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STATISTICAL REVIEW(S)



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Statistical Review and Evaluation Clinical Studies

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EXECUTIVE SUMMARY

Brief Overview of Clinical Studies

Formoterol fumarate inhalation solution (FFIS) 20 mcg/2mL BID is proposed to be indicated for the treatment of COPD in adult patients.

The sponsor submitted the results of four clinical trials; two Phase 2 trials and two Phase 3 trials (see Table 1). Only **one (1)** Phase 3 study (Study 201-065) provided confirmatory evidence for the effectiveness of FFIS. The second Phase 3 study, Study 059, was submitted to provide safety assessments. Study 059, with its original objectives of confirming both efficacy and safety, failed to produce evidence to support efficacy because of randomization errors (According to the sponsor, “*Due to a treatment sequence error that occurred during the double-blind treatment phase, most patients did not receive initial double-blind treatment according to the randomization schedule (page 4, 2.0 SYNOPSIS, dl-059.pdf).*”) Two Phase 2 dose-ranging studies, Studies 052 and 057 were submitted to provide supporting evidence of the effectiveness of FFIS. Only Study 57 provided additional evidence in the support the effectiveness of FFIS20.

The primary objective of Study 201-065 was to confirm the effectiveness and safety of FFIS. It was a randomized, double-blind, double-dummy, placebo and active-controlled 12-week study. The primary efficacy analysis was based on the comparison between FFIS 20 mcg/2mL, BID, and placebo. While this reviewer’s efficacy evaluation is focused on whether the superiority of FFIS to placebo can be demonstrated based on the sponsor’s data for Study 201-065, the safety evaluation is based on the sponsor’s safety report and the sponsor’s AE (adverse event) data for both Phase 3 studies (065 and 059).

Table 1 Studies reviewed

Study	Objective	Design	Evaluated
201-065	Efficacy and safety	Phase 3 randomized, double-blind, double-dummy, placebo- and active controlled	Efficacy and safety
DL-059	Efficacy and safety	Phase 3 randomized, double-blind, double-dummy, parallel group	Safety
DL-052	Dose-ranging	Phase 2 Randomized, Double-Blind, Double-Dummy, 5-Way, Crossover	Efficacy
DL-057	Dose-ranging	Phase 2 Randomized, Double-blind, Double-dummy, 7-Way, Crossover	Efficacy

Statistical Issues and Findings

The efficacy comparisons for Study 201-065 in Table 2 demonstrate the significant effectiveness of FFIS relative to placebo based on an LOCF analysis of the ITT data. The same statistical significance holds for the group of patients completing the study. The difference between FFIS (20 mcg) and Foradil® Aerolizer® (FA) (12 mcg) appears to be small.

Table 2 Efficacy findings based on week-12 mean AUC of FEV₁ (Study 201-065)

Treatment	Comparator	LS mean Difference	P value	95% confidence interval
FFIS (20 MCG) BID	PLACEBO	0.19	<0.0001	(0.12, 0.25)
FA 12 MCG BID	PLACEBO	0.21	<0.0001	(0.14, 0.28)
FFIS (20 MCG) BID	FA 12 MCG BID	0.02	0.55	(-0.05, 0.09) ¹

Source: EFF2 (ITT patients, missing AUC of FEV₁ estimated with LOCF)

1 – Note that negative values for the difference favor FFIS over FA.

In addition, the dose-ranging Study DL-057 provided some additional supportive evidence that FFIS20 is efficacious.

For the evaluation of safety based on the sponsor's report of adverse-event findings, Table 3, below, and Table 4 on the following page show the numbers and percentages of patients by AE, according to MedDRA Preferred Terms for Study 201-065 and Study 059 (the open label portion), respectively. Only AEs reported in 2%+ of the patients are displayed in these tables. A complete list of AEs can be found in the appendix. The AEs with a gray background are those AEs reported in more than 2% of the patients in both studies.

Table 3 Selected AE findings (Study 201-065)

AEs presented as: AEPTTXX; Group totals for FFIS, FA, and placebo: 123, 112, and 114	TREATMENT						N	%
	FFIS 20		FA 12		Placebo			
	N	%	N	%	N	%		
Chronic obstructive airways disease exacerbated	5	4.07	7	6.25	9	7.89	21	6.02
Headache	7	5.69	5	4.46	8	7.02	20	5.73
Nausea	6	4.88	4	3.57	3	2.63	13	3.72
Cough	2	1.63	5	4.46	5	4.39	12	3.44
Diarrhea	6	4.88	2	1.79	4	3.51	12	3.44
Dizziness	3	2.44	8	7.14	1	0.88	12	3.44
Dyspnoea	3	2.44	3	2.68	4	3.51	10	2.87
Dry mouth	4	3.25	2	1.79	2	1.75	8	2.29
Nasopharyngitis	4	3.25	2	1.79	2	1.75	8	2.29
Upper respiratory tract infection	2	1.63	3	2.68	2	1.75	7	2.01
Urinary tract infection	2	1.63	2	1.79	3	2.63	7	2.01
Vomiting	3	2.44	2	1.79	2	1.75	7	2.01

Source: AE1

Table 4 Selected AE findings (Study 059: open-label period)

AEs presented as: AEPTTXX; Group totals for FFIS and FA: 463 and 106	TREATMENT				N	%
	FFIS20		FA12			
	N	%	N	%		
Chronic obstructive airways disease exacerbated	73	15.77	19	17.92	92	16.17
Upper respiratory tract infection	47	10.15	13	12.26	60	10.54
Nasopharyngitis	36	7.78	7	6.60	43	7.56
Bronchitis	32	6.91	10	9.43	42	7.38
Sinusitis	27	5.83	4	3.77	31	5.45
Urinary tract infection	21	4.54	6	5.66	27	4.75
Bronchitis acute	22	4.75	3	2.83	25	4.39
Headache	20	4.32	5	4.72	25	4.39
Cough	19	4.10	4	3.77	23	4.04
Arthralgia	15	3.24	5	4.72	20	3.51
Back pain	13	2.81	7	6.60	20	3.51
Pneumonia	18	3.89	2	1.89	20	3.51
Diarrhoea	16	3.46	2	1.89	18	3.16
Hypertension	14	3.02	3	2.83	17	2.99
Influenza	14	3.02	3	2.83	17	2.99
Insomnia	11	2.38	5	4.72	16	2.81
Hyperlipidaemia	11	2.38	2	1.89	13	2.28
Dyspnoea	7	1.51	5	4.72	12	2.11
Nausea	9	1.94	3	2.83	12	2.11
Oedema peripheral	10	2.16	2	1.89	12	2.11
Pharyngolaryngeal pain	10	2.16	2	1.89	12	2.11

Source: AE3_4, for all TEAE only

Safety conclusions reported in this review are based on the findings shown in these tables.

Comments on Labeling

This reviewer evaluated the **Clinical Trials** subsection of the proposed labeling in **Proposed Labeling Text** section of the NDA submission for accuracy. In general, this reviewer agrees with the sponsor on the efficacy claims for FFIS 20. FFIS 20 was also shown to provide onset of significant bronchodilation (defined as 15% or greater increase from baseline in FEV1 within \approx minutes of oral inhalation after the first dose).

Common adverse events based on AEs reported in 2%+ of the patients include: COPD exacerbation, headache, nausea, cough, diarrhea, dizziness, dyspnoea, dry mouth, nasopharyngitis, upper respiratory tract infection, urinary tract infection, and vomiting. This reviewer suggests that these adverse events be considered for the ADVERSE REACTIONS portion of the labeling.

Conclusions and Recommendations

Efficacy Conclusions:

FFIS 20 at mcg/2mL, BID, was demonstrated to be statistically superior to placebo. FFIS 20 was also shown to provide significant onset of bronchodilation.

Safety Conclusions:

This reviewer's safety evaluation shows that, based on AEs reported in 2%+ of the patients, common adverse events include: COPD exacerbation, headache, nausea, cough, diarrhea, dizziness, dyspnoea, dry mouth, nasopharyngitis, upper respiratory tract infection, urinary tract infection, and vomiting. These AEs were observed in Study 065 and the open label portion of Study 059.

Recommendations:

From a statistician's viewpoint, FFIS 20 at mcg/2mL, BID, has been shown to be efficacious compared to placebo based on data from one Phase 3 confirmatory study (201-065) and based on supporting data from one Phase 2 dose-ranging study (DL-057). If the medical reviewer does not raise serious concerns about the AE findings from these studies, this reviewer would recommend that FFIS 20 at mcg/2mL, BID, be approved.

INTRODUCTION

OVERVIEW

Formoterol fumarate is a long-acting, selective beta2-agonist used in the treatment of patients with asthma and COPD. In the United States, formoterol fumarate is approved as a dry powder capsule formulation for oral inhalation with the Aerolizer® inhaler. It is manufactured by Novartis Pharmaceuticals Corporation and marketed in the US under the brand name Foradil® Aerolizer® 12 mcg (FA) by Schering-Plough Corporation for the maintenance treatment of asthma, for the prevention of exercise-induced bronchospasm in adults and in children at least 5 years of age, and for the maintenance treatment of COPD. Dey, L.P. is developing a Formoterol Fumarate Inhalation Solution (FFIS) to be delivered via nebulizer for the maintenance treatment of COPD (page 1, 2.7.3.1 Background and Overview, summary-clin-efficacy-copd.pdf).

The purpose of this NDA was to demonstrate that FFIS inhalation solution is a safe and effective treatment for COPD in adult patients.

Scope of Statistical Review

Pivotal Efficacy Studies

To confirm that FFIS is efficacious, the sponsor submitted one pivotal Phase 3 study: Study 201-065. A second Phase 3 study, Study 059, was submitted to provide safety assessment only. Study 059, with its original objectives of confirming both efficacy and safety, failed to produce evidence to support efficacy because of randomization errors; therefore, Study 201-065 alone is valid for efficacy evaluation. The problems with Study 059 were communicated to the Agency and the Agency in its September 20, 2005's correspondence agreed with the sponsor's decision of not reporting the efficacy portion of the study in the application. The adequacy of a single Phase 3 pivotal study is further discussed in the section, **Evaluation of additional evidence for efficacy** on page 27 of this report.

Study 201-065 was a randomized, double-blind, double-dummy, placebo and active-controlled 12-week study. The active control was FA 12 mcg BID. The planned statistical comparisons were the following:

1. FFIS 20 mcg BID vs. placebo (The primary analysis)
2. FA 12 mcg BID vs. placebo (A secondary analysis)
3. FFIS 20 mcg BID vs. FA 12 mcg BID (A secondary analysis)

The primary efficacy endpoint was the standardized AUC_{0-12} (L) for FEV_1 measured over a period of 12 hours following the AM dose of study medication at Week 12 (or last available measurement prior to Week 12).

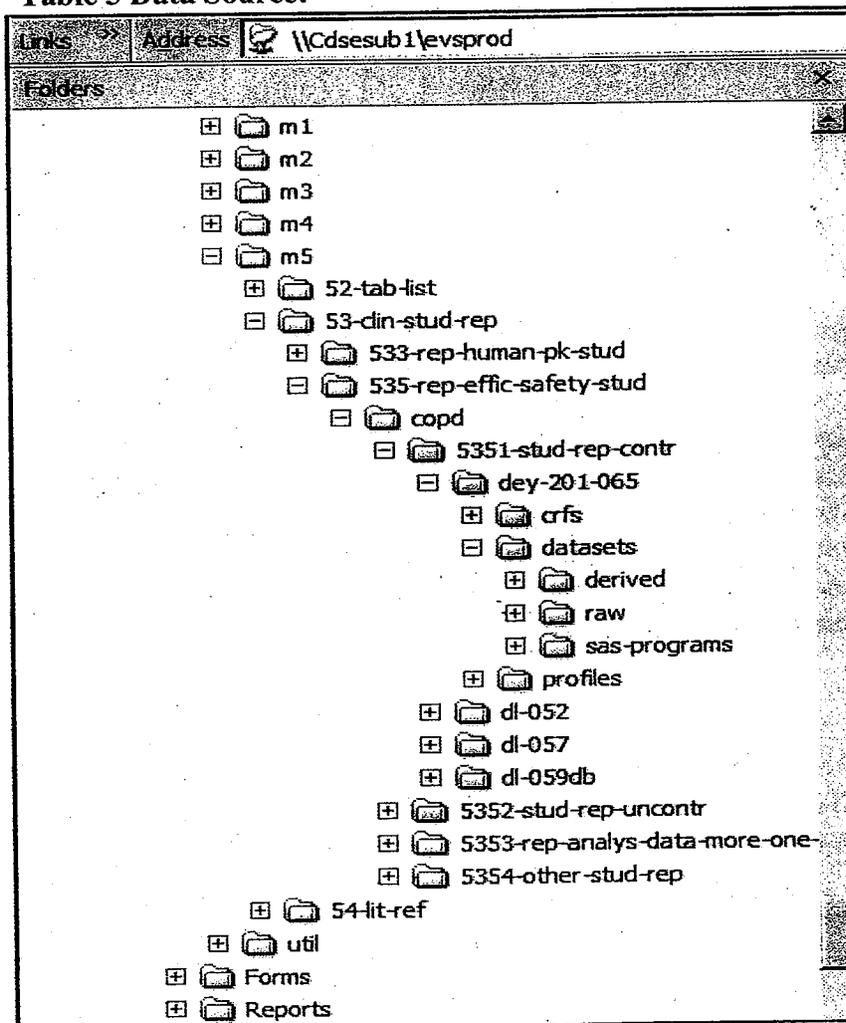
Other Efficacy Studies to Provide Supporting Evidence

Two dose-ranging studies, Studies DL-052 and DL-057 were also evaluated in order to provide supporting evidence for efficacy for the one Phase 3 confirmatory study (201-065).

DATA SOURCES

The sponsor submitted this application including the electronic datasets to the FDA Electronic Document Room (EDR). All the data are in SAS v.5 transport format. The organization of the submitted data is shown in Table 5.

