 056.

In Study 058, the pulse rate in the F24 group was statistically higher than the pulse rate in the placebo group at 1 and 2 hours post dosing after 3 months (estimated difference 2.1 and 2.7 beats per minute, respectively), and statistically higher than the pulse rate in the F12 group at 2 hours post dosing after 3 months (estimated difference 2.5 beats per

minute). In Study 058 the F24 group also demonstrated small, but statistically significant, drops in blood pressure when compared to placebo. These were seen at several time points at 3 and 6 months (estimated difference of 3.1mmHg for systolic, and 1.8 to 2.5mmHg for diastolic blood pressure).

6.3.3.3 ECGs

In Studies 056 (with 194 patients on F12, 192 on F24, 200 on placebo, and 194 on ipratropium) and 058 (with 211 patients on F12, 214 on F24, 220 on placebo, and 209 on theophylline) all patients underwent ECG testing at baseline and *pre-dose* after 12 weeks (Studies 056 and 058), and after 6, 9, and 12 months of treatment (*pre-dose*) (Study 058 only). [Vol. 33: page 8:45-48] In addition, 200 US patients underwent timed post-dose ECGs (5, 15, and 120 minutes) after 6, 9, and 12 months of treatment. The ECGs were interpreted by the local investigators, who were advised to seek consultation locally if they felt they were not qualified to interpret the ECGs. As a quality control measure, the Applicant routinely checked the veracity of 10% of all ECGs. *The submission does not state how frequently this measure revealed a discrepancy between the data from the ECG and the data recorded on the CRF.* The ECGs were defined as: "normal", "abnormal/clinically insignificant", or "abnormal/clinically significant". For the latter group, the investigator provided a description of the abnormality.

The ISS section of this submission contains a table that provides the ECG changes from baseline to "worst" recording, by treatment group in the key safety population [Vol. 33: page 8:47]. There were no remarkable differences between the Foradil and placebo groups regarding the changes from baseline to worst recording. The numbers of patients changing from "normal" at baseline to "abnormal/clinically significant" were 1 in the F12 group, 1 in the F24 group, and 0 in the placebo and ipratropium groups. The numbers of patients changing from "abnormal/clinically insignificant" to "abnormal/clinically significant" were 3 in the F12 group, 2 in the F24 group, and 0 in the placebo and ipratropium groups. [Vol. 33: page 8:47].

The local investigators were asked to measure and record the QT and RR intervals, and to calculate the corrected QT interval (QTc), using Bazett's formula ($QTc = QT/RR^{1/2}$). *However, some centers simply used the QT and QTc provided by the ECG machine. At these centers, the RR interval was "back-calculated" using Bazett's formula and the data provided by the ECG machine.* The Applicant states that this was the case in "a small number" (not quantified) of patients. [Vol. 33: page 8:47]. **Reviewer's Note: Because the intervals were determined by the local investigators, some of whom simply used the automated ECG machine readings, this QTc data is of limited value.**

The ISS in the submission did not contain an integration of the QTc data from the two pivotal trials. Therefore, the discussion below will address the results in each study separately.

For Study 056, *mean QT/QTc data are not provided.* The submission includes line listings for all patients who demonstrated a QTc > 0.46 seconds [Vol. 15: pages 8:199-

226]. The Applicant states that the percentages of patients whose QTc was <0.46sec at baseline and >0.46 seconds at 12 weeks (*pre-dose*) were: 5% for F12, 7% for F24, 8% for placebo, and 5% for ipratropium. [Vol. 14: page 8:70]

In Study 058 ECGs were performed at baseline (Visit 1), and *pre-dose* at 3, 6, 9, and 12 months. In addition, patients in the US had ECGs performed at 5-15 minutes post-dose, and immediately after the spirometry performed at 2 hours post dose at the same visits. In addition, US patients had a *pre-dose* ECG on the day of randomization. *Mean QT/QTc data were not provided in the original NDA submission.* The submission includes line listings for all patients who demonstrated a QTc>0.46 seconds [Vol. 22: pages 8:168-257]. The Applicant states that the percentages of patients whose QTc was <0.46sec at baseline and >0.46 seconds at 12 weeks (*pre-dose*) were: 16% for F12, 16% for F24, 14% for placebo, and 22% for theophylline. [Vol. 14: page 8:70] **Reviewer's Note: This data includes all of the ECGs, both pre- and post- dose. Separate analysis of the post-dose (US) QTc data is not provided. Post-dose ECGs would be more relevant for estimation of the drug's possible effect on the QTc interval.**

At the pre-NDA meeting the Division noted that central interpretation of the ECGs by a blinded, trained cardiologist would be preferable to the local readings by the individual investigators. The Applicant then arranged for centralized readings of the US ECGs. However, this information was not submitted with the original NDA. The data was submitted on June 18, 2001, in response to a request for information. Among the several analyses submitted in the June 18, 2001 submission were assessments of the chronic effects of Foradil on the QT and QTc (using Bazett's correction) intervals and assessments of the acute effects of Foradil on the QT and QTc intervals. To assess the chronic effects, the *pre-dose* QT and QTc intervals after 3, 6, 9, and 12 months were compared to the intervals measured on the baseline (Visit 2, *pre-treatment*) ECG. There was no remarkable change in *pre-dose* QT or QTc intervals in the placebo group or either of the Foradil groups [6/18/01 submission: pages 16-18]. Acute effects on the QT and QTc intervals were determined by comparing ECGs taken at baseline, 5-15 minutes, and immediately following the 2-hour spirometry assessment at 3, 6, and 12 months in study 058. The table below shows that there was no remarkable acute effect of Foradil on the QT or QTc intervals at any of the three visits.

Mean QT and QTc (Bazett's correction) at 3, 6, and 12 months [6/18/01 submission, pages 27, 30]									
	F12			F24			Placebo		
	n	QT	QTc	n	QT	QTc	n	QT	QTc
Visit 3 (3 months)									
0-hour	43	379.6	413.1	48	373.8	411.6	46	375.7	414.6
5-15 minutes	39	376.5	404.3	47	374.3	411.7	39	379.7	411.6
2 hours	40	384.0	408.8	46	378.8	412.9	39	384.7	413.0
Visit 4 (6 months)									
0-hour	37	382.1	410.4	47	381.7	413.3	42	382.4	415.8
5-15 minutes	36	377.6	404.9	43	380.5	414.6	39	380.0	411.3
2 hours	35	382.8	416.7	44	381.6	414.5	42	379.1	414.1
Visit 6 (12 months)									

0-hour	35	372.0	411.8	44	377.7	412.7	36	369.3	413.3
5-15 minutes	34	372.0	413.1	41	380.2	414.4	34	374.5	412.9
2 hours	35	370.1	412.1	43	379.2	415.7	34	371.7	410.1

No cases of torsade de pointes were reported [Vol. 33: page 8:58].

Holter monitors were not performed.

6.3.4 Human Reproduction Data

Few women of childbearing age were recruited into the pivotal COPD studies. The information on pregnancy that the Applicant provided is drawn from the global spontaneous reporting database [Vol. 33: page 8:50]. There have been a total of 20 spontaneous case reports of the use of Foradil during pregnancy: 5 reported a "normal baby," 7 reported a problem with the pregnancy or fetus, and 8 did not provide outcome information. The problems reported were spontaneous abortion, missed abortion, stillbirth, and any malformation.

6.4 SUBGROUP ANALYSES

6.4.1 Drug-Drug Interactions

The Applicant states that there is no new information regarding drug interactions since the 1999 Update of the ISS for formoterol fumarate powder for inhalation for the asthma indication.

6.4.2 Drug-Demographic Interactions

6.4.2.1 Age

There was a slight increase in the frequency of adverse events as age increased for both formoterol treatment groups. There was no age-related association with the placebo group. [Vol. 33: page 8:29]. The table below shows the incidences of AEs by age group.

