

Table 36. Trial DL-059 open-label period: Subjects with adverse events leading to discontinuation (safety population)

SYSTEM ORGAN CLASS Preferred term	FFIS 20 µg N=463	FA 12 µg N=106
CARDIAC DISORDERS	7 (1.5)	2 (1.9)
Myocardial infarction	3 (0.6)	0
Cardiac arrest	1 (0.2)	0
Cardiac failure congestive	1 (0.2)	0
Coronary artery disease	1 (0.2)	1 (0.9)
Supraventricular tachycardia	1 (0.2)	0
Palpitations	0	1 (0.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	7 (1.5)	2 (1.9)
Chronic obstructive airways disease exacerbated	5 (1.1)	2 (1.9)
Dyspnoea exacerbated	1 (0.2)	0
Pulmonary mass	1 (0.2)	0
INFECTIONS AND INFESTATIONS	5 (1.1)	0
Pneumonia	3 (0.6)	0
Bronchitis acute	2 (0.4)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (0.4)	0
Cervix carcinoma	1 (0.2)	0
Lung neoplasm malignant	1 (0.2)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.2)	0
Pain In Extremity	1 (0.2)	0
NERVOUS SYSTEM DISORDERS	1 (0.2)	1 (0.9)
Syncope	1 (0.2)	0
Cerebral haemorrhage	0	1 (0.9)
PSYCHIATRIC DISORDERS	1 (0.2)	1 (0.9)
Anxiety	1 (0.2)	0
Drug dependence	0	1 (0.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.2)	0
Pruritus	1 (0.2)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (0.9)
Multi-Organ Failure	0	1 (0.9)
VASCULAR DISORDERS	0	1 (0.9)
Atherosclerosis	0	1 (0.9)

Dey notes: "Two patients.. who discontinued due to AEs (cough and COPD exacerbation, respectively) during treatment with FFIS during the [open-label] phase do not appear in [the table] because AE onset for these patients was in the double-blind phase while the patients were treated with placebo (5901/18) or Foradil® (5908/9)."

[Source: section-1-15-report-body.pdf, table 14.3.1.3]

All adverse events

Table 37 is a tabulation of preferred terms that occurred at a 2% or greater increase in either treatment arm over the other.

Table 37. Trial DL-059 open-label period: Adverse events occurring at $\geq 2\%$ increase (subjects) over the other treatment arm

SYSTEM ORGAN CLASS Preferred term	FFIS 20 μ g N=463	FA 12 μ g N=106
INFECTIONS AND INFESTATIONS	227 (49)	55 (52)
URTI	47 (10.2)	13 (12.3)
Sinusitis	27 (5.8)	4 (3.8)
Bronchitis	32 (6.9)	10 (9.4)
Bronchitis Acute	22 (4.8)	3 (2.8)
Pneumonia	18 (3.9)	2 (1.9)
Tooth Abscess	1 (0.2)	4 (3.8)
Rhinitis	0	3 (2.8)
RESPIRATORY, THORACIC, & MEDIASTINAL DISORDERS	154 (33)	35 (33)
Dyspnea	7 (1.5)	5 (4.7)
MUSCULOSKELETAL & CONN. TISSUE DISORDERS	67 (14.5)	22 (20.8)
Back Pain	13 (2.8)	7 (6.6)
Muscle Cramp	10 (2.2)	0
NERVOUS SYSTEM DISORDERS	54 (11.7)	17 (16.0)
Dizziness	6 (1.3)	4 (3.8)
GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS	45 (9.7)	13 (12.3)
Asthenia	2 (0.4)	3 (2.8)
SKIN & SUBCUTANEOUS TISSUE DISORDERS	39 (8.4)	6 (5.7)
Rash	11 (2.4)	0
PSYCHIATRIC DISORDERS	32 (6.9)	9 (8.5)
Insomnia	11 (2.4)	5 (4.7)

[Source: Trial DL-059 open-label period section-1-15-report-body.pdf, Table 14.3.1.1.1.1]

The incidences of tremor and nervousness, associated with β -agonists, were not notably increased in FFIS (4 subjects in FFIS (0.9%) vs. none in FA and 1 subject in FFIS (0.2%) vs. none in FA, respectively). The incidence of arrhythmic events (palpitations, supraventricular tachycardia, ventricular tachycardia, tachycardia) was not notably increased in FFIS as compared to FA (numbers of subjects in FFIS 3(0.6%), 2 (0.4%), 2 (0.4%), and 1 (0.2%), respectively as compared to the numbers in FA: 1 (0.9%), 0, 0, and 1 (0.9%).