Table 5 Data Source:



STATISTICAL EVALUATION

The efficacy evaluation is primarily based on Study 201-065. Supporting evidence is sought from a Phase 2 dose-ranging study, Study DL-057. In consultation with the MO, safety evaluation is based on Study 201-065 and the open-label period of Study 059. We think it makes sense to analyze the safety data for the open-label period of Study 059, because the treatment assignments for the patients followed the study protocol. According to the protocol,

Patients who were randomized to FFIS 20 mcg during the double-blind phase continued to receive FFIS 20 mcg, and patients who were randomized to placebo in the double-blind phase were switched to FFIS 20 mcg in the open-label phase. Of the patients who were randomized to Foradil 12 mcg during the double-blind phase, half continued on Foradil 12 mcg during open-label treatment while the other half were switched to FFIS 12 mcg. Note that open-label extension treatment was based on the original randomized treatment assignment in the double-blind phase, and not the actual treatment received during double-blind due to the randomization sequence error (page 52, dl-59ol.pdf).

EVALUATION OF EFFICACY

Study Designs and Endpoints

Phase 3 Study 201-065

Study 201-065 is a randomized, double-blind, double-dummy, placebo and active-controlled 12-week trial. It was expected to demonstrate the efficacy and safety of FFIS 20 mcg/2mL, BID, for the treatment of patients with COPD.

Following the screening period, patients were randomized in a 1:1:1 ratio to 12 weeks of double-blind, double-dummy treatment with FFIS 20 mcg (delivered via nebulizer), Foradil® Aerolizer® (FA) 12 mcg, or placebo. In the double-dummy setting, treatment via Aerolizer was always given first followed by treatment with the nebulizer. Albuterol was used as a rescue medication during screening and the double-blind periods.

The planned statistical comparisons were the following:

1 FFIS 20 mcg BID vs. placebo

(The primary analysis)

- 2 FA 12 mcg BID vs. placebo
 3 FFIS 20 mcg BID vs. FA 12 mcg BID

(A secondary analysis)

(A secondary analysis)

The primary objective of the trial was to demonstrate a statistically significant outcome for the effectiveness of FFIS over placebo.

Study visits were scheduled at baseline (the day of randomization), Weeks 4, 8, and 12 (Table 6). FEV₁ measurements were collected before the AM dose of study medication; and at 5 and 30 minutes, 1, 2, 3, 6, 9, and 12 hours post-dose (page 75, 201-065.pdf).

Table 6 Study Time Line (Study 201-065)

STUDY PERIOD		SCREEN	DOUBLE-BLIND TREATMENT			ET	
		DAYS	DAY	WK 4	WK 8	WK 12	EARLY
		-14 TO -4	1	±3DAY	±3DAY	±3DAY	TERM
VISIT		1	2	3	4	5	-
Spirometry	Pre- and Post-Bronchodilator	X					
	12 hour spirometry		X	X	X	X	

Source: Page 56, Section 9.5.1, 201-065.pdf

The primary efficacy variable was the standardized AUC₀₋₁₂ (L) for FEV₁ measured over a period of 12 hours following the AM dose of study medication at Week 12 (or last available measurement prior to Week 12). FEV₁ baseline was defined as the FEV₁ measurement right before the randomization. The primary statistical analysis was based on the ITT patients, comprising all randomized patients who took double-blind study medication and had a baseline evaluation and at least one post-baseline evaluation (Page 72, 201-065.pdf).

The Secondary efficacy variables, quoted from the sponsor's study report (Pages 69-70, 201-065.pdf), included:

- Standardized AUC (L) for FEV₁ measurements performed over 12 hours after the AM dose of study medication on Day 1 and at Weeks 4, 8, and 12 (without last observation carried forward [LOCF]).
- Peak FEV₁ over 12 hours following the AM dose of study medication at Day 1 and Weeks 4, 8 and 12
- Trough FEV₁ at Day 1 and at Weeks 4, 8 and 12
- FEV₁ at all individual time points during the 12-hour post dose period on Day 1 and at Weeks 4, 8 and 12.
- Standardized AUC (L) for FVC measurements performed over 12 hours after the AM dose of study medication on Day 1 and at Weeks 4, 8 and 12.
- Total amount of albuterol rescue medication required on a daily basis was collected.

Secondary efficacy variables also include (Page 70, 201-065.pdf):

Overall total score comprising 3 domain scores based on the St. George's Respiratory Questionnaire (SGRQ)

In the protocol **Section 14.3 Missing Data**, the sponsor said, "For calculating AUC values, LOCF will be used to impute any missing FEV₁ or FVC values at time points later than 2 hours post-dose. Any patient who drops out prior to this time point will not be included in efficacy analyses; they will be included in safety analyses." Differing from the above statement, the sponsor in **Section 11.4.2.2 Handling of Dropouts or Missing Data** of the study report (under the **Section 11 Efficacy Evaluation**) stated that missing data were handled in the following fashion: (1) Missing FEV₁ measurements within the 12-hour assessment period at each visit were not carried forward. Therefore, for patients who did not complete the 12-hour assessment period, the last measured FEV₁ was not carried forward to the 12-hour time point. For example, if the 9-hour time point was the last assessment for a patient at a visit, the AUC was calculated based upon the FEV₁ assessments from time 0 to 9 hours and standardized by the amount of time observed (9 hours). (2) The LOCF method was used for patients with a missing Week 12 FEV₁ AUC₀₋₁₂ (L) value for the primary efficacy analysis. The last observed non-missing post-baseline standardized FEV₁ AUC₀₋₁₂ (L) was the value carried forward (Pages 112-113, 201-065.pdf). This reviewer does not consider such deviation from the protocol to be a major concern. And the use of standardized AUC is common and valid. In Table 18 and Figure 1, this reviewer will show that, across the treatments, at 9 hours post dose and beyond, more than 90% of the FEV₁ values were observed; so missing data was not a major issue.

For the primary efficacy analysis, an analysis of covariance (ANCOVA) model was used to compare the mean treatment differences in standardized FEV₁ AUC₀₋₁₂ (L). The ANCOVA model included fixed effects for **treatment** and **center**, with all 3 treatment groups included. FEV₁Baseline (last FEV₁ measured before first dose of study medication at Day 1) was included in the model as a covariate (Page 75, 201-065.pdf).

As far as the safety-data reporting is concerned, during the screening period, AEs that occurred between signing of consent and the Day 1/Randomization Visit were monitored; however, only serious AEs (SAEs) were collected. During the 12-week double-blind period, all AEs (serious and non-serious) were monitored and collected.

Phase 2 Studies DL-052 and DL-057

Study DL-052 was a randomized, double-blind, double-dummy, 5-way crossover study designed to determine a dose of FFIS that is comparable to Foradil (12 mcg) and to determine safety in adult patients with COPD. Patients were randomized in a 1:1:1:1:1 ratio to one of 5 treatment sequences using a Latin square. Each patient received the following treatments on separate days: placebo; Foradil 12 mcg; Foradil 24 mcg; FFIS 42 mcg; and FFIS 84 mcg. The primary efficacy variable was mean percent change from pre-dose in FEV₁ AUC (0-12h) (page 3, dl-52-section-1-15-report-body.pdf). Note that

the 20 mcg dose of FFIS being proposed for approval is lower than the two doses of FFIS studied in this trial.

Study DL-057 was a randomized, double-blind, double-dummy, 7-treatment crossover study designed to establish equipotent doses of FFIS administered via nebulizer and Foradil 12 mcg administered via Aerolizer. Each patient received the following treatments on separate days: FFIS (2.5, 5, 10, 20, and 40 mcg), Foradil (12 mcg), and placebo. The primary efficacy variable was FEV₁ AUC (page 2, dl-57-section-1-15-report-body.pdf). The two objectives of this trial were to identify the highest dose of FFIS that could be considered comparable to FA12 via a step-down procedure and, secondly, to identify the lowest dose of FFIS that could be considered comparable to FA12 via a confidence interval approach.

Patient Distributions of Demographic and Baseline Characteristics

Phase 3 Study 201-065

This section describes patient disposition, demographic characteristics, protocol compliance, and reasons for early withdrawal from the study.

There were 351 intent-to-treat (ITT) patients in Study 201-065. An ITT patient is a patient randomized who received at least one (1) dose of blinded study medication. In this study, all randomized patients were ITT patients. The numbers of completers and dropouts by time on study are shown in Table 7, below.

Table 7 Numbers and percentages of completers and dropouts by treatment based on efficacy data set EFF_D.XPT (Study 201-065)

Patient Completing (completer)	N by visit	% follow-up	% dropout	
FFIS 20 (N=123)	Day01	123	100%	0%
	Week04	114	93%	7%
	Week08	110	90%	11%
	Week12	106	86%	14%
FA 12 (N=114)	Day01	114	100%	0%
	Week04	101	89%	11%
	Week08	101	89%	11%
	Week12	98	86%	14%
Placebo (N=114)	Day01	114	100%	0%
	Week04	100	88%	12%
	Week08	92	81%	19%
	Week12	84	74%	26%

Source: EFF (based on EFF_D.XPT)

Table 8 shows the numbers and percentages of completers and dropouts by reasons. The overall percentage of retention was 82%, representing an acceptable retention rate, based on this reviewer's experience in seeing similar NDA (in indication, endpoint, etc.).

Table 8 Analysis of retention of patients (Study 201-065)

Reason For Discontinuation (decoded)	Treatment						Total	
	FFIS 20		FA 12		Placebo		N	%
	N	%	N	%	N	%		
Completer	106	86.18	98	85.96	84	73.68	288	82.06
Adverse event(s)	4	3.25	4	3.51	10	8.77	18	5.13
Protocol violation	1	0.81	6	5.26	3	2.63	10	2.85
Lost to follow-up	5	4.07	4	3.51	7	6.14	16	4.56
Withdrawal of consent	4	3.25	2	1.75	4	3.51	10	2.85
Other	3	2.44			6	5.26	9	2.56
Total	123	100.00	114	100.00	114	100.00	351	100.00

Source: DEMO, FINAL_D

Note that the definition of a completer in Table 8 is those patients with Week 12 efficacy data. The sponsor provided an alternative definition of completer as follows:

Completer population: The completer population consisted of patients who received at least 1 dose of study medication, did not have a major efficacy protocol violation, and had a pre-dose and Hour 12 FEV1 measurement at the Week 12 visit (Page 72, 201-065.pdf).

"Completers" thus defined in usual new drug applications are called evaluable or per protocol patients.

The following two tables, Table 9 and Table 10, are populated by the numbers and percentages of patients by treatment and by race and sex. About 87% were whites. The males were a little over 50% of all the ITT patients. The treatment groups were balanced based on these demographic measures.

Table 9 Number of patients by treatment and race (Study 201-065)

Race	Treatment						Total	
	FFIS 20		FA 12		Placebo		N	%
	N	%	N	%	N	%		
Asian					1	0.88	1	0.28
Black	11	8.94	13	11.40	12	10.53	36	10.26
Caucasian	108	87.80	95	83.33	98	85.96	301	85.75
Hispanic	4	3.25	6	5.26	3	2.63	13	3.70
Total	123	100.00	114	100.00	114	100.00	351	100.00

Source: DEMO

Table 10 Number of patients by treatment and sex (Study 201-065)

Sex	Treatment						Total	
	FFIS 20		FA 12		Placebo		N	%
	N	%	N	%	N	%		
Female	52	42.28	53	46.49	49	42.98	154	43.87
Male	71	57.72	61	53.51	65	57.02	197	56.13
Total	123	100.00	114	100.00	114	100.00	351	100.00

Source: DEMO

Table 11 Analysis of patient-age distribution by treatment (Study 201-065)

Treatment	#Patients	Mean	Min	Max	Lower quartile	Upper quartile
FFIS 20	123	61.84	40.00	83.00	56.00	67.00
FA 12	114	63.02	44.00	86.00	57.00	70.00
Placebo	114	63.49	42.00	86.00	57.00	70.00
Total	351	62.76	40.00	86.00	57.00	69.00

Source: DEMO

The average patient age was over 60 years old (Table 11). The age variation among the treatment groups appeared to be small.

The baseline was defined as the pre-dosing FEV₁ on the day of randomization. The following tables show the baseline FEV₁ by treatment. The baseline FEV₁ was used in the sponsor's statistical analyses as a covariate. The baseline average scores appear to be balanced across the treatment groups.

Table 12 Baseline FEV₁ (Study 201-065)

Treatment	#Patients	Mean	Std	Min	Max	Median
FFIS 20	123	1.32	0.43	0.47	2.61	1.27
FA 12	114	1.28	0.39	0.49	2.54	1.21
Placebo	114	1.32	0.48	0.45	2.56	1.25

Source: BASELINE

Phase 2 Studies DL-052 and DL-057

Patients' demographic characteristics for these Phase 2 studies are not described here in great details. This reviewer only wants to point out the similarities in demographic characteristics between Study DL-057 and Study 201-065.

In Study DL-057, males account for about 62% of the patients, as compared with a 56% in Study 201-065. In Study DL-057, whites account for about 90% of the patients, as compared with a 86% in Study 201-065. In Study DL-057, the average age is 56 years old, a little younger than the average of 63 years in Study 201-065. More details about the patients' demography can be found in the sponsor's Table 11.2.1 (page 71, dl-57-section-1-15-report-body.pdf).

Evaluation of Efficacy

Phase 3 Study 201-065

The primary statistical analysis was based on a comparison between FFIS and placebo. The following comparisons are considered secondary:

- FA 12 mcg BID vs. placebo (Secondary analysis)
- FFIS 20 mcg BID vs. FA 12 mcg BID (Secondary analysis)

The significance level was 0.05 for the two-sided T-test.

For the primary efficacy analysis, an analysis of covariance (ANCOVA) model was used to test for mean treatment differences in standardized FEV₁ AUC₀₋₁₂ (L). The ANCOVA model included fixed effects for **treatment** and **center (pooled)**. FEV₁Baseline (last FEV₁ measured before first dose of study medication at Day 1) was included as a covariate in the model (Page 75, 201-065.pdf). Some centers were pooled in order to obtain a minimum of 15 patients per pooled site (Page 113, 201-065.pdf). The pooling algorithm was specified in the SAP.