Incidence of AEs by Age		[Vol. 33: page 8:29]		
	F12 n (%)	F24 n (%)	All Foradil n (%) ¹	Pbo n (%)
Total Patients	405 (100)	406 (100)	811 (100)	420 (100)
Total Patients with AE	254 (63)	255 (63)	509 (63)	266 (63)
Age Range (years):				
<40	0	0	0	0
40-54	35 (57)	42 (58)	77 (58)	45 (63)
55-64	87 (62)	88 (62)	175 (62)	98 (68)
65-74	111 (66)	103 (62)	214 (64)	102 (61)
>74	21 (60)	22 (81)	43 (69)	21 (60)

¹both Foradil 12mcg BID and 24mcg BID dose groups

The Applicant provides some data on possible effect of age on pharmacokinetics of formoterol in COPD patients [Vol. 33: page 8:66]. Using data from the pharmacokinetic portion of Study 056, 12-hour urinary recovery of unchanged formoterol was compared in 5 patients <65 years of age and 4 patients ≥65 years of age, all of whom received 12 weeks of repeated dosing with formoterol 12mcg BID. There was an approximate 4% increase in the 12-hour urinary recovery in the older patients, suggesting the possibility of an effect of age on the pharmacokinetics of formoterol. Because of small sample sizes, no comparison was made for patients receiving formoterol 24mcg BID. Dr. Choi, the Office of Clinical Pharmacology and Biopharmaceutics reviewer, performed a different analysis to evaluate for an age effect. In his analysis of the age versus exposure for each individual patient (as opposed to the age group approach taken by the sponsor), no age effect was suggested. Dr. Choi's analysis can be found in his review of this NDA.

6.4.2.2 Gender

Only 20% of the patients in the database were women. A slightly higher percentage of women experienced AEs in all treatment groups, except for the F12 group. Interestingly, in the F12 group the incidences of AEs were similar (61% of women and 63% of men), whereas in the F24 group, 72% of women and 60% of men reported AEs. [Vol. 33: page 8:29]

6.4.2.3 Race

No conclusions on the effect of race on the incidence of AEs can be made because the number of non-white patients in the database is minimal (2%).

6.4.2.4 Cytochrome P450 Enzyme Status

A total of 239 patients had samples taken for analysis of their CYP2D6 and CYP2C19 metabolizer status. Of these, 11 patients were identified as being poor metabolizers for CYP2D6, and 7 patients were identified as being poor metabolizers for CYP2C19. Because of the small numbers of affected patients, the planned inferential statistical analyses were not performed. The Applicant provides the following descriptive assessments: 1) the incidence of AEs was not elevated in the poor metabolizer group; and 2) poor metabolizer status was not associated with an increased incidence of beta₂-agonist class effects.[Vol. 33: page 8:68]

The Medical Officer also reviewed the following data for the individual subjects who were found to be poor metabolizers: listing of adverse experiences, listing of pulse rates, and listing of investigator remarks. This information can be found in the volumes submitted to the OCPB reviewer [Vol. 12: pages 6:408-465]. No apparent safety signal arose from review of the listings of adverse events listing or investigator's remarks. No apparent safety signal arose from the pulse rate listings for patients who were CYP2D6 poor metabolizers. The only finding of note is that 4 of the 5 patients who were CYP2C19 poor metabolizers developed an increase in pulse rate after dosing with 24mcg BID of Foradil at one or more visits [Vol. 12: page 6-453]. This increase in heart rate was not seen at every visit. The table below provides the heart rates for each of the five patients at each visit during which serial heart rates are available.

Pulse rates of CYP2C19 poor metabolizers receiving F24 [Vol. 12: page 6-453]						
Center/ Patient	Visit	Baseline	1hr	2hrs	4hrs	12hrs
31/3901	2	73	108	100	88	77
	5	76	95	100	92	82
2/5045	3	56	72	64	72	64
	4	58	72	76	84	76
	6	52	68	92	84	80
33/6508	3	74	67	84	74	76
	4	74	80	78	78	71
	6	64	82	79	74	77
48/6437	3	88	72	80	82	84
	4	80	76	76	80	76
	6	88	120	120	130	130
52/6966	3	80	86	84	86	88
	4	68	70	72	74	73
	6	94	90	92	94	94

No increase in heart rate was seen in the two CYP2C19 poor metabolizers who were dosed with 12mcg BID of Foradil [Vol. 12: page 6:448]. **These data raise the possibility that CYP2C19 poor metabolizers may have greater systemic exposure and may develop clinically significant tachycardia with the 24mcg BID dose.** The tachycardia was not seen at the 12mcg BID dose, but the database includes only two CYP2C19 poor metabolizers exposed to this dose. As discussed in Section 3 of this review, the Division considered requiring that the Applicant study the effects of Foradil in patients who are CYP2C19 poor metabolizers more extensively. However, given the facts that 1) we plan to approve only the 12mcg BID dose, 2) the systemic exposure of the 12mcg BID dose in a patient who is a CYP2C19 poor metabolizer is not expected to exceed the systemic exposure achieved with a dose of 24mcg BID in patients with normal metabolism, and 3) there is ample clinical experience in patients taking 24mcg BID, the Division determined that further study of CYP2C19 poor metabolizers should not be required.

6.4.3 Drug-Disease Interactions

The Applicant provided an analysis of the incidence of AEs, by body system, according to baseline bronchodilator reversibility and according to baseline FEV₁ ($\leq 40\%$ versus $>40\%$ predicted). There was no clear trend in the incidence of AEs based on reversibility status. Patients with an FEV₁ $\leq 40\%$ of predicted reported more respiratory AEs than did those with and FEV₁ $>40\%$ in the F12 group (46% vs. 33%), and in the F24 group (44% vs. 32%). This trend was also seen in the theophylline group but was not seen in the placebo group, where the incidence of respiratory AEs was 37% for both the $\leq 40\%$ FEV₁ group and the $>40\%$ FEV₁ group. [Vol. 33: page 8:32]

6.5 SAFETY DATA FROM OTHER SOURCES

6.5.1 Post-Marketing Information

The Applicant provides information regarding spontaneous reports of AEs that have been received by Novartis and entered into their Drug Monitoring Information System (DMIS) database [Vol. 33: page 8:60-63]. This database does not include AEs from post-marketing studies or from New Zealand's Intensive Medicines Monitoring Program. The database does not attempt to separate the reports by indication (asthma vs. COPD). Since launch in 1990, Novartis has received a total of 556 reports. The most common body systems involved were: respiratory (96), nervous (81), cardiovascular (60), musculoskeletal (59), and skin (58). The most common serious AEs were in the cardiovascular (24) and respiratory (21) body systems. Using either production data (prior to 1/1/96) or sales data (after 1/1/96), the Applicant has derived figures to reflect the reporting frequencies of AEs and SAEs worldwide [Vol. 33: page 8:63]. For the period 1990-1999 the rate of reporting for AEs was 19/million "patient treatment months" (PTM) and the rate of reporting for SAEs was 3.9/million PTM.

6.5.2 Published Literature

A total of 30 publications, including 18 abstracts and 12 papers, have been published on the use of formoterol (including non-Novartis formulations) in COPD patients [Vol. 33: page 8:64-65]. One small study of note suggested that COPD patients with pre-existing arrhythmias and hypoxemia may be at risk of adverse myocardial events on taking long-acting beta-adrenoreceptor agonists (Chest, 1998; 114:411-415). This study was a randomized, single blind, balanced, crossover, placebo-controlled, single-dose study performed in 12 patients with COPD and pre-existing cardiac arrhythmias and hypoxemia (PaO₂<60mmHg). Study treatments were formoterol 12mcg BID, formoterol 24mcg BID, salmeterol 50mcg, and placebo. Holter monitoring showed a higher heart rate after formoterol 24mcg BID than after formoterol 12mcg BID and salmeterol, and supraventricular or ventricular premature beats more often after formoterol 24mcg BID. *Although the study included only 12 patients, the findings are interesting because patients with significant cardiovascular disease or known arrhythmias at study entry were excluded from participating in the two pivotal studies used to support this NDA.*

6.6 SUMMARY OF SAFETY

Overall, the integrated safety data from the two pivotal studies supports the safety of formoterol. The safety profiles of the two doses of Foradil were similar, although there was some evidence that the higher dose, 24mcg BID, is associated with more beta-adrenergic side effects and more adverse effects in older patients and women.