When the safety events were examined with respect to a dichotomization by age (<65 and ≥ 65 years old), and sex, no new safety concern emerged.

Analysis of adverse events in the open-label period of DL-059 by racial subgroup is not profitable due to the small numbers of subjects in groups other than "Caucasian."

Vital signs

Blood pressure and heart rate were balanced in the FFIS and Foradil[®] treatment arms at baseline in the open-label period of DL-059. Given the limitation imposed by the withdrawals of significant numbers of subjects from each treatment arm, there were no meaningful changes from baseline in either group in mean or median systolic or diastolic blood pressure or heart rate, measured at 10, 20, 30, 40, and 52 weeks after baseline.

Clinical laboratories and ECG

I reviewed summary data and shift summaries.

- There were no notable differences between FFIS and FA when hematology data were examined for mean differences from baseline or as shifts from normal at baseline to last postbaseline value.
- There were no notable differences between FFIS and FA when chemistry data were examined for mean differences from baseline or as shifts from normal, low, or high value at baseline to last postbaseline value. This includes glucose and potassium, parameters of special relevance to β -agonists generally.
- Urine pH and specific gravity showed no notable differences from baseline for either treatment group.
- There were no notable differences between treatment groups in mean PR, QT, QRS, RR, QTcB, or QTcF intervals.

Table 38 is a summary of the corrected-QT interval (QTc) data. Dey notes, "One patient in the FFIS group (Patient 5917/4) had a QTcB value of 514 msec and a QTcF value of 521 msec at Day 71 of open-label treatment that returned to normal values by the final ECG at Week 64...No adverse events were associated with these findings at Day 71." This was the only subject whose QTc exceeded 500 msec in the open-label period.

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Table 38. Trial DL-059 open-label period: Subjects with corrected QT change from baseline (week 12)

		change (msec)	FFIS 20 µg	FA 12 µg
QTcB	Week 22	n	395	90
		< 30	365 (92.4)	87 (96.7)
		30 - <60	28 (7.1)	3 (3.3)
		≥ 60	2 (0.5) ¹	0
	Week 64 or early term.	n	374	83
		< 30	330 (88.2)	77 (92.8)
		30 - <60	40 (10.7)	6 (7.2)
≥ 60	4 (1.1) ²	0		
QTcF	Week 22	n	395	90
		< 30	374 (94.7)	89 (98.9)
		30 - <60	19 (4.8)	1 (1.1)
		≥ 60	2 (0.5) ³	0
	Week 64 or early term.	n	374	83
		< 30	336 (89.8)	76 (91.6)
		30 - <60	35 (9.4)	7 (8.4)
≥ 60	3 (0.8) ⁴	0		

[Source: section-1-15-report-body.pdf, Table 12.5.3.1]

- ¹ Increases of 75 and 107 msec.
² Increases of 67, 70, 84, and 65 msec
³ Increases of 60 and 90 msec
⁴ Increases of 62, 80, and 87 msec

Comment

Dey's product was associated with a small numbers of cases of elevations of QTc. Since arrhythmic events specifically did not increase in the FFIS group, this apparent increase is not of concern. It is also possible that had the FA group been larger, some increases in QTc may have occurred in that group.

Summary of the results of DL-059

The double-blind period of DL-059 was invalidated for the determination of efficacy by major errors in treatment assignments. The open-label period of DL-059 did not reveal notable toxicities of FFIS over that of Foradil[®], given the limitation imposed by the very small size of the Foradil[®] treatment arm. Cardiac disorders occurred in FFIS-treated subjects, most of whom had predisposing clinical risks.