This reviewer verified the sponsor's analysis based on the sponsor's data. The sponsor's efficacy data, EFF_D.xpt was restructured (named EFF2) to suit this reviewer's review tool. The following tables show selected results from the ANCOVA using the following MIXED procedure in SAS:

```
ods select Nobs ClassLevels Tests3 LSMeans Diffs;
proc mixed data=n2200765.eff2 (where=(visit='Week12'));
class treatment center_pooled;
model aucfev=treatment center_pooled baseline/e3;
lsmeans treatment/CL pdiff alpha=0.05;
```

This reviewer used the above program to analyze the Week-12 AUC of FEV₁ with LOCF estimate for missing visits. The LOCF for missing data was specified in the sponsor's protocol. All ITT patients were included in the analysis. Selected results from the ANCOVA are shown in the following tables.

Table 13 Average Week-12 FEV₁ AUC for ITT patients

TREATMENT	#PATIENTS	MEAN	STD	MIN	MAX	MEDIAN
FFIS 20	123	1.51	0.52	0.50	3.52	1.45
FA 12	114	1.49	0.46	0.56	2.69	1.40
Placebo	114	1.33	0.57	0.57	3.35	1.23

Source: EFF2 (LOCF)

Table 14 Number of patients included in ANCOVA (ITT patients)

Number of Observations	
Number of Observations Read	351

Source: EFF2 (LOCF)

Table 15 Significance test of effects in the linear model (ITT patients)

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	2	330	22.46	<.0001
CENTER POOLED	17	330	1.98	0.0120
BASELINE	1	330	901.30	<.0001

Source: EFF2 (LOCF)

Table 16 LS means, std., 95% confidence intervals, and significant tests of FEV₁ AUC at Week 12 (ITT patients)

Least Squares Means								
Treatment	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
FA 12 mcg	1.51	0.024	330	62.49	<.0001	0.05	1.46	1.56
FFIS 20 mcg	1.49	0.023	330	64.33	<.0001	0.05	1.45	1.54
Placebo	1.31	0.024	330	54.34	<.0001	0.05	1.26	1.35

Source: EFF2 (LOCF)

Table 17 Comparisons between treatments (ITT patients)

Treatment comparison		Estimate	Standard Error	DF	t Value	Pr > t	Lower	Upper
Applying LOCF								
FA 12 mcg	FFIS 20 mcg	0.020	0.033	330	0.59	0.55	-0.046	0.085
FA 12 mcg	Placebo	0.21	0.034	330	6.04	<.0001	0.14	0.27
FFIS 20 mcg	Placebo*	0.19	0.033	330	5.58	<.0001	0.12	0.25
Using available data ¹								
FA 12	FFIS 20	0.018	0.035	266	0.52	0.60	-0.050	0.086
FA 12	Placebo	0.23	0.037	266	6.39	<.0001	0.16	0.31
FFIS 20	Placebo*	0.22	0.036	266	6.01	<.0001	0.15	0.29

Source: EFF (available data), EFF2 (LOCF)

*: Primary comparison.

¹ The results here are generated from the following SAS program:
options mstored sasstore=sasuser fmtsearch=(work n22007);
Data test;
set n2200765.eff; /* available data */
if visit='Week12' and baseline^=. and aucfev^=.;
run;
%freq(completer,distinct=patient,libref=,memname=test);

Based on the analysis, above, FFIS 20 proved to be superior to placebo ($P < 0.001$). Additionally, FA 12 proved to be superior to placebo ($p < 0.01$); the difference between FFIS 20 and FA 12 appeared to be small. The results based on available data and LOCF are shown to be consistent.

It is important to evaluate the appropriateness of the use of only observed data to compute AUC of FEV₁. Table 18 shows the number of observations (patients) at each time point. The number of observations decreases slightly over time (in hours) within each visit. About 80-90% of the patients have data at Hour 12 indicating that AUC's computed from these data were based on complete data for a majority of patients.

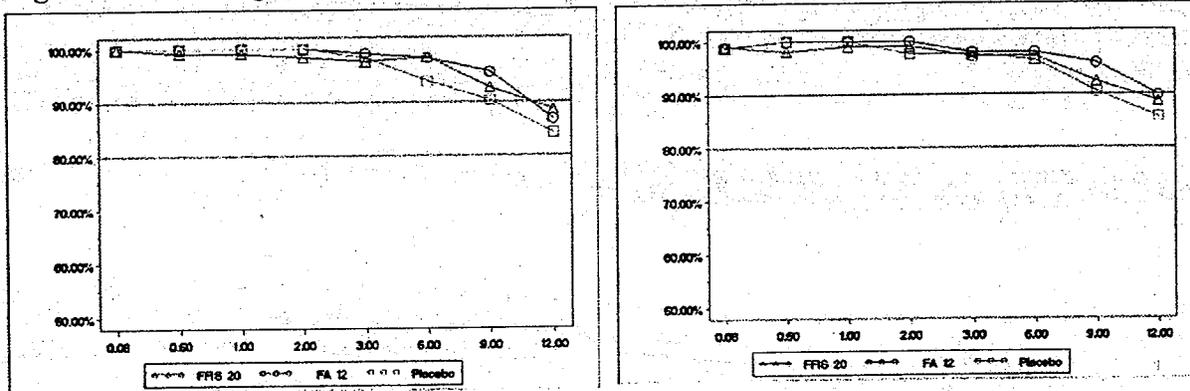
Table 18 Number of observations by time and treatment

Visit/Hour		FFIS 20	FA 12	PLACEBO
		#observations	#observations	#observations
Day 1	0.08	123	114	114
	0.50	122	114	114
	1.00	122	114	114
	2.00	121	114	114
	3.00	120	113	112
	6.00	121	112	107
	9.00	114	109	103
	12.00	109	99	96
Week 4	0.08	114	101	99
	0.50	114	101	98
	1.00	114	101	99
	2.00	114	101	97
	3.00	111	101	94
	6.00	111	98	94
	9.00	107	95	87
	12.00	102	91	85
Week 8	0.08	109	100	90
	0.50	109	100	89
	1.00	109	100	90
	2.00	109	100	90
	3.00	107	99	89
	6.00	106	99	85
	9.00	102	96	79
	12.00	99	92	74
Week 12	0.08	105	97	83
	0.50	104	98	84
	1.00	105	98	84
	2.00	105	98	82
	3.00	103	96	82
	6.00	103	96	81
	9.00	98	94	76
	12.00	94	88	72

Source: Spiro

Figure 1 depicts the percentages in Table 18, above. The Day 1 and Week 12 data show that more than 90% of the observations include at least 9 hours of FEV₁ measurements, enabling a quite accurate AUC calculation.

Figure 1 Percentages of observations by time and treatment



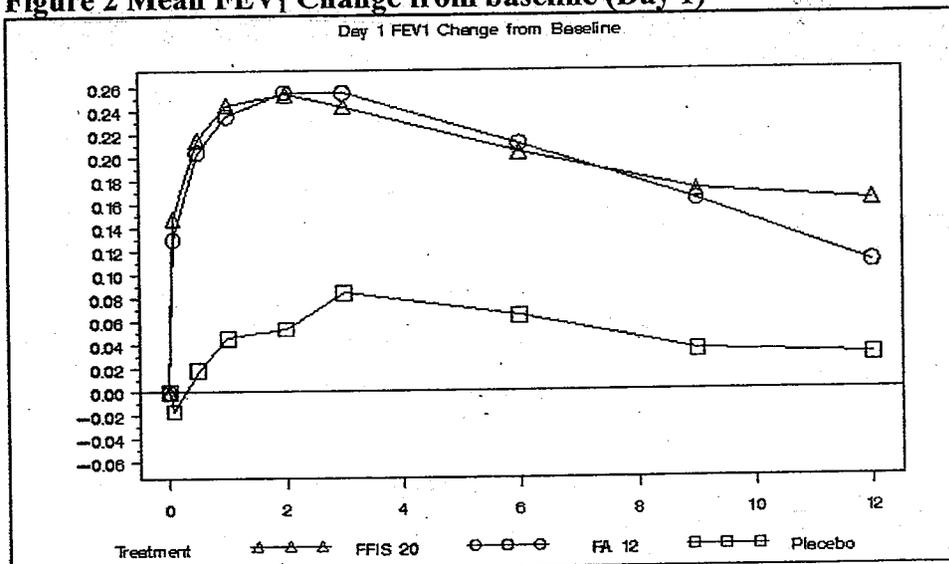
Day 1

Week 12

Source: SPIRO_PCTOBS (Day 1 and Week 12)

The following graphs (Figure 2 through Figure 5) depict FEV₁ changes from baseline (shown on vertical axis) over time, by treatment and visit. The horizontal axis represents time in hours.

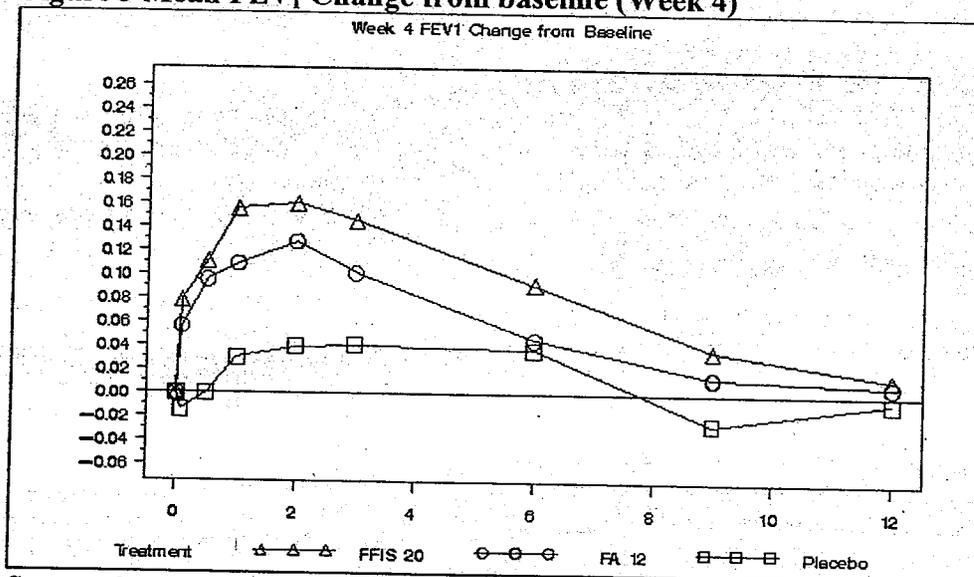
Figure 2 Mean FEV₁ Change from Baseline (Day 1)



Source: SPIRO

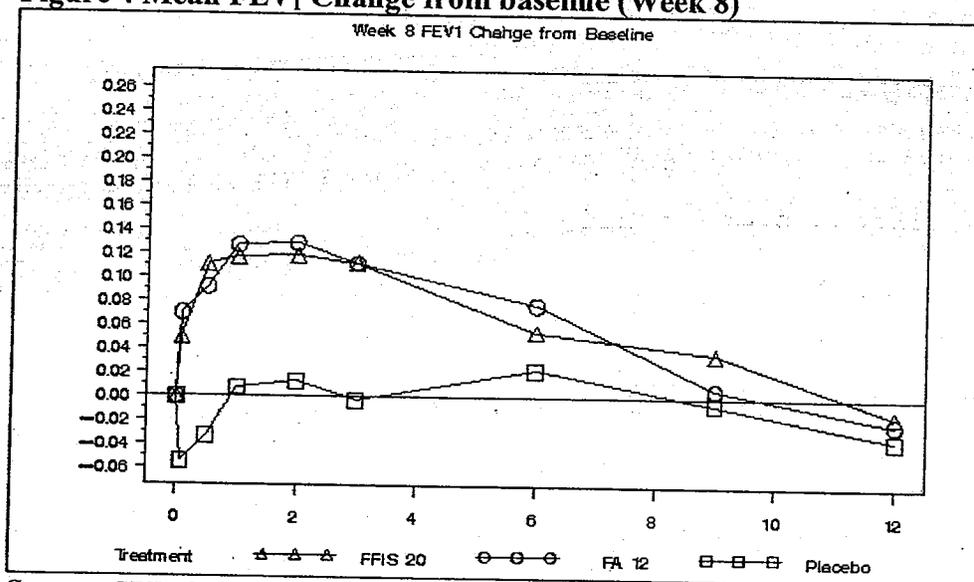
The FEV₁ changes from baseline at Day 1 appear greater in the FFIS and FA groups than in placebo group. FEV₁ changes in the FFIS and FA groups reach peak values at about 2 hours post dose. The difference between the FFIS and FA groups appears to be small.

Figure 3 Mean FEV₁ Change from baseline (Week 4)



Source: SPIRO

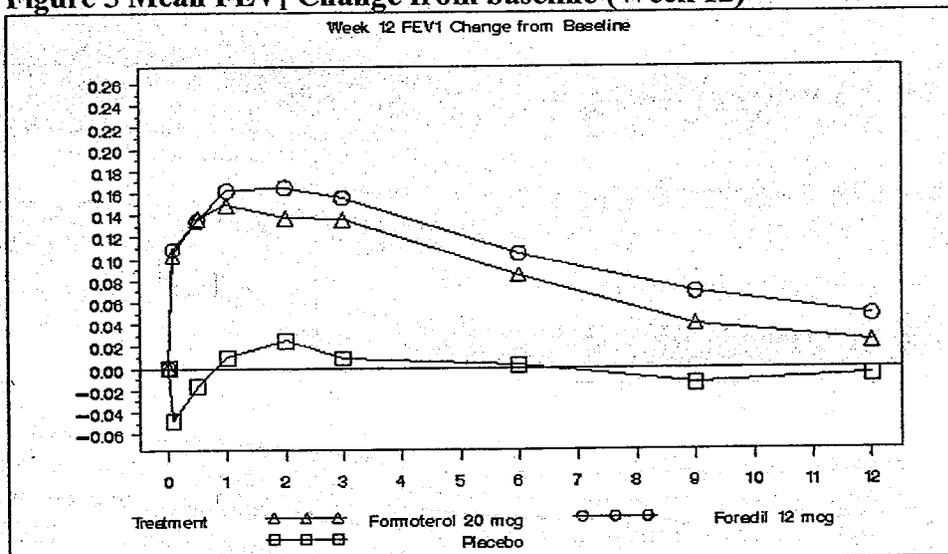
Figure 4 Mean FEV₁ Change from baseline (Week 8)



Source: SPIRO

The FEV₁ changes from baseline at Weeks 4 and 8 do not peak as high as at Day 1, though they appear to be greater than that in the placebo group.