The safety database presented included 811 patients who were treated with Foradil, 12mcg BID or 24mcg BID, in the context of two double blind, placebo-controlled, parallel group studies. A total of 316 of these received Foradil for >48 weeks. The generalizability of this population may be somewhat limited because most patients were white (97%) and most were men (approximately 80%). The mean baseline FEV₁ was

46% of predicted, and approximately half of the patients demonstrated bronchodilator reversibility at baseline. Many patients were receiving concomitant treatment with inhaled corticosteroids.

During the course of the studies, there was no difference between either of the Foradil groups and placebo in regard to overall discontinuation from the study or discontinuation due to specific reasons, such as unsatisfactory therapeutic response or adverse event.

Overall adverse events were not more common in either of the Foradil groups as compared with placebo. Specific AEs for which Foradil demonstrated both dose ordering and an increased frequency in one or both groups as compared with placebo were: muscle cramps, arthralgia, myalgia, tremor, fever, and abdominal pain. Adverse events that met these criteria and were also reported as drug-related were: muscle cramps, tremor, dysphonia, dyspnea, and abdominal pain. It should be noted that for the majority of these AEs, the frequency was quite low (e.g. 0.2 – 2%). The frequency was 3-4% for the Foradil 24mcg BID group for muscle cramps, arthralgia, tremor, and abdominal pain.

Specific attention was paid to cardiac AEs because of the known cardiac effects of beta-adrenoceptor agonists. There were no differences between either of the Foradil groups and placebo in regard to cardiac serious adverse events, cardiac adverse events, or moderate/severe cardiac adverse events. There was also no difference in regard to specific cardiac AEs such as hypertension, tachycardia, or angina/myocardial ischemia.

The Foradil groups had fewer SAEs than the placebo group, primarily as a result of fewer respiratory SAEs in the Foradil groups. There were four deaths during the studies, all of which occurred in patients being treated with Foradil. Three of the deaths were in the Foradil 12mcg BID group, and one was in the Foradil 24mcg BID group. Two of the deaths were likely unrelated to study drug (suicide, and traumatic brain injury), and two could possibly be related as they were cardiac in nature. However, it is difficult to come to any conclusion because of the small number of patients involved.

Laboratory data did not raise any significant safety concerns. The only differences between Foradil groups and placebo that are worthy of note is the slightly increased frequency of elevated SGOT/SGPT and decreased RBC seen in the Foradil 24mcg BID group. There were no notable differences between these groups in regard to serum potassium or glucose levels. Vital sign assessments suggested a minimal effect of Foradil 24mcg BID on pulse (increased) and blood pressure (decreased). ECG data also did not show definite differences between the Foradil and placebo groups. However, it should be noted that the number of patients whose ECG changed from either "Normal" or "Abnormal/Clinically Insignificant" to "Abnormal/Clinically Significant" was 4 in the Foradil 12mcg BID group, 3 in the Foradil 24mcg BID group, and 0 in the placebo group. Analyses of the QT and QTc intervals in a subset of patients in Study 058 did not suggest that Foradil has QT prolonging effects. Finally, a small study in the literature suggests that COPD patients with underlying arrhythmias and hypoxemia develop higher heart rates and more frequent supraventricular and ventricular premature beats after a single

dose exposure. Of note, patients with significant cardiovascular disease or known arrhythmias at study entry were excluded for participating in the two pivotal studies.

Subgroup analyses suggest that there is an increased frequency of AEs with increasing age, particularly in the Foradil 24mcg BID group.

The safety profile of the two Foradil doses seems similar, particularly in regard to serious adverse events. However, the higher dose demonstrated slightly more of the typical beta-adrenoceptor effects, such as muscle cramps and tremor. Other findings that suggest that the higher dose might be associated with slightly more toxicity include the slight effects on heart rate seen, the increased effect of age on adverse events, and the published report in patients with more significant underlying disease than was allowed in the pivotal studies. The significance of the increased frequency of elevated SGPT/SGPT and decreased RBC in the Foradil 24mcg BID group is not clear.

**APPEARS THIS WAY
ON ORIGINAL**

7 120-Day Safety Update

The 120-Day Safety Update, submitted on 1/31/01, contains three different integrations of safety data:

- 1) the COPD patient database,
- 2) the asthma patient database, and
- 3) the combined COPD and asthma database.

The COPD patient database portion does not contain new information. Rather, it represents a compilation of the data from the two pivotal studies (056 and 058) and one supportive study (FOR-INT-03). The ISS in the initial NDA submission included combined safety data for the two pivotal studies only, with the supportive study reported separately. The asthma patient database provides integrated safety data for the asthma population. The combined COPD and asthma patient population database has not been submitted previously.

In addition to these three integrations, the 120-Day Safety Update also contains updated information on deaths, SAEs, post-marketing safety, and published literature. The cut-off date for the information included in the 120-Day Safety Update was July 15, 2000.

All references in this section of the review refer to the 1/31/01 submission, unless stated otherwise.

7.1 COPD PATIENT DATABASE

The only difference between this database and the database included in the original NDA submission is that the current submission integrates the safety data from a supportive study (Study FOR-INT-03) along with the safety data from the two pivotal studies [Vol. 1: pages 9:111-126]. In the original NDA the safety data from this study was included separately. Study FOR-INT-03 was a double blind, crossover study comparing formoterol (12mcg BID) vs. albuterol when added to ipratropium bromide in 172 COPD patients. The duration of each treatment arm was 3 weeks. Combining Study FOR-INT-03 with the pivotal studies is of limited value because of the significant differences in study design, and the lack of a placebo arm in Study FOR-INT-03. A brief review of this updated database did not reveal any significant new information that would alter conclusions drawn from the ISS submitted with the original NDA.

Of note, the Applicant states that in the original ISS the method used to identify patients who withdrew from the study due to adverse event or laboratory abnormality was not the most conservative method [Vol. 1: page 9:119]. The updated table below represents the corrected data from the two pivotal studies (combined with the data from FOR-INT-03) for this assessment. Conclusions based on this analysis of withdrawals due to adverse events are not significantly different than the conclusions drawn from the analysis presented in the original ISS. The only difference of note is that the current analysis is more suggestive of a dose-response effect. The total patients withdrawing due to adverse

events was 3.9% in the F12 group, as compared with 6.7% in the F24 group. However, in the placebo group, this number was 8.3%.