10.1.4 Trial 201-065

Trial 201-065, "A 12-Week Double-Blind, Parallel-Group, Placebo- And Active-Controlled Trial To Evaluate The Efficacy And Safety Of Formoterol Fumarate Inhalation Solution 20 Mcg In The Treatment Of Patients With Chronic Obstructive Pulmonary Disease," is the only study submitted by Dey proposed as primary evidence of efficacy.

10.1.4.1 Protocol

The original protocol for this trial was dated January 21, 2005.

The trial was designed to test the effectiveness of FFIS in relation to placebo. A Foradil® treatment arm was included, although there was no intent to compare the FFIS to FA statistically. The FA arm also served as an active control, since the effectiveness of FA has been established previously. Since FFIS is an inhalation solution delivered by nebulizer and compressor and FA is a dry powder delivered by metered-dose inhaler, a double-dummy design had to be employed to blind the participants.

Periods of the trial

The protocol called for a screening and a treatment period:

Screening: a period of 4-14 days during which subjects were to receive placebo metered-dose inhaler and placebo inhalation solution.

Treatment: a 12-week period during which subjects were to take double-blind treatment: FFIS, FA, or placebo. Day 1 of the period was the randomization date. Visits were to occur subsequently at weeks 4, 8, and 12. The primary endpoint data, FEV₁, was to be collected prior to and at various times up to 12 hours after the dose of trial medication.

Subjects

Subjects with the following characteristics were to be enrolled in the trial:

Inclusion criteria

- Male and female patients at least 40 years of age
- A medical diagnosis of COPD including persistent presence of cough, sputum production, and/or shortness of breath on effort
- Post-bronchodilator FEV₁ ≥30% and <70% of predicted normal, and FEV₁/FVC ratio <70%
- At Day 1 visit, pre-dose FEV₁ within (±)15% of the screening and pre-bronchodilator FEV₁ and <70% of predicted normal
- A current or prior history of > 10-pack years of cigarette smoking

Exclusion criteria

- Diagnosis of asthma
- Chest radiograph taken up to 12 months prior to the date of randomization diagnostic of an active or significant disease other than COPD
- Unstable or clinically significant disease other than COPD that could place the subject at risk of complications, interfere with study participation, or confound trial objectives. This includes
 - a myocardial infarction within 6 months prior to screening
 - inability to withhold restricted medications
- Use of non-selective beta-blockers or monoamine oxidase inhibitors
- Radiation or chemotherapy within the previous 12 months
- History of lobectomy
- Exacerbation of COPD within 30 days prior to the screening visit, with exacerbation of COPD defined as a change in symptoms that require:
 - a) an increase in use or the addition of one or more of the following:
corticosteroids, antibiotics, or oxygen for >3 days; or
 - b) hospitalization or an extension of a hospitalization
or both a) and b)
- Respiratory tract infection within 30 days prior to the screening visit

- Requirement for daily use of supplemental oxygen for >12 hours/day, within 30 days prior to the screening visit
- Requirement for oral prednisone >10 mg every day or >20 mg every other day (or equivalent oral dose of a different corticosteroid) or instability of dose of oral steroid in the 30 days prior to the screening visit
- Abnormal or clinically significant laboratory test during screening unexplained or related to a condition excluded by the protocol criteria
- Electrocardiogram (ECG) with a QTc >0.46 seconds

Comment: Eligibility criteria were reasonably designed to include a relevant population with COPD without complicating conditions for efficacy and safety considerations.

Eligibility criteria also included restrictions to avoid pregnancy, and requirements for willingness and ability to follow protocol requirements and exclusion for a history of hypersensitivity to β_2 -agonists, use of an investigational drug or device within 30 days prior to screening, participation in the Dey trial DL-059, and a history of illegal drug abuse or alcohol abuse within the past 5 years.