Figure 5 Mean FEV₁ Change from baseline (Week 12)

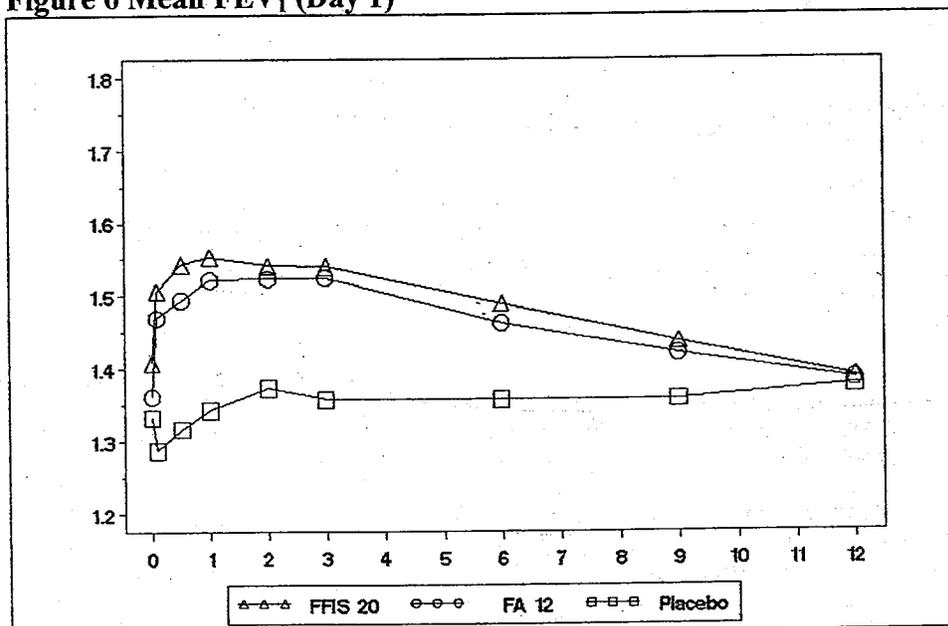


Source: SPIRO

The FEV₁ changes from baseline at Week 12 show greater values in the FFIS and FA groups than in placebo group. FEV₁ changes in the FFIS and FA groups reach peak values at about 1-2 hours post dose. The difference between the FFIS and FA groups appears to be small.

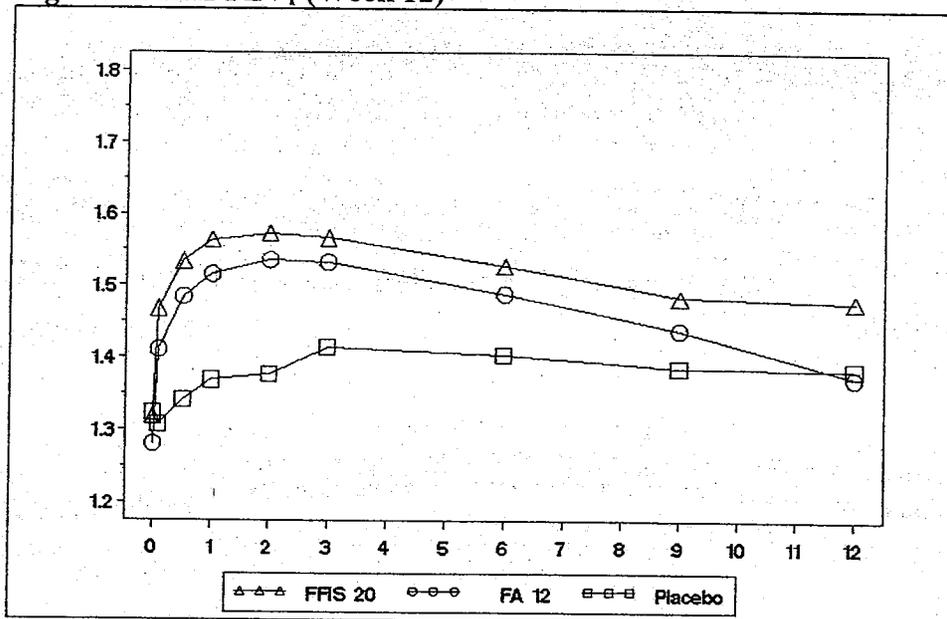
The following two graphs depict FEV₁ (shown on vertical axis) over time, by treatment and visit. The horizontal axis represents time in hours.

Figure 6 Mean FEV₁ (Day 1)



Source: SPIRO

Figure 7 Mean FEV₁ (Week 12)



Source: SPIRO

The FEV₁ at Week 12 show greater values in the FFIS and FA groups than in placebo group. FEV₁ values in the FFIS and FA groups reach peak values at about 1-2 hours post dose. The difference between the FFIS and FA groups appears to be small. The results shown in Figures 3 through 8 clearly illustrate the significant effect of FFIS on FEV₁ over time.

Analysis of Onset of Action (Study 201-065)

The sponsor in the package insert stated that FFIS 20 mcg/2 mL “was shown to provide onset of significant bronchodilation (defined as 15% or greater increase from baseline in FEV₁ within 5 minutes of oral inhalation after the first dose).” Note that the variable describing onset of action variable was not part of the secondary efficacy variables defined in the study protocol, rather was included in a supplemental analysis.

b(4)

A significant onset of action is defined by the sponsor as “15% or greater increase from baseline in FEV₁ within 5 minutes of oral inhalation after the first dose.” In Section 11.4.1.3.1 **Post-Dose Bronchodilation** of the study report, the sponsor stated, “Post-dose bronchodilation was defined as the number and percentage of patients who achieved a 15% or greater increase in FEV₁ from baseline (pre-dose FEV₁) at the 5 minute post-dose assessment.” This reviewer analyzed the onset of action based on the number of patients who cross the “15% + 5-minutes” threshold and based on the Day 1 and Week 12 data (a subset of SPIRO_D.XPT). This analysis leads to the following results:

b(4)

Table 19 Number of patients by treatment and onset of action (Study 201-065)

Table Of Treatment By Onset-of-action				
	Treatment	Onset of action (crossing the 15% + 5min threshold)		Total
		Not Crossed	Crossed	
Week 12	FFIS 20	81	25	106
	Placebo	80	4	84
	Total	161	29	190
Day 1	FFIS 20	85	38	123
	Placebo	105	9	114
	Total	190	47	237

Source: Spiro_D

For the Week 12 data, note that 25 patients reached 15% or greater increase from baseline in FEV₁ within 5 minutes of oral inhalation after the first dose in the FFIS group, compared with 4 patients in placebo group. Significantly more patients treated with FFIS were able to achieve a clinically important onset of action over those treated with placebo (Based on Fisher's Exact Test, for the Week 12 data, p=0.0004, and for the Day 1 data, p=0.00000547).

Evaluation of effectiveness based on not-standardized AUC of FEV₁

To examine the robustness of the test based on standardized AUC of FEV₁, the following analysis is based on not-standard AUC of FEV₁, which was derived using hourly FEV₁ values by this reviewer rather than the values of AUC of FEV₁ provided by the sponsor.

Table 20 Significance test of effects in the linear model (based on reviewer-derived AUC of FEV₁)

Type 3 Tests Of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
TREATMENT	2	266	18.36	<.0001
CENTER POOLED	17	266	1.90	0.0183
BASELINE	1	266	530.10	<.0001

Source: SPIROAUC

Table 21 LS means, std., 95% confidence intervals, and significant tests of FEV₁ AUC at Week 12 (based on reviewer-derived AUC of FEV₁)

Least Squares Means								
Treatment	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
FA 12	17.85	0.36	266	50.05	<.0001	0.05	17.14	18.55
FFIS 20	17.51	0.34	266	51.33	<.0001	0.05	16.84	18.18
Placebo	14.94	0.38	266	39.11	<.0001	0.05	14.19	15.70

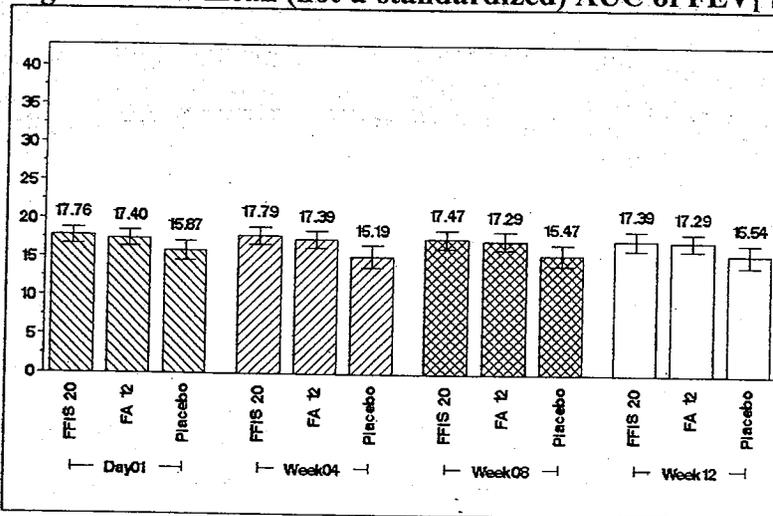
Source: SPIROAUC

Table 22 Comparisons between treatment groups (based on reviewer-derived AUC of FEV₁)

Differences Of Least Squares Means									
Treatment	Treatment	Estimate	Standard error	Df	T value	Pr > t	Alpha	Lower	Upper
FA 12	FFIS 20	0.33	0.49	266	0.68	0.4957	0.05	-0.63	1.30
FA 12	Placebo	2.90	0.52	266	5.58	<.0001	0.05	1.88	3.93
FFIS 20	Placebo	2.57	0.51	266	5.04	<.0001	0.05	1.56	3.57

Source: SPIROAUC

Figure 8 Raw mean (not-a-standardized) AUC of FEV₁ by treatment and visit



Source: EFF

Figure 8, above, depicts the mean AUC of FEV₁ by treatment and visit. AUCs were computed with trapezoid method using SAS procedure EXPAND. This graph enables a visualization of the findings in Table 22.

Based on the analysis, above in Table 21, Table 22 and Figure 8, FFIS 20 proved to be superior to placebo (P<0.001). Additionally, FA 12 proved to be superior to placebo (p<0.01); the difference between FFIS 20 and FA 12 appeared to be small. These results are consistent with those based on standardized AUC of FEV₁ as presented in the

sponsor's study report. This reviewer does not consider the use of standardized AUC of FEV₁ a concern of misleading conclusion.

The following SAS program produces Table 22.

```
options mstored sasstore=sasuser fmtsearch=( work n2200765);
ods select Nobs ClassLevels Tests3 LSMeans Diffs;
proc mixed data=n2200765.eff(where=(visit='Week12'));
class treatment center_pooled;
model AUC=treatment center_pooled baseline/e3;
lsmeans treatment/CL pdiff alpha=0.05;
run;
```

The derived variable, AUC, was computed using SAS PROC EXPAND. A portion of this reviewer's SAS program is quoted as follows.

```
**** Compute area by trapezoid rule ****;
proc expand data=indata1 out=&out method=join;
  convert y=total/observed=(beginning,total) transformout=(sum);
  %if %superq(byvar) ^= %then %do;
    by &byvar;
  %end;
  id x;
run;
**** program: nd1.program\mkMymacr\auc.sas ****;
```

Evaluation of effectiveness based on selected subgroups

The purpose for the following subgroup analyses is to show consistency of treatment effect across groups of selected demographic characteristics. Such analyses are of exploratory nature. In other words, rigorous inferential analyses based on p-values and confidence intervals are not appropriate.

Table 23 Subgroup analyses by selected demographic characteristics

DIFFERENCES OF LEAST SQUARES MEANS										
	Treatment	Treatment	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper
Female	FA 12	FFIS 20	0.041	0.033	133	1.23	0.2205	0.05	-0.025	0.10
	FA 12	Placebo	0.21	0.033	133	6.41	<.0001	0.05	0.14	0.28
	FFIS 20	Placebo	0.17	0.034	133	5.07	<.0001	0.05	0.10	0.24
Male	FA 12	FFIS 20	-0.002	0.055	176	-0.05	0.9604	0.05	-0.11	0.10
	FA 12	Placebo	0.17	0.056	176	3.15	0.0019	0.05	0.066	0.29
	FFIS 20	Placebo	0.18	0.054	176	3.33	0.0011	0.05	0.073	0.28
Non-whites	FA 12	FFIS 20	-0.020	0.14	35	-0.14	0.88	0.05	-0.32	0.27
	FA 12	Placebo	0.28	0.13	35	2.01	0.05	0.05	-0.0029	0.56
	FFIS 20	Placebo	0.30	0.15	35	1.95	0.05	0.05	-0.013	0.61
Whites	FA 12	FFIS 20	0.016	0.032	280	0.50	0.6199	0.05	-0.047	0.080
	FA 12	Placebo	0.18	0.033	280	5.59	<.0001	0.05	0.12	0.25
	FFIS 20	Placebo	0.17	0.032	280	5.30	<.0001	0.05	0.10	0.23
Patient 65 and younger	FA 12	FFIS 20	-0.0042	0.050	195	-0.08	0.9330	0.05	-0.10	0.094
	FA 12	Placebo	0.18	0.052	195	3.47	0.0006	0.05	0.078	0.28
	FFIS 20	Placebo	0.18	0.050	195	3.71	0.0003	0.05	0.087	0.28
Patient 66 and older	FA 12	FFIS 20	0.070	0.038	115	1.82	0.0708	0.05	-0.0061	0.14
	FA 12	Placebo	0.22	0.037	115	6.10	<.0001	0.05	0.15	0.30
	FFIS 20	Placebo	0.15	0.039	115	4.01	0.0001	0.05	0.079	0.23

Source: EFF2 (LOCF)

The subgroup analyses, above, showed that for the selected demographic characteristics, the treatment effects appear to be consistent across subgroups.