Withdrawals due to Adverse Events: Updated Method (Studies 056, 058, FOR-INT-03) [Vol. 1: page 9:120]						
	F12 n (%)	F24 n (%)	All Foradil n (%) ¹	Pbo n (%)	IB n (%)	Theo n (%)
Total Patients	568 (100)	406 (100)	974 (100)	420 (100)	194 (100)	209 (100)
Total Patients Who Discontinued due to AE	22 (3.9)	27 (6.7)	49 (5)	35 (8.3)	9 (4.6)	50 (23.9)
Maximum Duration of Treatment	1 year	1 year	1 year	1 year	3 months	1 year
Body System:						
Respiratory	6 (1.1)	12 (3)	18 (1.8)	21 (5.0)	7 (3.6)	7 (3.3)
Cardiovascular	7 (1.2)	2 (0.5)	9 (0.9)	3 (0.7)	0	6 (2.9)
Musculoskeletal	3 (0.5)	4 (1.0)	7 (0.7)	3 (0.7)	0	2 (1.0)
Nervous	3 (0.5)	6 (1.5)	9 (0.9)	1 (0.2)	0	23 (11)
Digestive	2 (0.4)	3 (0.7)	5 (0.5)	3 (0.7)	1 (0.5)	30 (14.4)
Body as a Whole	3 (0.5)	2 (0.5)	5 (0.5)	2 (0.5)	2 (1.0)	5 (2.4)
Special Senses	0	2 (0.5)	2 (0.2)	1 (0.2)	0	1 (0.5)
Infections/Infestations	0	0	0	0	0	2 (1)
Skin/Appendages	0	0	0	1 (0.2)	0	0
Heme/Lymphatic	0	0	0	2 (0.5)	0	0
Urogenital/Repro	0	0	0	1 (0.2)	0	1 (0.5)
Endocrine	0	0	0	1 (0.2)	0	0
Body system unknown	2 (0.4)	0	2 (0.2)	0	0	2 (1.0)

7.2 ASTHMA PATIENT DATABASE

The asthma patient database included in this submission differs from previously submitted integrated safety summaries (submitted to NDA 20-831) in that it adds the safety data from several additional asthma studies (FOR-INT-02, Protocol 49, FORS01, FORS02, MXF1/F, Protocol 62, and Protocol 73) [Vol. 1: pages 9:31-111]. These trials are of various designs (crossover, parallel group, open-label, double-blind), various durations (ranging from 1 day to 12 months), various patient populations (children, adults), and included a total of 1646 patients [Vol. 1: page 9:30]. The integrated safety information from the updated asthma population will not be reviewed in this document.

7.3 COMBINED COPD AND ASTHMA PATIENT DATABASE

The Applicant has compiled safety data from all multiple-dose, controlled studies, including both the asthma studies and the COPD studies [Vol. 1: page 9:127-149]. This database, referred to as the "combined safety population," includes 21 asthma studies and 3 COPD studies (Studies 056, 058, and FOR-INT-03). The studies involve the following treatment groups: Formoterol fumarate inhalation powder (For Powder), other formoterol comparator formulations (For Comp), placebo (pbo), salbutamol (albuterol) (Salb), salmeterol (salm), ipratropium bromide (IB), and Theophylline (Theo). In addition, 21 patients received budesonide as a comparator during asthma trials. These patients are not included in the following tables.

7.3.1 Demographics

A total of 4024 patients received treatment with formoterol fumarate inhalation powder (Foradil) in the combined safety population. The majority of these patients received treatment for at least 12 weeks. A total of 570 patients received treatment with Foradil for greater than 48 weeks. The table below summarizes the durations of exposure for each of the treatment groups.

Overall Exposures in the Combined Safety Population							[Vol. 1: page 9:129]
	For Powder N (%)	Salb N (%)	Salm N (%)	IB N (%)	Theo N (%)	Pbo N (%)	For Comp N (%)
Total Patients	4024	1067	505	194	209	1389	546
≤1 day	26 (0.6)	3 (0.3)	0	0	4 (1.9)	17 (1.2)	5 (0.9)
2-7 days	50 (1.2)	13 (1.2)	3 (0.6)	1 (0.5)	21 (10.0)	35 (2.5)	8 (1.5)
>1wk-4 wks	402 (10)	271 (25.4)	6 (1.2)	7 (3.6)	13 (6.2)	72 (5.2)	64 (11.7)
>4wks-12 wks	665 (16.5)	194 (18.2)	25 (5.0)	53 (27.3)	13 (6.2)	279 (20.1)	180 (33.0)
>12wks-24wks	1818 (45.2)	520 (48.7)	230 (45.5)	133 (68.6)	15 (7.2)	585 (42.1)	289 (52.9)
>24wks-36wks	389 (9.7)	66 (6.2)	241 (47.7)	0	9 (4.3)	88 (6.3)	0
>36wks-48wks	104 (2.6)	0	0	0	15 (7.2)	34 (2.4)	0
>48wks	570 (14.2)	0	0	0	119 (56.9)	279 (20.1)	0

As indicated in the table above, the combined safety population includes a total of 4024 patients who were treated with Foradil. Of these, 2553 were treated with 12mcg BID and 1250 were treated with 24mcg BID. The majority of these (approximately 70%) were treated for ≤24 weeks [Vol. 1: page 9:129]. The combined safety population was 58% men and 91% white. Thirteen percent were aged 5-12 years, 3% were age 13-18 years, and 21% were age 65 years or older. Twenty percent of those treated with 12mcg BID, and 25% of those treated with 24mcg BID were age 65 years or older.

7.3.2 Disposition

The table below describes the principle reason for withdrawal from the study for the combined safety population, by treatment group. Eighty-seven percent of the patients treated with Foradil completed the studies, as compared to 83% of those treated with placebo. The lowest rate of study completion was seen in the theophylline group (61%). The rate of withdrawal due to adverse event was 4.6% in the Foradil group and 5.8% in the placebo group. Death is listed as the principal reason for discontinuation in 6 patients, 5 in the Foradil group and 1 in the salbutamol (albuterol) group. The occurrence of death in the combined safety database is discussed in the section titled "Deaths, Serious Adverse Events, and Withdrawals Due to Adverse Events" below.

Patient Disposition by Treatment Group (Combined Safety Population) [Vol. 1: page 9:132]							
	For Powder N (%)	Salb N (%)	Salm N (%)	IB N (%)	Theo N (%)	Pbo N (%)	For Comp N (%)
Total no. of patients	4024	1067	505	194	209	1389	546
Total no. completed	3320 (86.7)	856 (87.9)	450 (89.1)	177 (91.2)	128 (61.2)	1146 (82.5)	474 (86.8)
Total no. discontinued	509 (13.3)	55 (10.9)	55 (10.9)	17 (8.8)	81 (38.8)	243 (17.5)	72 (13.2)
Not stated	195	93	0	0	0	0	0
Reason for Discontinuation							
Adverse event	177 (4.6)	40 (4.1)	20 (4.0)	9 (4.6)	48 (23.0)	80 (5.8)	39 (7.1)
Noncompliance	49 (1.3)	9 (0.9)	5 (1.0)	2 (1.0)	11 (5.3)	32 (2.3)	4 (0.7)
Protocol criteria not met	61 (1.6)	14 (1.4)	7 (1.4)	2 (1.0)	6 (2.9)	21 (1.5)	9 (1.6)
Withdrew consent	80 (2.1)	16 (1.6)	10 (2.0)	2 (1.0)	9 (4.3)	47 (3.4)	6 (1.1)
Lost to follow-up	55 (1.4)	10 (1.0)	7 (1.4)	0	3 (1.4)	13 (0.9)	3 (0.5)
Unsatisf. therapeutic effect	56 (1.5)	20 (2.1)	4 (0.8)	1 (0.5)	2 (1.0)	36 (2.6)	10 (1.8)
Death	5 (0.1)	1 (0.1)	0	0	0	0	0
Administrative problem	19 (0.5)	3 (0.3)	2 (0.4)	0	0	10 (0.7)	0
Abnormal lab value	5 (0.1)	2 (0.2)	0	0	2 (1.0)	1 (0.1)	1 (0.2)
Abnormal test result	2 (0.1)	2 (0.2)	0	1 (0.5)	0	3 (0.2)	0
No longer requires treatment	0	1 (0.1)	0	0	0	0	0

7.3.3 Adverse Events

In the combined safety population, the most frequently affected body systems for the Foradil group were respiratory (38%), infections/infestations (17%), nervous (16%), digestive (11%), body as a whole (10%), and musculoskeletal (9%) systems [Vol. 1: page 9:134]. The frequencies of adverse events in all of these systems were lower than was seen in the placebo group. The only body system for which the frequency of adverse events was greater in the Foradil group than in the placebo group was the cardiovascular system (3.7% vs. 2.8%). The table below shows the most frequently affected body systems by Foradil *total daily dose*, only for those body systems that showed dose-ordering. In general, the finding of dose ordering might suggest that the effects are attributable to the drug. This is not definitive evidence, as dose ordering might simply reflect differences in populations studied with lower doses as compared with higher doses. Also, with the exception of the cardiovascular and musculoskeletal systems, the occurrence of adverse events in the body systems listed was greater in the placebo group than in any of the Foradil groups.