Treatment and blinding

The treatments were to be:

- Placebo Aerolizer® and FFIS (20 mcg), both twice daily
- Foradil® Aerolizer® and placebo inhalation solution, both twice daily
- Placebo Aerolizer® and placebo inhalation solution, both twice daily

Inhalation solution (placebo and FFIS) was to be delivered *via* the Pari LC Plus nebulizer with a Proneb compressor.

A double-dummy treatment technique was used to help maintain the blind. For each subject, treatment with the Aerolizer® was always to be given first.

Clinical supplies were packaged and supplied to the sites by Dey to maintain the blind.

Concomitant medications

Restrictions on concomitant medications included:

- Corticosteroids: In addition to restrictions for eligibility, the protocol stipulated that inhaled or intranasal corticosteroids, or oral or parenteral steroids be taken prior to study medications
- Caffeinated foods and beverages were not to be taken for at least 8 hours prior to spirometry
- Prohibited medications (with required washouts prior to the screening pulmonary function tests), were
 - Short- and long-acting inhaled and oral β_2 agonists
 - Xanthines
 - Inhaled and systemic anticholinergics; inhaled anticholinergic/ β -agonist inhalers
 - Tricyclic antidepressants
 - β_2 -receptor antagonists
 - Nedocromil or cromolyn sodium
 - Oral or parenteral corticosteroids >10 mg/day or >20 mg every other day

Albuterol was not to be used within 8 hours of spirometry

Procedures

The protocol mandated a 4-weekly monitoring of vital signs, ECG, spirometry, adverse events, and use of concomitant medications including albuterol as “rescue” for symptoms of asthma (Table 39). Collection of clinical hematology and chemistry data and Holter monitoring occurred at screening and the end of subject involvement in the trial.

Comment

The collection of clinical laboratory data was inadequate to determine any early changes that may have occurred with treatment, but given the extent of knowledge of β_2 -agonists generally, and given the information from trial DL-056, the data collection scheme was adequate.

Table 39. Protocol 201-065: Schedule of procedures

STUDY PERIOD	Screen	Double-blind Treatment				Early Termination
	Days - 14 to -4	Day 1	Week 4 ±3days	Week 8 ±3days	Week 12 ±3days	
VISIT	1	2	3	4	5	-
PROCEDURES:						ET
Written Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Medical History	X					
Physical Examination	X				X	X
Vital Signs (a)	X	X	X	X	X	X
ECG (b)	X		X	X	X	X
Holter Monitoring (c)	X				X	
Chest X-Ray	X					
Labs: Hematology, Serum Chemistry, Urinalysis, Serum Pregnancy	X				X	X
Spirometry: Pre- and Post-BD	X					
12 hour Spirometry		X	X	X	X	
SGRQ		X			X	X
Demonstrate Study Med+ Delivery	X	X				
Randomization		X				
Dispense: Study Diary	X	X	X	X		
Study Medication	X	X	X	X		
Rescue Medication	X	X	X	X		
Collect/Review: Study Diary		X	X	X	X	X
Study Medication		X	X	X	X	X
Rescue Medication		X	X	X	X	X
Review/Record: Smoking Status	X	X	X	X	X	X
AEs	X	X	X	X	X	X
Concomitant medications incl. albuterol	X	X	X	X	X	X

(a) Vital Signs (T, HR, RR, BP) should be measured with the patient seated and rested (>5mins).
 (b) ECGs should be obtained pre-dose and between 2 and 3 hours post-dose at Weeks 4, 8, and 12.
 (c) Holter monitoring should occur prior to the Day 1 and Week 12 visits.
 [Source: appendix_16-1-01-protocol.pdf, table 4.1.]

Discontinuations due to worsening

The protocol did not mandate discontinuation of subjects for exacerbations of COPD, but allowed investigator discretion. Specifically, the protocol stated that COPD exacerbations or

respiratory infections requiring treatment with antibiotics, a short-course of oral corticosteroids, or oxygen would not cause a subject to be discontinued from trial “as long as the therapy is: a) “short course”, <15 days, b) is not-used more than twice during the double-blind period, and c) is separated by >14 days.”