Evaluation of additional evidence for efficacy

Study 201-065 was the only Phase 3 confirmatory clinical study for efficacy. The other Phase 3 confirmatory clinical study, Study 059, did not produce meaningful efficacy results. There sponsor explained, "Due to a treatment sequence error that occurred during the double-blind treatment phase, most patients did not receive initial double-blind treatment according to the randomization schedule (page 4, 2.0 SYNOPSIS, dl-059.pdf)." Consequently, no efficacy portion of Study 059 was reported. Based on the Agency's comments of 9/20/2005 regarding supportive information (see below) this reviewer evaluated the results from two Phase 2 dose-finding studies, Studies 52 and 57 to determine whether these studies provided additional evidence of efficacy.

1.2.5 Dey is proposing to analyze data from the pivotal efficacy study, Clinical Study 201-065, according to the Statistical Analysis Plan provided in Section 7. Does the Agency agree that the resulting analyses will support NDA approval?

FDA Response:

The Division agrees with the methods prescribed in the statistical analysis plan for Study 201-065. Regarding approvability, the results of this statistical analysis, along with the other information submitted in the NDA, will be carefully evaluated by the Division as part of the NDA review process.

Phase 2 Studies DL-052 and DL-057

Study 52

Study 52 was a Phase 2 dose-finding study. The characteristics of Study 52 are quoted from the sponsor's report as follows.

Primary Objectives:

The primary objective of this study was to define a comparable dose of formoterol fumarate inhalation solution (FFIS) to 12 mcg Foradil and determine safety in patients with stable chronic obstructive pulmonary disease (COPD).

Methodology:

This study used a randomized, double-blind, double-dummy, 5-way crossover design to determine a dose of FFIS that is comparable to Foradil (12 mcg) and to determine safety in adult patients with COPD. Patients were randomized in a 1:1:1:1:1 ratio to receive each of the following treatments on separate days: placebo; Foradil 12 mcg; Foradil 24 mcg; FFIS 42 mcg; and FFIS 84 mcg.

The primary efficacy variable was AUC_(0-12h) of the mean percent change in FEV₁ for each treatment following single-dose administration of study medication.

To determine whether this study can provide additional support of the only available Phase 3 confirmatory study, Study 201-065, please consider the following difference between this study and Study 201-065:

- The lowest dose regimen of FFIS was 42 mcg in this study, while the only dose of FFIS used in Study 201-065 was 20 mcg.

Therefore, the evidence this study provided does not lend direct support to the efficacy seen in Study 201-065. For this reason, this reviewer did not reanalyze the data of Study 52. Only the sponsor's results are presented here.

For the purposes of reference, this reviewer notes that this study did demonstrate a positive dose-response trend. The sponsor concluded, "AUC_(0-12h) of the mean percent change was numerically greater with each active treatment versus placebo. Within the active treatments, AUC_(0-12h) of the mean percent change ranged from +131%*hours with Foradil 12 mcg to +228%*hours with FFIS 84 mcg." More details can be found in the following table.

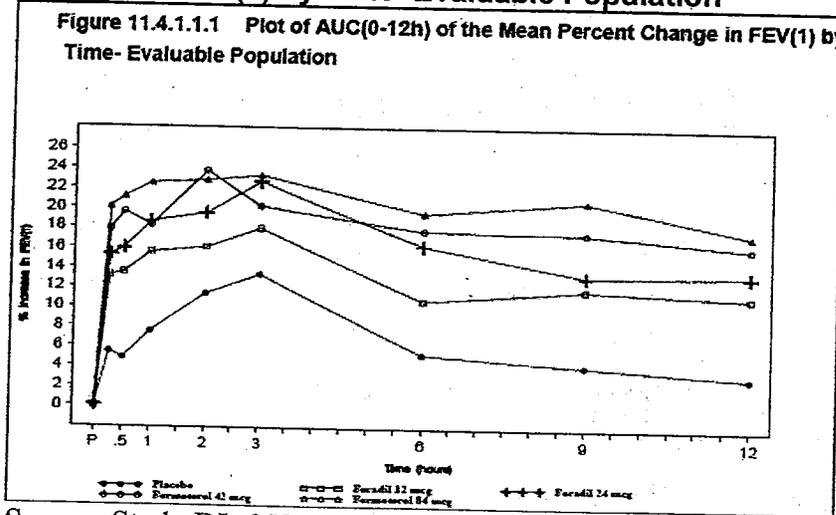
(The sponsor's) Table 11.4.1.1.1 AUC_(0-12h) of the Mean Percent Change in FEV₁(1): Evaluator Population

	TREATMENT				
	PLACEBO	FORADIL 12 MCG	FORADIL 24 MCG	FFIS 42 MCG	FFIS 84 MCG
	N=35	N=35	N=35	N=35	N=35
AUC (0-12h) of Mean Percent Change in FEV ₁ (%*hours)					
Mean (SD)	73 (147)	131 (127)	165 (149)	191 (164)	228(256)
Min, Max	-58, 680	-139, 440	-98, 533	-158, 557	-117, 1234

Source: Study DL-052 report

The following graph further illustrates the dose-response relationship.

(The sponsor's) Figure 11.4.1.1.1 Plot of AUC(0-12h) of the Mean Percent Change in FEV₁(1) by Time-Evaluator Population



Source: Study DL-052 report

In conclusion, the evidence this study provided does not provide direct support for the efficacy of FFIS20 demonstrated in Study 201-065. The relevance of the results of Study DL-052 to the results of Study 201-065 is considered weak.

Study 57

Study 57 was a Phase 2 dose-finding study. The characteristics of Study 57 are quoted from the sponsor's report as follows.

Overall Study Design and Plan: Description

This study used a multi-center, randomized, double-blind, double-dummy, 7-way crossover design to help establish equipotent doses of FFIS administered via pneumatic nebulizer and Foradil (12 mcg) administered via the Aerolizer. Each patient received 1 of the following 7 treatments (A, B, C, D, E, F, or G) in a random order on separate days:

Treatments by Group

GROUP	TREATMENT	DOSE*
A	FFIS + Placebo Aerolizer	2.5 mcg
B	FFIS + Placebo Aerolizer	5 mcg
C	FFIS + Placebo Aerolizer	10 mcg
D	FFIS + Placebo Aerolizer	20 mcg
E	FFIS + Placebo Aerolizer	40 mcg
F	Foradil Aerolizer + Placebo Inhalation Solution	12 mcg
G	Placebo Aerolizer + Placebo Inhalation Solution	N/A

Primary Efficacy Variable

The primary efficacy variable was the FEV₁ AUC_(0-12h) for each treatment following single-dose administration of study medication.

The statistical analysis was done by comparing each dose of FFIS (40, 20, 10, 5, and 2.5 mcg) with FA 12 mcg in descending order of FFIS dose. The sponsor described the statistical testing procedures as follows:

A confidence interval (CI) approach was used to determine the lowest dose of FFIS that was comparable to Foradil (12 mcg). This was accomplished by demonstrating near equivalency by testing each dose of FFIS, from highest to lowest, against Foradil (12 mcg) until a dose of FFIS just below and just above Foradil was found. A 90% CI was constructed on the log-transformed ratio of the treatment means. Equivalency was defined as the 90% CI that fell within a range of 80% to 125%. For the dose just above Foradil percent mean change, the upper bound of the 90% CI might have exceeded the 125% limit slightly as long as the lower bound was below the mean value and within the 80 to 125% range. (Page 65, dl-57-section-1-15-report-body.pdf)

Please note that comparisons between FFIS doses and FA12 thus defined are not the same statistical comparison planned in Study 201-065. A significantly positive finding of effectiveness of FFIS20, if demonstrated in this study, may add some assurance to the significant efficacy finding of FFIS in Study 201-065.

The sponsor's analysis was based on FEV₁ AUC_(0-12h). Based on this reviewer's reading of the data-definition table (define.pdf), an analysis of the data file (efficacy.xpt), it is determined that the variable used in the primary analysis (named IAUCT) is, in fact, the AUC_(0-12h) of the change from **pre-dosing** FEV₁ other than FEV₁. This explains why in the table, below, some numbers appear as negative. The sponsor failed to clearly explain the definition of FEV₁ used in the study report.

The sponsor's analysis is summarized in the following table and bar graph from the sponsor's report:

(The sponsor's) Table 11.4.1.1.1 FEV (1) AUC (0-12h): Completer Population

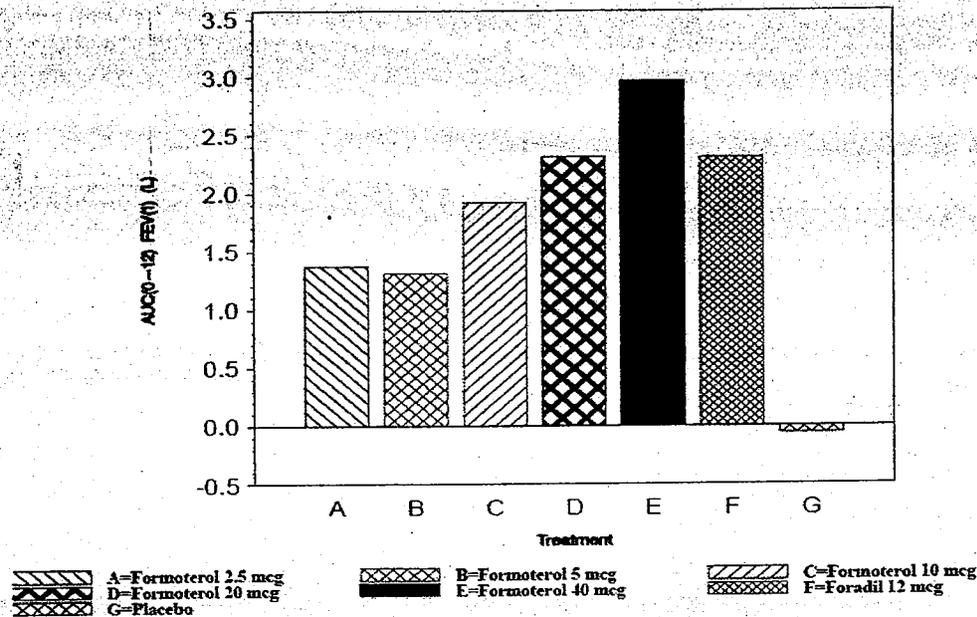
	TREATMENT						
		FA	FFIS	FFIS	FFIS	FFIS	FFIS
	PCO	12 MCG	2.5 MCG	5 MCG	10 MCG	20 MCG	40 MCG
	N=47	N=47	N=47	N=47	N=47	N=47	N=47
Mean (SD)	-0.1 (2.4)	2.3 (2.2)	1.4 (2.5)	1.3 (2.1)	1.9 (2.0)	2.3 (2.8)	3.0 (2.4)
Min, Max							

b(4)

In addition to the above results, the sponsor reported total FEV₁ of 19.9 for FFIS 20 and 17.5 for placebo; a difference of about 2.4. Note that this difference is similar to the difference computed by this reviewer for Study 201-065 where a difference of 2.9 was

seen for the total (non-standardized) FEV₁ (see Table 21 and Table 22). So, consistent results were seen for the FFIS dose of 20 mcg across two studies.

(The sponsor's) Figure 11.4.1.1.1 Mean FEV₁ AUC₍₀₋₁₂₎ (Lxhr): Completer Population



Here, Treatment D is FFIS 20 mcg.

The test statistic was based on the between-treatment comparisons of log-transformed mean FEV₁ AUC_(0-12h), according to the protocol:

$$\begin{aligned} & \text{Log}(\text{Mean FEV}_1 \text{ AUC of FFIS} / \text{Mean FEV}_1 \text{ AUC of FA}) \\ & = \text{log}(\text{Mean FEV}_1 \text{ AUC of FFIS}) - \text{log}(\text{Mean FEV}_1 \text{ AUC of FA}) \end{aligned}$$

CI's were used to assess between-treatment equivalency for all FFIS doses versus Foradil 12 mcg. Equivalency was defined as 90% CIs within the range of 80% to 125%. Within this range, FFIS doses of 10 mcg and 20 mcg most closely approximated Foradil 12 mcg in that the 90% CIs enclosed 100% (100% implies equivalence). A hierarchical testing procedure was used whereby the highest dose of FFIS was compared to Foradil, followed by the next highest dose, until the first non-significant p-value was obtained as an indicator of equivalence. Using the hierarchical testing procedure, FFIS 20 mcg was the first dose determined to be not significantly different from Foradil (p=0.1721), and the testing procedure ended at this dose based on the p-value.

(The sponsor's) Table 11.4.1.1.2 Between-Treatment Comparisons of Log-Transformed FEV₁ AUC (0-12h): Completer Population

TRANSFORMED FEV ₁ AUC (0-12H): COMPLETER POPULATION				
COMPARATOR	REATMENT	EQUIVALENCY RESULTS		
		EXPONENTIATED MEAN RATIO (%)	90% CI*	P-VALUE**
FA 12 mcg	FFIS 40 mcg	105	103, 108	0.0011
FA 12 mcg	FFIS 20 mcg	102	100, 105	0.1721
FA 12 mcg	FFIS 10 mcg	100	97, 102	NA
FA 12 mcg	FFIS 5 mcg	97	94, 99	NA
FA 12 mcg	FFIS 2.5 mcg	96	93, 98	NA

* Equivalency was established if the 90% CIs fell within the range of 80% to 125%.

** P-values were based on a step-down procedure comparing successive mean changes between treatments.

Based on the evaluation of this study, this reviewer concludes:

- A positive dose-response relationship was demonstrated for FFIS.
- Numerically and statistically, FFIS 40 mcg appears to be more effective than FA12 mcg in terms of AUC of FEV₁.
- FFIS 20 mcg is more effective than placebo and appears to be comparable to FA 12 mcg.

In conclusion, Study 57 provided additional evidence in support of efficacy of the 20 mcg dose of FFIS.