Body Systems Most Frequently Affected by Adverse Events , Showing Dose Ordering with Foradil Daily Dose (Combined Safety Population)			
	<i>Foradil Total Daily Dose</i>		
	12mcg N (%)	24mcg N (%)	48mcg N (%)
Total Patients	237 (100)	2553 (100)	1250 (100)
Total Patients with AE	119 (50.2)	1506 (59.0)	784 (62.7)
Body System:			
Respiratory	82 (34.6)	961 (37.6)	477 (38.2)
Musculoskeletal	10 (4.2)	225 (8.8)	128 (10.2)
Nervous	15 (6.3)	397 (15.6)	237 (19.0)
Digestive	11 (4.6)	264 (10.3)	154 (12.3)
Cardiovascular	2 (0.8)	85 (3.3)	61 (4.9)

In the combined safety database, 60% of Foradil patients experienced one or more AEs, as compared with 65% in the placebo group. The most frequently reported AEs in the Foradil group were: viral infection (15%), asthma (11%), headache (10%), upper respiratory tract infection (8%), rhinitis (7%), pharyngitis (6%), and coughing (5%) [Vol. 1: page 9:136]. The frequencies of all of these AEs were greater in the placebo group than in the Foradil group. The table below provides the specific adverse events that both 1) occurred in ≥1% of patients in the Foradil group, and 2) occurred more frequently in the Foradil group than in the placebo group.

Specific AEs Occurring in ≥1% of the Foradil group and more frequently in the Foradil group than the placebo group							
	For Powder N (%)	Salb N (%)	Salm N (%)	IB N (%)	Theo N (%)	Pbo N (%)	For Comp N (%)
Total # of patients	4024	1067	505	194	209	1389	546
Total # of patients with an AE	2409 (59.9)	576 (54%)	392 (77.6)	110 (56.7)	142 (67.9)	904 (65.1)	201 (36.8)
Adverse Event							
Dyspnea	124 (3.1)	39 (3.7)	3 (0.6)	13 (6.7)	9 (4.3)	40 (2.9)	10 (1.8)
Tremor	101 (2.5)	20 (1.9)	3 (0.6)	0	12 (5.7)	6 (0.4)	10 (1.8)
Infection Chest	100 (2.5)	38 (3.6)	28 (5.5)	4 (2.1)	4 (1.9)	13 (0.9)	4 (0.7)
Pain Chest	68 (1.7)	13 (1.2)	10 (2.0)	3 (1.5)	4 (1.9)	22 (1.6)	2 (0.4)
Cramps muscle	56 (1.4)	4 (0.8)	4 (0.8)	2 (1.0)	1 (0.5)	3 (0.2)	1 (0.2)

The table below includes all of the specific AEs for which dose ordering was demonstrated. As discussed above, the presence of dose ordering might suggest that the AE is treatment-related. Many of the adverse effects that appear in this table might be expected with a beta-adrenergic agonist. These include tremor, muscle cramps, tachycardia, and palpitations. Interestingly, COPD exacerbation was more frequent as the Foradil dose increased. Combining the information in the table above and the table below, two AEs were both more frequent in the Foradil group as compared with placebo, and showed dose ordering. These two AEs are tremor and muscle cramps. (Note that the Foradil doses are listed as total daily doses.)

Specific Adverse Events Showing Dose-Ordering with Foradil Daily Dose (Combined Safety Population) 9:138]			
	Foradil Total Daily Dose		
	12mcg N (%)	24mcg N (%)	48mcg N (%)
Total Patients	237 (100)	2553 (100)	1250 (100)
Total Patients with AE	119 (50.2)	1506 (59.0)	784 (62.7)
Headache	8 (3.4)	251 (9.8)	142 (11.4)
Rhinitis	11 (4.6)	159 (6.2)	92 (7.4)
Pharyngitis	8 (3.4)	149 (5.8)	75 (6.0)
Sinusitis	4 (1.7)	122 (4.8)	61 (4.9)
Tremor	0	41 (1.6)	60 (4.8)
COPD Exacerbated	0	47 (1.8)	42 (3.4)
Pain Abdominal	2 (0.8)	39 (1.5)	40 (3.2)
Nausea	3 (1.3)	41 (1.6)	26 (2.1)
Arthralgia	2 (0.8)	39 (1.5)	23 (1.8)
Dizziness	1 (0.4)	36 (1.4)	21 (1.7)
Cramps muscle	1 (0.4)	22 (0.9)	33 (2.6)
Cramps muscle/leg ¹	2 (0.8)	47 (1.8)	44 (3.5)
Diarrhea	1 (0.4)	30 (1.2)	21 (1.7)
Myalgia	1 (0.4)	26 (1.0)	15 (1.2)
Gastroenteritis	1 (0.4)	23 (0.9)	16 (1.3)
Otitis Media	1 (0.4)	22 (0.9)	14 (1.0)
Tachycardia	0	19 (0.7)	15 (1.2)
Palpitation	0	19 (0.7)	13 (1.0)
Nervousness	1 (0.4)	15 (0.6)	14 (1.1)
Mouth Dry	0	16 (0.6)	12 (1.0)
Sprains and Strains	0	14 (0.5)	13 (1.0)

¹The table provided by the sponsor includes "cramps muscle" and "cramps leg" as separate entities. The entry in this table entitled "cramps muscle/leg" combines these two.

7.3.4 Deaths, Serious Adverse Events, and Withdrawals Due to Adverse Events

In the combined safety database there were 6 deaths in multiple-dose, controlled trials: 5 in the Foradil group and 1 in the salbutamol (albuterol) group. All of these deaths were previously reported, either in the original COPD NDA (four deaths on Foradil), or in the asthma NDA and its supplements (1 death on Foradil and 1 death on albuterol). The deaths in the COPD studies are described in the Overview of Safety, elsewhere in this document. The death in the Foradil group of the asthma study was due to asthma exacerbation (patient found unresponsive after calling for help for severe exacerbation of asthma) [source: Medical Officer Review of NDA 20-831, dated 5/20/98, Dr. Anthracite]. The table below summarizes the six deaths that occurred in multiple-dose, controlled trials in the combined safety database.

Deaths occurring in multiple-dose controlled trials, combined safety population					
[Source: fax from Applicant, dated 6/1/01]					
Center/Pt. #	Study/Population	Treatment/Daily Dose	Description of Event	Age (yrs)	Sex
0171/4313	PROT41/ Asthma	Albuterol	Hemorrhagic pancreatitis	26	F
0161/4625	PROT41/ Asthma	Foradil 48mcg	Asthma (found unresponsive after calling for help for severe exacerbation of asthma)	66	F
1/5502	058/ COPD	Foradil 24mcg	MI	61	M
52/6960	058/ COPD	Foradil 24mcg	Suicide	53	M
86/7685	058/ COPD	Foradil 24mcg	Chest Pain; sudden death	67	M
3/7875	058/ COPD	Foradil 48mcg	Post-traumatic brain swelling after a fall	59	M

One additional death occurred in a single-dose asthma trial (MTA02) [Fax from Applicant dated 6/1/01]. This 60 year-old patient was found dead in his bed, presumably related to a myocardial infarction, 17 days after a single dose of Foradil. Because of the timing, a causal relationship with Foradil is unlikely.