Statistical analysis

The primary efficacy variable was the standardized absolute area-under-the curve of FEV₁ in liters measured over 12 hours (AUC₍₀₋₁₂₎ (L) for FEV₁) following the morning dose of study medication at Week 12, determined in randomized patients who took double-blind study medication and had a baseline evaluation and at least 1 post-baseline evaluation (called the ITT population by Dey). It was analyzed statistically by ANCOVA, with the last FEV₁ measured before the first dose of trial drug on day 1 as a covariate. The primary contrast was between FFIS and placebo. A “completer” population was also specified as subjects who completed the double-blind period of the trial without a major protocol violation

Secondary outcomes, measured on the modified ITT population as described for the primary endpoint, included:

- standardized absolute AUC₍₀₋₁₂₎ (L) for FEV₁ at day 1 and weeks 4 and 8
- peak FEV₁ over the 12 hours following the morning dose at day 1 and weeks 4, 8, and 12
- “trough” FEV₁ at “approximately” 12 hours following morning dose at day 1 and weeks 4, 8, and 12
- FEV₁ “at all individual time points” during the 12 hours after morning dose at day 1 and weeks 4, 8, and 12
- standardized AUC₍₀₋₁₂₎ (L) for FVC during the 12 hours after morning dose at day 1 and weeks 4, 8, and 12
- daily albuterol use, averaged over the treatment period
- difference in results on St. George’s Respiratory Questionnaire between week 12 and day 1. The protocol declared that a difference of 4 points “is considered to be clinically relevant.”

Continuous secondary variables were to be analyzed according to the method described for the primary endpoint. Categorical variables were to be analyzed using the Cochran-Mantel-Haenszel test.

Comment

Several of the secondary endpoints are different ways of looking at the effect of FFIS on spirometrically determined lung function and are more appropriately considered sensitivity analyses. The albuterol use data provide more independent evidence of effect. Results of the St. George’s Respiratory Questionnaire can in principle be supportive, but there is inadequate support in the NDA submission for the proposed minimally important clinical difference of 4 points.

The sample size of the trial was calculated to give 90% power to detect a difference of 0.172 liters in standardized AUC₍₀₋₁₂₎ between FFIS and placebo, at an α level of 0.05. This calculation depended upon a standard deviation of 0.40-liters from Dahl et al. (2001). This sample size was notably less than that of DL-059, the trial that 201-065 replaced.

The protocol stated that FEV₁ and FVC data missing after 2 hours after administration of trial medication was to be imputed by LOCF and that subjects who dropped out prior to this time point would not be included in the efficacy analysis. However, the statistical analytical plan stated that in the case of missing data during the 12-hour FEV₁ measurement period after administration of trial

drug, the AUC would be standardized by the time observed. For missing visit areas-under-the-curve after baseline, the last available AUC was substituted.

Changes to the protocol

Dey made no changes to the protocol, but made minor changes to the statistical analytical plan, that is, changes to aspects of the plan other than the primary analysis, mostly prior to unblinding the data (one minor change was made after unblinding). These changes, as they did not affect the primary analysis, would not be expected to change the overall judgment of efficacy of FFIS.

Comment

The trial as designed was an adequate exploration of the effect of FFIS on bronchodilation. Although the primary contrast was to placebo, the trial included a critical comparison to FA. The trial included information on use of rescue medication as an objective measure of effect, and included diary information, which can be used to support a clinical effect of the β_2 -agonists.

10.1.4.2 Results

Investigational treatments

The investigational agents and modes of delivery were:

- Dey Formoterol Fumarate Inhalation Solution: Formulation Code/Batch Number: C062A
- Comparator Products: Foradil® Aerolizer® (manufactured by Novartis), Formulation Code/Batch Number: S4A026E
Mode of Administration: Dry Powder Inhaler via Foradil® Aerolizer®
- Placebo Inhalation Solution (manufactured by Dey, L.P.): Formulation Code/Batch Number: C070, C075
- Placebo Dry Powder (manufactured by _____); Formulation Code/Batch Number: 1253032-04, 1253032-05, 1253032-06
Mode of Administration: Dry Powder Inhaler via Aerolizer®

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Subjects

Three hundred fifty-one subjects enrolled at 38 sites, all in the United States. No site had a notable preponderance of subjects (Table 40).