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Evaluation of Safety

Phase 3 Study 201-065

In Study 201-065, a total of 184 AEs based on MedDRA preferred term were reported. Table 24 shows the numbers and percentages of patients by AE in MedDRA preferred terms for AEs reported in 2%+ of the patients. For a complete list of AEs, see the appendix. Note that the AEs with a gray background are the AEs reported in both Study 201-065 (Table 24) and Study 059 (open label portion, Table 25)

Table 24 Selected AE findings (Study 201-065)

AEs presented as: AEPTTXX; Group totals for FFIS, FA, and placebo: 123, 112, and 114	TREATMENT						N	%
	FFIS 20		FA 12		PLACEBO			
	N	%	N	%	N	%		
Chronic obstructive airways disease exacerbated	5	4.07	7	6.25	9	7.89	21	6.02
Headache	7	5.69	5	4.46	8	7.02	20	5.73
Nausea	6	4.88	4	3.57	3	2.63	13	3.72
Cough	2	1.63	5	4.46	5	4.39	12	3.44
Diarrhea	6	4.88	2	1.79	4	3.51	12	3.44
Dizziness	3	2.44	8	7.14	1	0.88	12	3.44
Dyspnoea	3	2.44	3	2.68	4	3.51	10	2.87
Dry mouth	4	3.25	2	1.79	2	1.75	8	2.29
Nasopharyngitis	4	3.25	2	1.79	2	1.75	8	2.29
Upper respiratory tract infection	2	1.63	3	2.68	2	1.75	7	2.01
Urinary tract infection	2	1.63	2	1.79	3	2.63	7	2.01
Vomiting	3	2.44	2	1.79	2	1.75	7	2.01

Source: AE1

Phase 3 Study 059: Open-label period

The treatment assignment for the open-label period is described as follows.

9.4.1 Treatments Administered

Patients who were randomized to FFIS 20 mcg during the double-blind phase continued to receive FFIS 20 mcg, and patients who were randomized to placebo in the double-blind phase were switched to FFIS 20 mcg in the open-label phase. Of the patients who were randomized to Foradil 12 mcg during the double-blind phase, half continued on Foradil 12 mcg during open-label treatment while the other half were switched to FFIS 12 mcg. Note that open-label extension treatment was based on the original randomized treatment assignment in the double-blind phase, and

not the actual treatment received during double-blind due to the randomization sequence error.

More details can be found in the sponsor's report on page 52 of dl-ol.pdf.

There were 427 reported AEs based on MedDRA preferred term. Among the 427 AEs, 404 were TEAE, treatment-emergent AEs. Many only occurred in one patient. Some occurred among many. Table 25 shows some of the most frequently occurred TEAEs. This table shows the numbers and percentages of patients by TEAE in MedDRA preferred terms. Only TEAEs reported in 2%+ of the patients are displayed in Table 25. For a complete list of TEAEs, see the appendix. Note that the AEs with a gray background are the AEs reported in both studies: Study 201-065 and Study 059 (open label portion).

Table 25 Selected TEAE findings (Study 059: open-label period)

AEs presented as: AEPTTXX; Group totals for FFIS and FA: 463 and 106	TREATMENT				N	%
	FFIS20		FA12			
	N	%	N	%		
Chronic obstructive airways disease exacerbated	73	15.77	19	17.92	92	16.17
Upper respiratory tract infection	47	10.15	13	12.26	60	10.54
Nasopharyngitis	36	7.78	7	6.60	43	7.56
Bronchitis	32	6.91	10	9.43	42	7.38
Sinusitis	27	5.83	4	3.77	31	5.45
Urinary tract infection	21	4.54	6	5.66	27	4.75
Bronchitis acute	22	4.75	3	2.83	25	4.39
Headache	20	4.32	5	4.72	25	4.39
Cough	19	4.10	4	3.77	23	4.04
Arthralgia	15	3.24	5	4.72	20	3.51
Back pain	13	2.81	7	6.60	20	3.51
Pneumonia	18	3.89	2	1.89	20	3.51
Diarrhoea	16	3.46	2	1.89	18	3.16
Hypertension	14	3.02	3	2.83	17	2.99
Influenza	14	3.02	3	2.83	17	2.99
Insomnia	11	2.38	5	4.72	16	2.81
Hyperlipidaemia	11	2.38	2	1.89	13	2.28
Dyspnoea	7	1.51	5	4.72	12	2.11
Nausea	9	1.94	3	2.83	12	2.11
Oedema peripheral	10	2.16	2	1.89	12	2.11
Pharyngolaryngeal pain	10	2.16	2	1.89	12	2.11

Source: AE3_4, for all TEAE only

A comparison between the 12-week Study 201-065 and the 12-month Study 059 (open label) shows that generally there were more AEs reported in Study 059 than in Study 201-065, as would be expected with longer exposure.

An Overall Look of Studies 201-065 and 059 for safety-signal detection purposes

Studies 201-065 and 059 OL extension were different from study purpose to design. Both produced AE findings in data sets named AE, in which many variables bore the same names though their definition could vary. A complete safety evaluation based on pooled data is not considered appropriate in this reviewer's view.

However, by evaluating the safety data of the two studies separately, this reviewer found that the safety results were consistent. Common adverse events in both studies included: COPD exacerbation, headache, nausea, cough, diarrhea, dizziness, dyspnoea, dry mouth, nasopharyngitis, upper respiratory tract infection, urinary tract infection, and vomiting. This observation is based on AEs reported in 2%+ of the patients. No appreciable differences were seen between FFIS20 and FA12.

Results and Conclusions

The results for the efficacy comparisons in Study 201-065 are summarized in Table 34. These significant results in a single study coupled with supportive evidence from Study 57 demonstrate the significant effectiveness of FFIS relative to placebo.

Table 26 Efficacy findings based on week-12 mean AUC of FEV₁ (Study 201-065)

Treatment	Comparator	P-value
FFIS (20 mcg) BID	Placebo	<0.0001
FA 12 mcg BID	Placebo	<0.0001
FFIS (20 mcg) BID	FA 12 mcg BID	0.5546*

Source: EFF2 (ITT patients, missing AUC of FEV₁ estimated with LOCF)

The evaluation of safety based on the sponsor's report of adverse-event findings in Study 201-065 and Study 059 (open label) found that, common adverse events for FFIS20 include: COPD exacerbation, headache, nausea, cough, diarrhea, dizziness, dyspnoea, dry mouth, nasopharyngitis, upper respiratory tract infection, urinary tract infection, and vomiting. This observation is based on AEs reported in 2%+ of the patients.

Comments on Labeling

This reviewer evaluated the **Clinical Trials** subsection of the proposed labeling in **Proposed Labeling** section of the NDA submission for accuracy shown in the following text.

2 Page(s) Withheld

 Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

CONCLUSIONS AND RECOMMENDATIONS

Efficacy Conclusions:

FFIS 20 at mcg/2mL, BID, was demonstrated to be statistically superior to placebo. FFIS 20 was also shown to provide significant onset of bronchodilation.

Safety Conclusions:

The evaluation of safety based on the sponsor's report of adverse-event findings in Study 201-065 and Study 059 (open label) found that, common adverse events include: COPD exacerbation, headache, nausea, cough, diarrhea, dizziness, dyspnoea, dry mouth, nasopharyngitis, upper respiratory tract infection, urinary tract infection, and vomiting.

Recommendations:

From a statistician's viewpoint, FFIS 20 at mcg/2mL, BID, has been shown to be efficacious compared to placebo based on data in one Phase 3 confirmatory study (201-065) and some supporting evidence from one Phase 2 dose-ranging study (DL-057). If the medical reviewer does not raise serious concerns about the AE findings from these studies, this reviewer would recommend that FFIS 20 at mcg/2mL, BID, be approved.

Appendix

Table 27 and Table 28 show a complete list of AEs by treatment.

Table 27 Numbers and percentages of AEs (Study 201-065)

AEs presented as: AEPTTXX; Group totals for FFIS, FA, and placebo: 123, 112, and 114	TREATMENT						N	%
	FFIS 20		FA 12		PLACEBO			
	N	%	N	%	N	%		
Chronic obstructive airways disease exacerbated	5	4.07	7	6.25	9	7.89	21	6.02
Headache	7	5.69	5	4.46	8	7.02	20	5.73
Nausea	6	4.88	4	3.57	3	2.63	13	3.72
Cough	2	1.63	5	4.46	5	4.39	12	3.44
Diarrhea	6	4.88	2	1.79	4	3.51	12	3.44
Dizziness	3	2.44	8	7.14	1	0.88	12	3.44
Dyspnoea	3	2.44	3	2.68	4	3.51	10	2.87
Dry mouth	4	3.25	2	1.79	2	1.75	8	2.29
Nasopharyngitis	4	3.25	2	1.79	2	1.75	8	2.29
Upper respiratory tract infection	2	1.63	3	2.68	2	1.75	7	2.01
Urinary tract infection	2	1.63	2	1.79	3	2.63	7	2.01
Vomiting	3	2.44	2	1.79	2	1.75	7	2.01
Pharyngolaryngeal pain	2	1.63	2	1.79	2	1.75	6	1.72
Sinusitis			4	3.57	2	1.75	6	1.72
Nasal congestion	2	1.63			3	2.63	5	1.43
Pain in extremity	1	0.81	3	2.68	1	0.88	5	1.43
Abdominal pain upper	1	0.81	2	1.79	1	0.88	4	1.15
Anxiety	2	1.63			2	1.75	4	1.15
Palpitations	2	1.63			2	1.75	4	1.15
Wheezing	1	0.81	1	0.89	2	1.75	4	1.15
Arthralgia	1	0.81	1	0.89	1	0.88	3	0.86
Atrial fibrillation			1	0.89	2	1.75	3	0.86
Bronchitis	2	1.63			1	0.88	3	0.86
Constipation	1	0.81			2	1.75	3	0.86
Depression			2	1.79	1	0.88	3	0.86
Dyspnoea exacerbated			3	2.68			3	0.86
Ear infection	1	0.81	1	0.89	1	0.88	3	0.86
Electrocardiogram qt prolonged	1	0.81			2	1.75	3	0.86
Gastroenteritis viral	2	1.63	1	0.89			3	0.86
Hoarseness	1	0.81	1	0.89	1	0.88	3	0.86
Hypertension			2	1.79	1	0.88	3	0.86
Influenza					3	2.63	3	0.86
Insomnia	3	2.44					3	0.86
Pyrexia			1	0.89	2	1.75	3	0.86
Respiratory tract congestion					3	2.63	3	0.86
Skin infection					3	2.63	3	0.86
Vertigo			2	1.79	1	0.88	3	0.86
Atrioventricular block first degree	1	0.81	1	0.89			2	0.57
Balance disorder			1	0.89	1	0.88	2	0.57
Carotid bruit					2	1.75	2	0.57
Cellulitis	1	0.81	1	0.89			2	0.57
Cerumen impaction			2	1.79			2	0.57

AEs presented as: AEPTTXX; Group totals for FFIS, FA, and placebo: 123, 112, and 114	TREATMENT						N	%
	FFIS 20		FA 12		PLACEBO			
	N	%	N	%	N	%		
Chest discomfort	1	0.81			1	0.88	2	0.57
Chest pain	1	0.81	1	0.89			2	0.57
Cystitis			2	1.79			2	0.57
Eczema			1	0.89	1	0.88	2	0.57
Fatigue					2	1.75	2	0.57
Heart rate increased	1	0.81			1	0.88	2	0.57
Intervertebral disc protrusion			2	1.79			2	0.57
Irritability			1	0.89	1	0.88	2	0.57
Muscle cramp	1	0.81	1	0.89			2	0.57
Muscle spasms	1	0.81			1	0.88	2	0.57
Myalgia	2	1.63					2	0.57
Oedema peripheral	1	0.81			1	0.88	2	0.57
Pain			1	0.89	1	0.88	2	0.57
Post procedural pain	1	0.81	1	0.89			2	0.57
Postnasal drip					2	1.75	2	0.57
Postoperative infection					2	1.75	2	0.57
Rash	2	1.63					2	0.57
Road traffic accident	1	0.81	1	0.89			2	0.57
Sinus congestion					2	1.75	2	0.57
Stomach discomfort	2	1.63					2	0.57
Tooth abscess					2	1.75	2	0.57
Urticaria	1	0.81			1	0.88	2	0.57
Abdominal distension	1	0.81					1	0.29
Abdominal pain			1	0.89			1	0.29
Abdominal tenderness			1	0.89			1	0.29
Anaemia					1	0.88	1	0.29
Animal bite	1	0.81					1	0.29
Appendicitis					1	0.88	1	0.29
Arthropod bite	1	0.81					1	0.29
Asthenia	1	0.81					1	0.29
Axillary pain	1	0.81					1	0.29
Back injury					1	0.88	1	0.29
Back pain	1	0.81					1	0.29
Basal cell carcinoma					1	0.88	1	0.29
Blood glucose increased			1	0.89			1	0.29
Blood pressure increased					1	0.88	1	0.29
Breast abscess					1	0.88	1	0.29
Bronchitis acute			1	0.89			1	0.29
Candidiasis					1	0.88	1	0.29
Carpal tunnel syndrome			1	0.89			1	0.29
Cataract					1	0.88	1	0.29
Chest wall pain			1	0.89			1	0.29
Chondrocalcinosis	1	0.81					1	0.29
Chromaturia					1	0.88	1	0.29
Conjunctival haemorrhage			1	0.89			1	0.29
Conjunctivitis allergic	1	0.81					1	0.29
Contusion			1	0.89			1	0.29
Dermatitis contact			1	0.89			1	0.29
Diabetes mellitus					1	0.88	1	0.29
Diverticulitis	1	0.81					1	0.29
Diverticulum					1	0.88	1	0.29
Drug withdrawal headache	1	0.81					1	0.29