No deaths occurred in completed trials during the reporting period for this Safety Update. However, one additional death occurred in a 71 year-old male COPD patient who was being treated with Foradil (12mcg BID) in an on-going COPD study (FOR-NL-04) [Vol. 1: page 9:149]. He died of COPD exacerbation. This death is also discussed in the section below titled "Updated Information on Deaths, SAEs, Post-marketing Safety, and Published Literature".

For the combined safety database, serious adverse events occurred in 3.7% of patients treated with Foradil and 4.2% of patients treated with placebo. In both the Foradil group and the placebo group, the most frequently affected body system was the respiratory system (2.2% and 2.4%, respectively) [Vol. 1: page 9-142]. The most frequent specific SAEs in the Foradil group were: asthma (1.3%), COPD exacerbated (0.3%), and dyspnea (0.2%). The frequencies of these SAEs in the placebo group were: 0.4%, 1.2%, and 0.1%, respectively [Vol. 1: page 9:143].

In the combined safety database, the percentage of patients withdrawing from a study due to an adverse event was 5.5% in the Foradil group and 6.9% in the placebo group [Vol. 1: page 9:146]. The most frequent events resulting in withdrawal in the Foradil group were: asthma (1.4%), tremor (0.4%), headache (0.3%), dyspnea (0.3%), insomnia (0.2%), COPD exacerbated (0.2%), and dizziness (0.2%). No patients in the placebo group withdrew due to tremor or insomnia.

7.3.5 Updated Information on Deaths, SAEs, Post-marketing Safety, and Published Literature

This 120-Day Safety Update includes updated information on deaths, SAEs, post-marketing safety, and published literature for the period of 2/16/00 through 7/15/00 [Vol. 1: pages 9:149-165].

One death was reported during this period. This occurred in a COPD study designated FOR-NL-04. The patient, a 71 year-old man who was being treated with Foradil, was admitted to the hospital for COPD exacerbation after an unknown duration of treatment. He died 2-3 weeks later. The investigator indicated that the death was unlikely related to the study drug [Vol. 1: page 9:149-150 and Vol. 20: page 9:379 (case narrative)].

Seven patients (including the death described above) experienced SAEs in ongoing clinical trials during the reporting period. Three of these were in asthma trials. These were: 2 events of asthma exacerbation (one on Foradil open-label, and one for which the code has not yet been broken), and 1 event of mild hypoxemia/ worsening pulmonary function (on albuterol). The latter case was felt by the investigator to be related to study drug, albuterol. The table below summarizes the SAEs reported from ongoing COPD trials during the reporting period. Narratives for these cases were reviewed by Dr. Sullivan [Vol. 20: pages 9:379-380].

SAEs in ongoing COPD trials during the reporting period					[Vol. 1: page 9:150]
Protocol Center/Patient Country	Age/Sex	SAE	Treatment	Investigator Attribution	Outcome
FOR-NL-04 4/604 Netherlands	72F	COPD	Foradil	Unlikely	Complete recovery
FOR-NL-04 4/379 Netherlands	71M	COPD	Foradil	Unlikely	Death
FOR-D-09 02/102 Germany	65F	Infective exacerbation of COPD	Berodual (fenoterol/ ipratropium)	Not related	Condition improving
FOR-D-09 07/91 Germany	61F	Feverish infection	Formoterol fumarate	Unlikely	Unknown

During the reporting period, 51 spontaneous reports of adverse events were entered into the Applicant's database. The most common body systems involved were: cardiac (10), general disorders and administration site condition (8), gastrointestinal (6), and skin and subcutaneous tissue disorders (6). Seven of the 51 events were considered to be serious. The serious events were: dyspnea/deterioration of disease, overdose, ventricular tachycardia, asthmatic attack, muscle pain/tremor/overdose effect/ increased creatinine kinase, hypersensitivity/ erythema/ headache/ face edema/ malaise, and erythematous skin eruption/ purpura. [Vol. 1: pages 9:152-153] The outcome of the overdose case, which involved a 7 year-old child ingesting 30 Foradil capsules, is unknown. Case narratives

for these serious events were reviewed by Dr. Sullivan [Vol. 20: page 9:373-376]. The case of muscle pain/ tremor/ overdose effect/ increased creatinine kinase was felt to be probably related to Foradil (24mcg BID), as it occurred after 2 weeks of treatment and resolved upon withdrawal of Foradil. No re-challenge was carried out. The case of hypersensitivity/ erythema/ headache/ face edema/ malaise was felt to be definitely related. This patient developed symptoms after her first inhalation of 24mcg, and then developed symptoms again after her second dose, the next morning. She was treated with IM corticosteroid injection and recovered.

Four SAEs have been reported from a post-marketing observational study undertaken by the Applicant in Germany. The table below summarizes these events.

SAEs in post-marketing observational study PMS Study III				[Vol. 1: page 9:155]
Case Number	Age/Sex	SAE	Foradil Total Daily Dose	Outcome
PHNU2000DE01070	35F	Facial swelling	24mcg	Complete recovery
PHNU2000DE01288	69M	Cardiac failure	Not stated	Death
PHNU2000DE01385	81M	Emphysema, bronchitis, colon carcinoma	24mcg	Death
PHNU2000DE01398	79F	Asthma exacerbation	24mcg	Complete recovery

The 120-Day Safety Update also briefly summarizes the published literature for the reporting period [Vol. 1: page 9:157-163]. This summary provides no significant new information.

7.4 SUMMARY

This 120-Day Safety Update provided analyses of three different data sets: the COPD population, the asthma population, and the combined (COPD and asthma) population. Of the three data sets, only the combined data set was examined in depth. The data provided in the analysis of the COPD population was previously submitted with the original NDA submission, and the new approach to the analysis (the addition of the non-pivotal trial to the data set) did not add meaningful information. The corrected version of the table reflecting withdrawals due to adverse events did not significantly change any conclusions drawn from the original NDA submission.

At a pre-NDA meeting, the Division asked the Applicant to integrate the safety data from the two development programs (asthma and COPD) into a single data set. The analysis of the "combined safety population" included in this submission is the Applicant's response to that request. A total of 4024 patients who received treatment with Foradil, and 1389 patients who received treatment with placebo are included in this combined safety population. The majority of these patients received treatment for at least 12 weeks, and 570 patients received treatment with Foradil for greater than 48 weeks. As was the case with the COPD data set, the majority of these patients were white (91%). The seven most common adverse events reported by patients treated with Foradil (viral infection, asthma, headache, upper respiratory tract infection, rhinitis, pharyngitis, and coughing) occurred

more frequently in the placebo group. Five adverse events occurred more frequently in the Foradil group: dyspnea, tremor, infection chest, pain chest, and cramps muscle. Of these, tremor and muscle cramps were seen with increased frequency as the dose of Foradil increased ("dose-ordering"), further suggesting a causative association with Foradil. The occurrence of tremor and muscle cramps in patients receiving a total daily dose of 48mcg of Foradil was 4.8% and 3.5%, respectively.

Overall, serious adverse events were more common in the placebo group (4.2%) than in the Foradil group (3.7%). Likewise, withdrawals due to adverse event were more common in the placebo group (6.9%) than in the Foradil group (5.5%). A small fraction of Foradil patients withdrew from the study due to tremor (0.4%) and insomnia (0.2%). No patients in the placebo group withdrew for these reasons.

The number of deaths during multiple-dose, controlled trials in the combined safety database were greater in the Foradil group (5) than in the placebo group (0) [Vol. 1: page 9:139]. However, evidence for a causal association with the use of Foradil is weak, as the causes of death were varied (2 cardiac, 1 asthma, 1 suicide, and 1 post-traumatic brain swelling).

The remaining data provided in the 120-Day Safety Update, including the post-marketing experience and review of the published literature does not add significantly to the safety assessment.