Table 40. Trial 201-065: Enrollment numbers by site

Subjects/site	Number of sites
1-5	12
6-10	14
11-14	4
16-20	5
22-28	3

Comment

Enrollment in trial 201-065 was notably less by design (a little over one-half) than that in DL-059, the trial it replaced.

Notable baseline demographic characteristics are shown in Table 41. These were balanced among the treatment arms.

Table 41. Trial 201-065: Baseline demographics (modified ITT population)

	FFIS n=123	FA n=114	Placebo n=114
Age (Years)			
Mean (SD)	61.8 (8.64)	63.0 (9.41)	63.5 (9.18)
Median	62.0	64.0	63.0
Range	40, 83	44, 86	42, 86
Less than 65	75 (61.0)	63 (55.3)	62 (54.4)
65 or greater	48 (39.0)	51 (44.7)	52 (45.6)
Gender (n, %)			
Male	71 (57.7)	61 (53.5)	65 (57.0)
Female	52 (42.3)	53 (46.5)	49 (43.0)
Race (n, %)			
Caucasian	108 (87.8)	95 (83.3)	98 (86.0)
Hispanic	4 (3.3)	6 (5.3)	3 (2.6)
Black	11 (8.9)	13 (11.4)	12 (10.5)
Asian	0	0	1 (0.9)

[Source: section-1-15-report-body.pdf, table 11.2.1]

The trial population was generally considerably older than the lower limit of eligibility. There were more men than women in the trial, consistent with the proportions of men and women with COPD in the U.S.¹ The trial population was predominantly Caucasian, unlike the more similar prevalence of the disease among “white,” “black,” and “other” populations.¹ However, this does not limit the applicability of the trial result to the non-“white” population.

About half the subjects were stated that they smoked at some point in the trial. The trial population had notable obstructive airways disease, which was balanced for severity across treatment groups (Table 42).

Across the treatment groups 61-64% of subjects used at least one drug for obstructive airway disease at baseline. From 39-43% of subjects took salbutamol, from 15-18% took Combivent®, from 13-15% took Seretide Mite®, from 6-9% took ipratropium bromide, and use of numerous other medications for COPD (less commonly used in this trial) was also balanced.

Table 42. Trial 201-065: Baseline pulmonary characteristics (ITT population)

		FFIS 20 µg	FA 12 µg	Placebo
Actual FEV ₁ (L)	Pre-Bronchodilator			
	<i>n</i>	123	114	113
	Mean (SD)	1.35 (0.460)	1.30 (0.392)	1.36 (0.496)
	Median	1.25	1.25	1.25
	Min, Max	0.45, 2.88	0.50, 2.59	0.41, 2.79
	Post-Bronchodilator			
	<i>n</i>	122	114	114
	Mean (SD)	1.51 (0.466)	1.49 (0.423)	1.51 (0.465)
	Median	1.44	1.44	1.38
	Min, Max	0.54, 2.70	0.75, 2.95	0.65, 2.70
FEV ₁ / FVC	Pre-Bronchodilator			
	<i>n</i>	123	114	113
	Mean (SD)	0.53 (0.098)	0.53 (0.103)	0.54 (0.100)
	Median	0.52	0.53	0.55
	Min, Max	0.30, 0.74	0.32, 0.71	0.31, 0.72
	Post-Bronchodilator			
	<i>n</i>	122	114	114
	Mean (SD)	0.54 (0.096)	0.54 (0.091)	0.54 (0.093)
	Median	0.55	0.56	0.55
	Min, Max	0.31, 0.69	0.36, 0.69	0.32, 0.69
% Predicted FEV ₁	Pre-Bronchodilator			
	<i>n</i>	123	114	113
	Mean (SD)	44.27 (11.499)	43.91 (11.614)	45.27 (13.208)
	Median	44.24	42.75	45.72
	Min, Max	19.36, 70.21	19.97, 69.27	20.71, 76.60
	Post-Bronchodilator			
	<i>n</i>	122	114	114
	Mean (SD)	49.61 (11.153)	50.13 (11.022)	49.93 (11.837)
	Median	50.49	51.17	50.91
	Min, Max	29.44, 69.50	30.07, 70.47	26.74, 72.22
	Median	50.49	51.17	50.91
	Min, Max	29.44, 69.50	30.07, 70.47	26.74, 72.22