AEs presented as: AEPTTXX; Group totals for FFIS, FA, and placebo: 123, 112, and 114	TREATMENT						N	%
	FFIS 20		FA 12		PLACEBO			
	N	%	N	%	N	%		
Dysgeusia			1	0.89			1	0.29
Dyspepsia			1	0.89			1	0.29
Dysphagia					1	0.88	1	0.29
Dysphonia					1	0.88	1	0.29
Dysuria	1	0.81					1	0.29
Ear pain					1	0.88	1	0.29
Ecchymosis	1	0.81					1	0.29
Ejaculation failure			1	0.89			1	0.29
Electrocardiogram qt corrected interval prolonged			1	0.89			1	0.29
Epistaxis			1	0.89			1	0.29
Erythema			1	0.89			1	0.29
Eye infection			1	0.89			1	0.29
Eye infection viral					1	0.88	1	0.29
Eye irritation	1	0.81					1	0.29
Faeces pale					1	0.88	1	0.29
Flank pain	1	0.81					1	0.29
Foot fracture	1	0.81					1	0.29
Ganglion			1	0.89			1	0.29
Gastritis			1	0.89			1	0.29
Gastroenteritis			1	0.89			1	0.29
Gastrointestinal discomfort					1	0.88	1	0.29
Gastroesophageal reflux disease					1	0.88	1	0.29
Haemoglobin decreased					1	0.88	1	0.29
Herpes simplex			1	0.89			1	0.29
Hypercholesterolaemia	1	0.81					1	0.29
Hyperhidrosis			1	0.89			1	0.29
Hypersensitivity	1	0.81					1	0.29
Hypokalaemia					1	0.88	1	0.29
Hypotension					1	0.88	1	0.29
Incontinence			1	0.89			1	0.29
Infected cyst	1	0.81					1	0.29
Influenza like illness			1	0.89			1	0.29
Injury			1	0.89			1	0.29
Irritable bowel syndrome					1	0.88	1	0.29
Joint dislocation			1	0.89			1	0.29
Joint swelling			1	0.89			1	0.29
Keratoconjunctivitis sicca			1	0.89			1	0.29
Laceration			1	0.89			1	0.29
Laryngospasm					1	0.88	1	0.29
Lichen planus	1	0.81					1	0.29
Limb injury					1	0.88	1	0.29
Loose stools					1	0.88	1	0.29
Lymph gland infection	1	0.81					1	0.29
Mean cell volume decreased					1	0.88	1	0.29
Meningioma					1	0.88	1	0.29
Migraine			1	0.89			1	0.29
Mountain sickness acute	1	0.81					1	0.29
Muscle strain			1	0.89			1	0.29
Neck pain			1	0.89			1	0.29
Neoplasm	1	0.81					1	0.29
Nervousness	1	0.81					1	0.29
Non-cardiac chest pain	1	0.81					1	0.29

AEs presented as: AEPTXT; Group totals for FFIS, FA, and placebo: 123, 112, and 114	TREATMENT						N	%
	FFIS 20		FA 12		PLACEBO			
	N	%	N	%	N	%		
Ocular icterus					1	0.88	1	0.29
Otitis media	1	0.81					1	0.29
Pain exacerbated	1	0.81					1	0.29
Pancreatic carcinoma					1	0.88	1	0.29
Periorbital oedema	1	0.81					1	0.29
Pharyngitis	1	0.81					1	0.29
Photosensitivity reaction	1	0.81					1	0.29
Pollakiuria			1	0.89			1	0.29
Productive cough					1	0.88	1	0.29
Prostate cancer	1	0.81					1	0.29
Pulmonary congestion	1	0.81					1	0.29
Rectal perforation					1	0.88	1	0.29
Renal failure acute			1	0.89			1	0.29
Respiratory disorder			1	0.89			1	0.29
Respiratory tract infection			1	0.89			1	0.29
Rhinitis	1	0.81					1	0.29
Rigors					1	0.88	1	0.29
Salivary gland pain					1	0.88	1	0.29
Sialoadenitis					1	0.88	1	0.29
Sinus headache	1	0.81					1	0.29
Skin lesion					1	0.88	1	0.29
Sleep apnoea syndrome			1	0.89			1	0.29
Sneezing	1	0.81					1	0.29
Stomatitis					1	0.88	1	0.29
Stress symptoms			1	0.89			1	0.29
Syphilis					1	0.88	1	0.29
Tension headache	1	0.81					1	0.29
Thrombocytopenia					1	0.88	1	0.29
Tinea pedis	1	0.81					1	0.29
Tooth infection			1	0.89			1	0.29
Toothache					1	0.88	1	0.29
Tremor			1	0.89			1	0.29
Urine flow decreased			1	0.89			1	0.29
Vision blurred	1	0.81					1	0.29
Visual disturbance			1	0.89			1	0.29
Vulvovaginal discomfort			1	0.89			1	0.29
Weight increased	1	0.81					1	0.29
Wound infection			1	0.89			1	0.29

Source: AE1

Table 28 Numbers and percentages of TEAEs (Study 059: open label)

AEs presented as: AEPTTXXT; Group totals for FFIS and FA: 463 and 106	TREATMENT				N	%
	FFIS20		FA12			
	N	%	N	%		
Chronic obstructive airways disease exacerbated	73	15.77	19	17.92	92	16.17
Upper respiratory tract infection	47	10.15	13	12.26	60	10.54
Nasopharyngitis	36	7.78	7	6.60	43	7.56
Bronchitis	32	6.91	10	9.43	42	7.38
Sinusitis	27	5.83	4	3.77	31	5.45
Urinary tract infection	21	4.54	6	5.66	27	4.75
Bronchitis acute	22	4.75	3	2.83	25	4.39
Headache	20	4.32	5	4.72	25	4.39
Cough	19	4.10	4	3.77	23	4.04
Arthralgia	15	3.24	5	4.72	20	3.51
Back pain	13	2.81	7	6.60	20	3.51
Pneumonia	18	3.89	2	1.89	20	3.51
Diarrhoea	16	3.46	2	1.89	18	3.16
Hypertension	14	3.02	3	2.83	17	2.99
Influenza	14	3.02	3	2.83	17	2.99
Insomnia	11	2.38	5	4.72	16	2.81
Hyperlipidaemia	11	2.38	2	1.89	13	2.28
Dyspnoea	7	1.51	5	4.72	12	2.11
Nausea	9	1.94	3	2.83	12	2.11
Oedema peripheral	10	2.16	2	1.89	12	2.11
Pharyngolaryngeal pain	10	2.16	2	1.89	12	2.11
Anxiety	9	1.94	2	1.89	11	1.93
Rash	11	2.38			11	1.93
Wheezing	8	1.73	3	2.83	11	1.93
Depression	8	1.73	2	1.89	10	1.76
Dizziness	6	1.30	4	3.77	10	1.76
Muscle cramp	10	2.16			10	1.76
Coronary artery disease	7	1.51	2	1.89	9	1.58
Viral infection	6	1.30	3	2.83	9	1.58
Arthritis	8	1.73			8	1.41
Cataract	7	1.51	1	0.94	8	1.41
Constipation	7	1.51	1	0.94	8	1.41
Diabetes mellitus	7	1.51	1	0.94	8	1.41
Gastroesophageal reflux disease	8	1.73			8	1.41
Pulmonary congestion	8	1.73			8	1.41
Sinus congestion	5	1.08	3	2.83	8	1.41
Vomiting	6	1.30	2	1.89	8	1.41
Chest pain	5	1.08	2	1.89	7	1.23
Ear infection	5	1.08	2	1.89	7	1.23
Lower respiratory tract infection	6	1.30	1	0.94	7	1.23
Pain in extremity	6	1.30	1	0.94	7	1.23
Post procedural pain	5	1.08	2	1.89	7	1.23
Dyspnoea exacerbated	5	1.08	1	0.94	6	1.05
Pyrexia	5	1.08	1	0.94	6	1.05
Sciatica	4	0.86	2	1.89	6	1.05
Asthenia	2	0.43	3	2.83	5	0.88
Candidiasis	4	0.86	1	0.94	5	0.88
Eye infection	4	0.86	1	0.94	5	0.88
Fatigue	4	0.86	1	0.94	5	0.88

AEs presented as: AEPTTXX; Group totals for FFIS and FA: 463 and 106	TREATMENT				N	%
	FFIS20		FA12			
	N	%	N	%		
Gastroenteritis viral	5	1.08			5	0.88
Herpes zoster	5	1.08			5	0.88
Lymphadenopathy	3	0.65	2	1.89	5	0.88
Myocardial infarction	5	1.08			5	0.88
Nasal congestion	4	0.86	1	0.94	5	0.88
Non-cardiac chest pain	4	0.86	1	0.94	5	0.88
Stomach discomfort	5	1.08			5	0.88
Syncope	4	0.86	1	0.94	5	0.88
Tooth abscess	1	0.22	4	3.77	5	0.88
Toothache	5	1.08			5	0.88
Acute sinusitis	3	0.65	1	0.94	4	0.70
Anaemia	3	0.65	1	0.94	4	0.70
Benign prostatic hyperplasia	4	0.86			4	0.70
Cardiac failure congestive	4	0.86			4	0.70
Contusion	3	0.65	1	0.94	4	0.70
Crackles lung	3	0.65	1	0.94	4	0.70
Dermatitis contact	3	0.65	1	0.94	4	0.70
Diverticulitis	3	0.65	1	0.94	4	0.70
Dyspepsia	3	0.65	1	0.94	4	0.70
Hypercholesterolaemia	2	0.43	2	1.89	4	0.70
Hypersensitivity	2	0.43	2	1.89	4	0.70
Intervertebral disc protrusion	3	0.65	1	0.94	4	0.70
Muscle strain	3	0.65	1	0.94	4	0.70
Myalgia	2	0.43	2	1.89	4	0.70
Nephrolithiasis	4	0.86			4	0.70
Osteoarthritis	2	0.43	2	1.89	4	0.70
Otitis media	4	0.86			4	0.70
Pain	3	0.65	1	0.94	4	0.70
Palpitations	3	0.65	1	0.94	4	0.70
Respiratory tract congestion	4	0.86			4	0.70
Respiratory tract infection	3	0.65	1	0.94	4	0.70
Rhinitis allergic	4	0.86			4	0.70
Skin lesion	3	0.65	1	0.94	4	0.70
Tremor	4	0.86			4	0.70
Viral upper respiratory tract infection	2	0.43	2	1.89	4	0.70
Cellulitis	3	0.65			3	0.53
Fall	3	0.65			3	0.53
Foot fracture	3	0.65			3	0.53
Gastritis	3	0.65			3	0.53
Gastroenteritis	3	0.65			3	0.53
Gout	3	0.65			3	0.53
Herpes simplex	3	0.65			3	0.53
Hyperglycaemia	2	0.43	1	0.94	3	0.53
Inguinal hernia	3	0.65			3	0.53
Liver function test abnormal	3	0.65			3	0.53
Lobar pneumonia	1	0.22	2	1.89	3	0.53
Malaise	3	0.65			3	0.53
Oral candidiasis	3	0.65			3	0.53
Osteoporosis	2	0.43	1	0.94	3	0.53
Radiculopathy	3	0.65			3	0.53
Respiratory disorder	2	0.43	1	0.94	3	0.53
Rhinitis			3	2.83	3	0.53

AEs presented as: AEPTTXT; Group totals for FFIS and FA: 463 and 106	TREATMENT				N	%
	FFIS20		FA12			
	N	%	N	%		
Rhinorrhoea	3	0.65			3	0.53
Rhonchi	3	0.65			3	0.53
Rib fracture	3	0.65			3	0.53
Seasonal allergy	1	0.22	2	1.89	3	0.53
Sleep apnoea syndrome	2	0.43	1	0.94	3	0.53
Tendonitis	2	0.43	1	0.94	3	0.53
Tooth infection	3	0.65			3	0.53
Urticaria	3	0.65			3	0.53
Vertigo	2	0.43	1	0.94	3	0.53
Vision blurred	2	0.43	1	0.94	3	0.53
Abdominal hernia	2	0.43			2	0.35
Abdominal pain	2	0.43			2	0.35
Abdominal pain upper	2	0.43			2	0.35
Acute myocardial infarction	2	0.43			2	0.35
Aortic aneurysm	1	0.22	1	0.94	2	0.35
Aphthous stomatitis	2	0.43			2	0.35
Arteriosclerosis	2	0.43			2	0.35
Back injury	2	0.43			2	0.35
Bile duct obstruction	1	0.22	1	0.94	2	0.35
Blood cholesterol increased	2	0.43			2	0.35
Bursitis	2	0.43			2	0.35
Chest discomfort	1	0.22	1	0.94	2	0.35
Cholecystitis	2	0.43			2	0.35
Cholelithiasis	2	0.43			2	0.35
Chronic obstructive airways disease	2	0.43			2	0.35
Cyst			2	1.89	2	0.35
Dental discomfort	2	0.43			2	0.35
Dermatitis	2	0.43			2	0.35
Dermatitis atopic	2	0.43			2	0.35
Diabetes mellitus non-insulin-dependent			2	1.89	2	0.35
Diverticulum	2	0.43			2	0.35
Ear pain			2	1.89	2	0.35
Eczema	2	0.43			2	0.35
Electrocardiogram qt prolonged	2	0.43			2	0.35
Erythema	2	0.43			2	0.35
Fungal infection	2	0.43			2	0.35
Gingival infection			2	1.89	2	0.35
Haemorrhoids	2	0.43			2	0.35
Hoarseness	2	0.43			2	0.35
Hot flush	1	0.22	1	0.94	2	0.35
Hypokalaemia	2	0.43			2	0.35
Hyponatraemia	1	0.22	1	0.94	2	0.35
Hypotension	2	0.43			2	0.35
Increased upper airway secretion	2	0.43			2	0.35
Influenza like illness			2	1.89	2	0.35
Intermittent claudication	2	0.43			2	0.35
Laceration	2	0.43			2	0.35
Laryngitis	1	0.22	1	0.94	2	0.35
Limb injury	2	0.43			2	0.35
Lung infection	2	0.43			2	0.35
Lung neoplasm malignant	1	0.22	1	0.94	2	0.35
Menopausal symptoms	2	0.43			2	0.35