In summary, the most informative portion of this 120-Day Safety Update is the integration of the safety data from the asthma program and the COPD program. This integrated analysis supports the safety conclusions drawn from the analysis of the COPD program. It suggests that the overall rate of AEs and SAEs are no greater with Foradil than with placebo and that certain specific AEs that are expected with the use of beta-adrenergic agonists (such as tremor and muscle cramps) are attributable to Foradil. Finally, the combined database, which is comprised mostly of white patients, is not entirely representative of the demographics of the US population.

**APPEARS THIS WAY
ON ORIGINAL**

8 Use in Special Populations

Discussions of the analyses of gender, age, and race effects on the safety and efficacy of Foradil are included in the sections of this review entitled Overview of Efficacy, Overview of Safety, and Executive Summary.

The application does not include a pediatric program. This is appropriate because COPD is a disease of older adults.

**APPEARS THIS WAY
ON ORIGINAL**

9 Labeling Review

The Applicant submitted draft labeling on May 4, 2001. The most significant changes to the proposed label are:

- The proposed [redacted] will not be allowed. This claim is not justified.
- References to [redacted] will be deleted. [redacted] are not justified.
- The section of the label pertaining to the QTc data will be re-written. This section [redacted]
- The section of the label pertaining to the adverse events in COPD patients will be re-written. [redacted]
- The clinical trials section will be re-written to improve its clarity.

**APPEARS THIS WAY
ON ORIGINAL**

10 Conclusion/Recommendations

The results of the two pivotal trials submitted with this application indicate that both the 12mcg BID dose and the 24mcg BID dose of Foradil are effective in the maintenance treatment of COPD. However, there is no evidence that the efficacy of the 24mcg BID dose is superior to that of the 12mcg BID dose.

The recommendation of the Medical Officer is that the 12mcg BID dose be approved.

The Applicant has proposed to _____

The safety database presented suggests that Foradil 12mcg BID is acceptably safe for use in this patient population. However, the Applicant should be required to commit to further study of the cardiac safety of this drug, using 24-hour Holter monitoring. Studies of asthmatic patients have been performed using Holter monitoring; however, given the differences in the patient populations, Holter monitoring should be performed in COPD patients as well.

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ON ORIGINAL**

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

/s/

Eugene Sullivan
7/17/01 04:42:38 PM
MEDICAL OFFICER

Badrul Chowdhury
7/19/01 12:30:58 PM
MEDICAL OFFICER
I concur.

**APPEARS THIS WAY
ON ORIGINAL**

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #: 21-279	APPLICATION TYPE: NDA
SPONSOR: Novartis Pharmaceuticals	PROPRIETARY NAME: Foradil Inhalation Powder
INVESTIGATOR: Multiple	USAN NAME: Formoterol fumarate
CATEGORY: Long-acting β 2-agonist bronchodilator	ROUTE: Oral Inhalation
MEDICAL OFFICER: Eugene J. Sullivan, MD, FCCP	REVIEW DATE: December 18, 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission Type</u>	<u>Comments</u>
September 22, 2000	September 25, 2000	Original NDA	

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
	NDA 20-831 (Foradil asthma indication)	

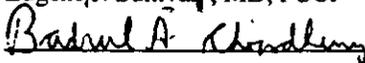
REVIEW SUMMARY: This is a 45-day clinical review of NDA #21-279. This NDA is for Foradil, a dry powder inhalation formulation of formoterol fumarate intended for the treatment of COPD. The Applicant has previously submitted an application for the same product for the treatment of asthma (NDA #20-831). NDA #20-831 is currently under review. Approval of this application (NDA #21-279) will be contingent upon approval of NDA #20-831. This application includes two Phase 3 pivotal studies comparing two doses of formoterol, placebo and an active comparator. In addition, one supportive study comparing formoterol to placebo when taken in combination with ipratropium was submitted. Two features of this application that will require specific attention during the review process are the proposed _____ . The application contains all of the elements necessary for filing. The application will be accepted for filing and the clinical review will proceed according to the timeline provided in section IX of this review. DSI auditing of individual clinical study centers will not be requested.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

NDA/Efficacy/Label Supplements: **SUITABLE FOR FILING** **NOT SUITABLE FOR FILING**

SIGNATURES

Medical Reviewer:		Date: 12/18/00
	Eugene J. Sullivan, MD, FCCP	
Medical Team Leader:		Date: 12/18/00
	Badrul Chowdhury, MD, PhD	

I. General Information

This NDA is submitted by Novartis Pharmaceuticals Corporation for a new, long-acting β_2 -adrenergic receptor agonist called formoterol fumarate inhalation powder (Foradil®). The application is intended to support the use of Foradil® in patients with COPD. The Applicant has previously submitted an NDA to support the use of this product in patients with asthma (NDA # 20-831). NDA 20-831 is currently under review. The proposed dose is 12mcg BID

II. Background and Rationale

Formoterol belongs to a class of drugs referred to as β -adrenergic agonists and is selective for the β_2 -adrenergic receptors. The β_2 -adrenergic agonists are widely used as bronchodilators among patients with asthma and COPD. Many of the commonly used β_2 -adrenergic agonists, such as albuterol and terbutaline, have a rapid onset of action but a relatively short duration of action (4-6 hours). One currently approved β_2 -adrenergic agonist, salmeterol, has a duration of action which is sufficiently long to allow BID dosing. However, salmeterol's onset of action is less rapid. The Applicant proposes that Foradil® will provide a clinical advantage over the currently available β_2 -adrenergic agonists because it has a rapid onset of action and a prolonged duration of action (>12 hours).

Foradil® inhalation powder is formulated as a gelatin-coated dry powder capsule that utilizes a specific delivery device, the Aerolizer™.

III. Regulatory and Foreign Marketing History

A. Regulatory History

Novartis has previously submitted an NDA for this product. NDA #20-831 was submitted by Novartis in support of approval to market Foradil Inhalation Powder for the treatment of asthma, including exercise-induced asthma. That application is under review in DPADP.

List of related applications

Product	Indication	Application	Status
Foradil® Inhalation Powder	Asthma	NDA #20-831	Action is pending
	Exercise-induced asthma		

B. Foreign Marketing History

Foradil®, in various formulations, has been approved for marketing for at least one indication in 79 countries.

However, many countries have included a portion of the COPD indication (reversible COPD) in the label for the original approved use, reversible obstructive airway disease. The list of countries which have approved any formulation of Foradil® includes Canada, Germany, Australia, and the United Kingdom. This list does not include Japan [Vol. 1.1, p3:26-36].

The dry powder capsule formulation, which is the subject of this NDA, has never been rejected or withdrawn in any country.

IV. Items Required for Filing and Reviewer Comments

A. Necessary Elements (21 CFR 314.50)

Necessary Elements

Type	Status	Location
Application Form (FDA 356h)	Present	Vol. 1.1, Page 1-2
Investigator Debarment Certification	Present	Vol. 1.1, Page 16-1
Financial Disclosure	Incomplete*	Vol. 1.1, Pages 19-1-20
Statements of Good Clinical Practice	Present	In ISE introduction
Environmental Assessment	?*	
Proposed labeling changes	Present	Vol. 1.1, p3:1-18
Integrated Summary of Effectiveness	Present	Vol. 1.30, p8:1
Integrated Summary of Safety	Present	Vol. 1.33, p8:1
Integrated Summary of Benefits and Risks	Present	Vol. 1.1, p3:201-5
Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures	Present	In ISS introduction
Statistical Analyses	Present	
Pediatric Use Section	Present (Pediatric Waiver)	Vol. 1.1, Pages 20-1-2
Case Report Tabulations	Present	CD-ROM
Case Report Forms (for patients who died or did not complete study)	Present	CD-ROM
Patent Information	Not Present*	

*These deficiencies are not grounds for refusal to file the application. The project manager will address these deficiencies with the Applicant.

V. Preliminary Review of Package Insert

The application does not contain the complete proposed package insert. Rather, the Applicant has submitted proposed additional labeling statements to be added to the proposed

Foradil label submitted to NDA 20-831. This seems reasonable; however, it must be noted that NDA 20-831 has not yet been approved and the final package insert has not been established.

The proposed additional labeling statements are:

of

VI. Clinical Studies

This submission includes two clinical studies that are considered pivotal in support of the approval of formoterol fumarate for the COPD indication. One additional study, performed outside of the US, is also submitted in support of the safety and efficacy of formoterol fumarate in COPD. In addition, there are four ongoing, non-US, post-marketing clinical trials in COPD. The pivotal and supporting studies are outlined in the table below.

A. Pivotal Studies (056 and 058)

The two pivotal studies, Study 056 and Study 058, share many similar features. Both are multinational, randomized, placebo-controlled studies comparing the effects of formoterol 12 mcg bid, formoterol 24mcg bid, placebo, and an active control. In Study 056 the active control arm is ipratropium bromide 40mcg qid (double dummy) and in Study 058 the active control arm is open-label theophylline. In both studies the primary variable is FEV₁ AUC 0-12 hours at 3 months. The duration of Study 056 is 12 weeks and the duration of Study 058 is 12 months.

The inclusion criteria for both studies include: age >40 years, >10 pack-year smoking history, American Thoracic Society criteria for the diagnosis of COPD, positive symptom scores on ≥ 4 of the 7 days prior to randomization, baseline FEV₁ <70% of predicted and >0.75 liters, and baseline FEV₁/FVC <88% for men and 89% for women. The last of the criteria listed represent European Respiratory Society guidelines for the diagnosis of COPD. Bronchodilator reversibility is assessed at baseline for the purposes of subsequent subset analyses of efficacy data based upon reversibility status. The St. Georges Respiratory Questionnaire is administered at baseline in both studies, at 3 months in Study 056, and at 6 and 12 months in Study 058.

Study 056 included 44 patients randomized to treatment at 6 US centers. Study 058 included 199 patients randomized to treatment at 19 US centers.

B. Supporting Study (FOR-INT-03)

Study FOR-INT-03 is submitted as a supportive study. It is a randomized, double-blind, double-dummy, 2-period crossover study comparing Foradil (12mcg BID) and albuterol (200mcg QID), when used in combination with Atrovent (40mcg QID). Each treatment period is 3 weeks. The study was performed outside the US and included 172 subjects. The primary variable was mean AM PEFr during the last week of treatment. This study was intended as a Phase 4 study to assess combination therapy with ipratropium and the efficacy data is not integrated with the efficacy data from the two pivotal studies in the Integrated Summary of Efficacy (ISE). The efficacy data is included in the ISE under the "population groups" section to address the group of patients receiving combination treatment with ipratropium. No data from this study is proposed to be included in the product label.

C. Ongoing Non-US COPD Studies

There are four ongoing non-US post-marketing studies of formoterol in patients with COPD:

1. Study FOR-NL-04: An open-label comparison of Foradil versus regular treatment in 1200 patients in the Netherlands. Outcomes include FEV₁ and quality of life.
2. Study FOR-D-09: An open-label comparison of Foradil (12-24mcg BID) versus Berodual (1-2 puffs TID) in 100 patients in Germany. Outcomes include PEF, FEV₁, Raw, and adverse events.
3. Study CFOR258 IA-02: A placebo-controlled, double-blind, double-dummy, single dose crossover study comparing Foradil (12 and 24mcg), salmeterol (Serevent™ Diskus, 50

and 100mcg), and placebo in 50 patients in Greece, Italy, France, and the Netherlands. The outcome is FEV₁ AUC.

4. Study CFOR258 IA-04: A placebo-controlled comparison of Foradil (24mcg), salbutamol (Ventodisk®, 400mcg), and placebo in 24 patients in France. Treatment with Foradil and placebo will be double-blind, and treatment with salbutamol will be single-blind. The outcome will be FEV₁ AUC.

Efficacy data from these studies are not presented. SAEs from these studies are provided in narrative form in a supplement to the ISS.

**APPEARS THIS WAY
ON ORIGINAL**

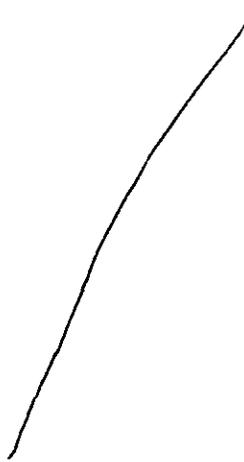
Summary of Pivotal and Supportive Studies

Designation/ Location	Study Number	Treatment Groups	Number of Subjects	Duration	Design	Primary Variable
Pivotal Studies/ US and Non-US	056	Formoterol 12mcg BID Formoterol 24mcg BID Ipratropium bromide Placebo	194 192 194 <u>200</u> Total: 780	12 weeks	R, DB, PC, DD	FEV ₁ AUC 0-12 hours at 3 months
	058	Formoterol 12 mcg BID Formoterol 24mcg BID Theophylline Placebo	211 214 209 <u>220</u> Total: 854	12 months	R, DB, PC Theophylline dosed in open-label fashion	FEV ₁ AUC 0-12 hours at 3 months
Supportive Study/ Non-US	FOR-INT-03	Formoterol 12mcg BID/ Atrovent 40mcg QID Albuterol 200mcg QID/ Atrovent 40mcg QID	172	3-week treatment periods	R, DB, DD, 2-period XO	Mean AM PEFR during the last week of treatment

**APPEARS THIS WAY
ON ORIGINAL**

VII. DSI Review / Audit

The Agency's Division of Scientific Investigation can, at the request of the reviewing division, perform audits of individual clinical study centers in order to investigate the integrity of the data. DSI auditing of clinical centers will not be requested for the studies in this NDA.

**VIII. Summary**

This NDA is for Foradil, a dry powder inhalation formulation of formoterol fumarate intended for the treatment of COPD. The Applicant has previously submitted an application for the same product for the treatment of asthma (NDA #20-831). NDA #20-831 is currently under review. Approval of this application (NDA #21-279) will be contingent upon approval of NDA #20-831. This application includes two Phase 3 pivotal studies comparing two doses of formoterol, placebo and an active comparator. In addition, one supportive study comparing formoterol to placebo when taken in combination with ipratropium was submitted. Two features of this application that will require specific attention during the review process are the proposed

The application contains all of the elements necessary for filing. The application will be accepted for filing and the clinical review will proceed according to the timeline provided in section IX of this review. DSI auditing of individual clinical study centers will not be requested.

**APPEARS THIS WAY
ON ORIGINAL**

IX. Timeline for Clinical Review

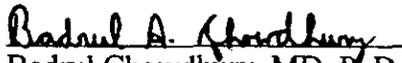
The table below outlines the proposed timeline for completion of the clinical review of this application.

Timeline for Review

Milestone	Target Date for Completion
Pivotal Studies	
Study 056	12/20/00
Study 058	1/24/01
Supportive Study	
FOR-INT-03	2/14/01
Overview of Efficacy	4/11/01
Integrated Summary of Safety	5/16/01
Draft Review	6/13/01
Final Review	7/3/01

Reviewed by:


 Eugene J. Sullivan, MD, FCCP
 Medical Officer, DPADP


 Badrul Chowdhury, MD, PhD
 Medical Team Leader, DPADP

cc: Original NDA
 HFD-570 / Division File
 HFD-570 / Sullivan / Medical Officer
 HFD-570 / Chowdhury / Medical Team Leader
 HFD-570 / Jani / Project Manager

/s/

Eugene Sullivan
12/19/00 07:42:41 AM
MEDICAL OFFICER

Badrul Chowdhury
12/19/00 10:24:59 AM
MEDICAL OFFICER
I concur

**APPEARS THIS WAY
ON ORIGINAL**

The 120 day safety update was reviewed as part of the medical review dated June 11, 2001.

APPEARS THIS WAY
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