AEs presented as: AEPTXT; Group totals for FFIS and FA: 463 and 106	TREATMENT				N	%
	FFIS20		FA12			
	N	%	N	%		
Multi-organ failure	1	0.22	1	0.94	2	0.35
Muscle spasms	1	0.22	1	0.94	2	0.35
Neck pain	2	0.43			2	0.35
Neuroma	2	0.43			2	0.35
Nocturia	2	0.43			2	0.35
Oedema	2	0.43			2	0.35
Pharyngitis			2	1.89	2	0.35
Pneumothorax	2	0.43			2	0.35
Postnasal drip	1	0.22	1	0.94	2	0.35
Prostatitis	1	0.22	1	0.94	2	0.35
Pruritus	1	0.22	1	0.94	2	0.35
Renal cyst	2	0.43			2	0.35
Respiratory tract infection viral	1	0.22	1	0.94	2	0.35
Restless legs syndrome	1	0.22	1	0.94	2	0.35
Rheumatoid arthritis	2	0.43			2	0.35
Sinus headache	1	0.22	1	0.94	2	0.35
Skin laceration	1	0.22	1	0.94	2	0.35
Soft tissue injury	2	0.43			2	0.35
Somnolence	2	0.43			2	0.35
Spinal column stenosis			2	1.89	2	0.35
Staphylococcal infection	2	0.43			2	0.35
Supraventricular tachycardia	2	0.43			2	0.35
Tachycardia	1	0.22	1	0.94	2	0.35
Thermal burn	2	0.43			2	0.35
Ventricular tachycardia	2	0.43			2	0.35
Visual disturbance	1	0.22	1	0.94	2	0.35
White blood cell count increased	2	0.43			2	0.35
Abdominal pain lower	1	0.22			1	0.18
Abscess oral	1	0.22			1	0.18
Acne	1	0.22			1	0.18
Anastomotic ulcer haemorrhage			1	0.94	1	0.18
Angina pectoris			1	0.94	1	0.18
Angina unstable	1	0.22			1	0.18
Angioneurotic oedema	1	0.22			1	0.18
Ankle fracture	1	0.22			1	0.18
Anorexia	1	0.22			1	0.18
Arthritis infective	1	0.22			1	0.18
Atherosclerosis			1	0.94	1	0.18
Bartholin's cyst	1	0.22			1	0.18
Bartholinitis	1	0.22			1	0.18
Basal cell carcinoma	1	0.22			1	0.18
Beta haemolytic streptococcal infection	1	0.22			1	0.18
Blister	1	0.22			1	0.18
Blood creatinine increased	1	0.22			1	0.18
Blood glucose increased	1	0.22			1	0.18
Blood testosterone decreased	1	0.22			1	0.18
Blood triglycerides increased	1	0.22			1	0.18
Blood uric acid increased	1	0.22			1	0.18
Bone spur			1	0.94	1	0.18
Breast discharge			1	0.94	1	0.18
Breath sounds decreased			1	0.94	1	0.18
Bronchial infection	1	0.22			1	0.18

AEs presented as: AEPTXT; Group totals for FFIS and FA: 463 and 106	TREATMENT				N	%
	FFIS20		FA12			
	N	%	N	%		
Bundle branch block right			1	0.94	1	0.18
Bunion	1	0.22			1	0.18
Cachexia	1	0.22			1	0.18
Cardiac arrest	1	0.22			1	0.18
Cardiac murmur	1	0.22			1	0.18
Carotid bruit	1	0.22			1	0.18
Carpal tunnel syndrome	1	0.22			1	0.18
Cartilage injury	1	0.22			1	0.18
Cerebral haemorrhage			1	0.94	1	0.18
Cerebral infarction	1	0.22			1	0.18
Cerumen impaction	1	0.22			1	0.18
Cervix carcinoma	1	0.22			1	0.18
Coagulopathy			1	0.94	1	0.18
Colonic polyp	1	0.22			1	0.18
Colonoscopy	1	0.22			1	0.18
Concussion			1	0.94	1	0.18
Confusional state	1	0.22			1	0.18
Conjunctivitis allergic	1	0.22			1	0.18
Corneal abrasion	1	0.22			1	0.18
Deafness unilateral			1	0.94	1	0.18
Dehydration	1	0.22			1	0.18
Dental caries			1	0.94	1	0.18
Dermal cyst	1	0.22			1	0.18
Diplopia	1	0.22			1	0.18
Drug dependence			1	0.94	1	0.18
Drug hypersensitivity	1	0.22			1	0.18
Dry mouth	1	0.22			1	0.18
Dry skin	1	0.22			1	0.18
Dry throat	1	0.22			1	0.18
Dupuytren's contracture	1	0.22			1	0.18
Dyslipidaemia	1	0.22			1	0.18
Dysphagia			1	0.94	1	0.18
Dysuria	1	0.22			1	0.18
Electrocardiogram abnormal	1	0.22			1	0.18
Electrocardiogram change	1	0.22			1	0.18
Electrocardiogram qt corrected interval prolonged	1	0.22			1	0.18
Electrocardiogram t wave abnormal	1	0.22			1	0.18
Electrocardiogram t wave inversion	1	0.22			1	0.18
Erectile dysfunction			1	0.94	1	0.18
Exostosis	1	0.22			1	0.18
Eye haemorrhage	1	0.22			1	0.18
Feeling abnormal			1	0.94	1	0.18
Femoral neck fracture	1	0.22			1	0.18
Fibromyalgia	1	0.22			1	0.18
Fracture	1	0.22			1	0.18
Furuncle			1	0.94	1	0.18
Gait abnormal	1	0.22			1	0.18
Ganglion	1	0.22			1	0.18
Gastric ulcer	1	0.22			1	0.18
Gastric ulcer haemorrhage	1	0.22			1	0.18
Gastrointestinal infection	1	0.22			1	0.18
Gingival pain			1	0.94	1	0.18

AEs presented as: AEPTXT; Group totals for FFIS and FA: 463 and 106	TREATMENT				N	%
	FFIS20		FAI2			
	N	%	N	%		
Gingivitis			1	0.94	1	0.18
Glaucoma	1	0.22			1	0.18
Gravitational oedema	1	0.22			1	0.18
Groin abscess	1	0.22			1	0.18
Gun shot wound			1	0.94	1	0.18
Haematochezia	1	0.22			1	0.18
Haematoma			1	0.94	1	0.18
Haematuria	1	0.22			1	0.18
Haemoglobin increased	1	0.22			1	0.18
Hand fracture			1	0.94	1	0.18
Heat rash	1	0.22			1	0.18
Helicobacter pylori antibody positive			1	0.94	1	0.18
Hemiparesis			1	0.94	1	0.18
Hepatic enzyme increased	1	0.22			1	0.18
Hepatic steatosis	1	0.22			1	0.18
Hernia pain	1	0.22			1	0.18
Hiatus hernia	1	0.22			1	0.18
Hiccups			1	0.94	1	0.18
Hodgkin's disease	1	0.22			1	0.18
Hypercalcaemia	1	0.22			1	0.18
Hyperhidrosis	1	0.22			1	0.18
Hyperkalaemia	1	0.22			1	0.18
Hypertriglyceridaemia	1	0.22			1	0.18
Hypoaesthesia			1	0.94	1	0.18
Hyporeflexia	1	0.22			1	0.18
Hypoxia	1	0.22			1	0.18
Iliac artery thrombosis	1	0.22			1	0.18
Impetigo	1	0.22			1	0.18
Infection	1	0.22			1	0.18
Inflammation	1	0.22			1	0.18
Ingrowing nail			1	0.94	1	0.18
Intention tremor	1	0.22			1	0.18
Intertrigo	1	0.22			1	0.18
Intervertebral disc compression	1	0.22			1	0.18
Intervertebral disc degeneration	1	0.22			1	0.18
Intraocular pressure increased			1	0.94	1	0.18
Joint sprain	1	0.22			1	0.18
Jugular vein distension	1	0.22			1	0.18
Kidney infection			1	0.94	1	0.18
Laboratory test abnormal	1	0.22			1	0.18
Labyrinthitis			1	0.94	1	0.18
Leukocytosis	1	0.22			1	0.18
Leukopenia	1	0.22			1	0.18
Lipoma	1	0.22			1	0.18
Localised exfoliation	1	0.22			1	0.18
Localised osteoarthritis			1	0.94	1	0.18
Lung nodule			1	0.94	1	0.18
Lymphadenopathy mediastinal	1	0.22			1	0.18
Lymphoedema			1	0.94	1	0.18
Macular degeneration			1	0.94	1	0.18
Mountain sickness acute	1	0.22			1	0.18
Multiple fractures	1	0.22			1	0.18

AEs presented as: AEPTTXX; Group totals for FFIS and FA: 463 and 106	TREATMENT				N	%
	FFIS20		FA12			
	N	%	N	%		
Muscle injury	1	0.22			1	0.18
Musculoskeletal discomfort			1	0.94	1	0.18
Musculoskeletal stiffness			1	0.94	1	0.18
Mycetoma mycotic	1	0.22			1	0.18
Mycobacterium avium complex infection	1	0.22			1	0.18
Myopathy			1	0.94	1	0.18
Nail infection	1	0.22			1	0.18
Nasal cavity mass	1	0.22			1	0.18
Nasal discomfort	1	0.22			1	0.18
Nasal oedema	1	0.22			1	0.18
Nasal polyps	1	0.22			1	0.18
Nephrosclerosis	1	0.22			1	0.18
Nerve compression	1	0.22			1	0.18
Nervousness	1	0.22			1	0.18
Neuropathic pain	1	0.22			1	0.18
Night sweats	1	0.22			1	0.18
Nodule	1	0.22			1	0.18
Non-small cell lung cancer	1	0.22			1	0.18
Obesity	1	0.22			1	0.18
Oesophageal pain			1	0.94	1	0.18
Oral infection			1	0.94	1	0.18
Oral pain	1	0.22			1	0.18
Pain exacerbated	1	0.22			1	0.18
Pancreatic disorder	1	0.22			1	0.18
Pancreatitis	1	0.22			1	0.18
Pancreatitis acute	1	0.22			1	0.18
Peptic ulcer	1	0.22			1	0.18
Peripheral vascular disorder	1	0.22			1	0.18
Perirectal abscess	1	0.22			1	0.18
Pharyngeal erythema	1	0.22			1	0.18
Pharyngitis streptococcal	1	0.22			1	0.18
Pleural effusion			1	0.94	1	0.18
Pleurisy	1	0.22			1	0.18
Pleuritic pain	1	0.22			1	0.18
Pneumoperitoneum	1	0.22			1	0.18
Poor peripheral circulation	1	0.22			1	0.18
Pre-existing condition improved			1	0.94	1	0.18
Premenstrual syndrome	1	0.22			1	0.18
Prostate cancer	1	0.22			1	0.18
Prostate infection			1	0.94	1	0.18
Proteinuria	1	0.22			1	0.18
Pseudomonas infection	1	0.22			1	0.18
Psoriasis	1	0.22			1	0.18
Pulmonary mass	1	0.22			1	0.18
Pulmonary oedema			1	0.94	1	0.18
Rales	1	0.22			1	0.18
Rectal haemorrhage	1	0.22			1	0.18
Renal artery stenosis	1	0.22			1	0.18
Renal insufficiency	1	0.22			1	0.18
Respiratory failure	1	0.22			1	0.18
Respiratory fume inhalation disorder	1	0.22			1	0.18
Retinal detachment	1	0.22			1	0.18

AEs presented as: AEPTTXX; Group totals for FFIS and FA: 463 and 106	TREATMENT				N	%
	FFIS20		FA12			
	N	%	N	%		
Retinal exudates	1	0.22			1	0.18
Road traffic accident	1	0.22			1	0.18
Rotator cuff syndrome	1	0.22			1	0.18
Scab	1	0.22			1	0.18
Scar			1	0.94	1	0.18
Seborrhoea	1	0.22			1	0.18
Shoulder blade pain	1	0.22			1	0.18
Sialoadenitis			1	0.94	1	0.18
Sinobronchitis			1	0.94	1	0.18
Skeletal injury	1	0.22			1	0.18
Skin bacterial infection	1	0.22			1	0.18
Skin infection	1	0.22			1	0.18
Skin papilloma	1	0.22			1	0.18
Skin ulcer	1	0.22			1	0.18
Sneezing	1	0.22			1	0.18
Spinal compression fracture	1	0.22			1	0.18
Spinal fracture	1	0.22			1	0.18
Stomatitis	1	0.22			1	0.18
Stress incontinence			1	0.94	1	0.18
Syncope vasovagal	1	0.22			1	0.18
Temporal arteritis	1	0.22			1	0.18
Tenosynovitis stenosans	1	0.22			1	0.18
Terminal dribbling	1	0.22			1	0.18
Thrombocythaemia	1	0.22			1	0.18
Thyroid disorder	1	0.22			1	0.18
Thyroid nodule	1	0.22			1	0.18
Tonsillitis	1	0.22			1	0.18
Tooth impacted	1	0.22			1	0.18
Tooth loss	1	0.22			1	0.18
Tracheobronchitis	1	0.22			1	0.18
Transient ischaemic attack	1	0.22			1	0.18
Troponin increased	1	0.22			1	0.18
Tuberculin test positive	1	0.22			1	0.18
Tympanic membrane perforation	1	0.22			1	0.18
Upper respiratory tract congestion	1	0.22			1	0.18
Urinary incontinence	1	0.22			1	0.18
Urinary retention	1	0.22			1	0.18
Vaginal mycosis	1	0.22			1	0.18
Vaginitis bacterial	1	0.22			1	0.18
Vitamin b12 deficiency			1	0.94	1	0.18
Vitreous floaters	1	0.22			1	0.18
Weight decreased	1	0.22			1	0.18
Wrist fracture	1	0.22			1	0.18

Source: AE3_4: TEAE only

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/s/

Ted Guo
2/1/2007 01:20:30 PM
BIOMETRICS
Statistical review

Joy Mele
2/1/2007 01:40:41 PM
BIOMETRICS



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation Clinical Studies

NDA/Serial Number: NDA 22-007

Drug Name: Formoterol Fumarate Inhalation Solution 20 mcg/2 mL

Indication(s): Formoterol Fumarate Inhalation Solution at 20 mcg/2 mL, BID, is proposed to be indicated for the treatment of COPD. _____

Applicant: Dey, L.P. **b(4)**

Date(s): Applicant's letter date: June 28, 2006

Review Priority: Standard

Biometrics Division: Biometrics Division 2

Statistical Reviewer: Ted Guo, Ph.D., Biometrics Division 2

Concurring Reviewers: Ruthanna Davi, M.S., Team Leader, Biometrics Division 2

Medical Division: Division of Pulmonary and Allergy Products (ODE II)

Clinical Team: James Kaiser, M.D., Medical Officers (ODE II)

Project Manager: Akilah Green (ODE II)

Keywords: NDA review, clinical studies

FILING CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Safety and efficacy for gender, racial, and geriatric subgroups investigated	Yes
Data sets in EDR conform to applicable guidance.	Yes

The submission is filable from a statistical perspective.

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/s/

Ted Guo
8/24/2006 01:10:38 PM
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Stats filing review

Ruth Davi
8/24/2006 02:11:54 PM
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