[Source: section-1-15-report-body.pdf, table 14.1.3]

Discontinuations

Discontinuations (Table 42) occurred almost twice as frequently in the placebo group as in each active group. For placebo subjects, adverse events were marginally the most common reason for discontinuation. In the active groups, adverse events and unexplained loss of the subject to trial monitoring (“Lost to follow-up”) were the primary reasons for discontinuation.

Table 43. Trial 201-065: Subject disposition

	FFIS	FA	Placebo
Patients Randomized (N)	123	114	114
ITT Population (n, %)	123 (100.0)	114 (100.0)	114 (100.0)
Patients Completed (n, %)	106 (86.2)	98 (86.0)	84 (73.7)
Patients Discontinued (n, %)	17 (13.8)	16 (14.0)	30 (26.3)
Reason For Discontinuation (n, %)*			
Adverse Event	4 (3.3)	4 (3.5)	10 (8.8)
Protocol Violation	1 (0.8)	6 (5.3)	3 (2.6)
Lost to Follow-up	5 (4.1)	4 (3.5)	7 (6.1)
Withdrawal of Consent	4 (3.3)	2 (1.8)	4 (3.5)
Other	3 (2.4)	0	6 (5.3)
Time To Treatment Discontinuation			
N	17	16	30
Mean (SD)	40.5 (30.53)	26.6 (28.64)	40.9 (27.53)
Median	30.0	15.5	28.5
Min, Max	3, 97	1, 87	3, 88

[Source: section-1-15-report-body.pdf, table 10.1.1]

Protocol violations

Protocol violations related to subject assessments and enrollment were infrequent enough to permit an assessment of efficacy and safety. A review of all protocol violations showed that the numbers and nature of these violations, including violations that might have an effect on the primary outcome measure (such as the absence or timing of an FEV₁ measurement) were balanced, and would not be expected to have had a notable influence on the primary efficacy analysis.

Treatment "compliance"

Dey measured compliance with the treatment regimen as a proportion of doses returned at clinic visits to those expected to have been taken. When measured this way, between 96.5% and 98.4% of subjects (least in FA, most in FFIS) took between 80-120% of assigned doses of their nebulizer or Aerolizer® treatments. One subject (in the FA arm) was noted as taking over 120% of assigned treatment, for both nebulizer and Aerolizer® treatment.

Concomitant medication use

An imbalance in the use of specific concomitant medications might signal a difficulty in the interpretation of safety or efficacy findings. Use of concomitant medications for respiratory conditions was balanced among the treatment arms, and use of medications for other conditions did not fall into a concerning pattern (not shown).

Efficacy

Table 44 shows mean FEV₁ at baseline and the standardized area-under-the-curve of FEV₁ at week 12 for the ITT population. This summary used a last-observation-carried forward technique of imputation.

Table 44. Trial 201-065: Baseline FEV₁ and end-of-trial (week 12) postbronchodilator FEV₁ AUC_(0-12h), last observation carried forward (ITT population)

	FFIS 20 µg	FA 12 µg	Placebo
Baseline FEV ₁ (L)			
n	123	114	114
Mean (SD)	1.32 (0.431)	1.28 (0.393)	1.32 (0.484)
Median	1.27	1.21	1.25
Range	0.47, 2.61	0.49, 2.54	0.45, 2.56
Standardized Week 12 FEV ₁ AUC ₍₀₋₁₂₎ (L)*			
n	123	114	114
Mean (SD)	1.51 (0.518)	1.49 (0.461)	1.33 (0.566)
Median	1.44	1.39	1.21
Range	0.50, 3.52	0.56, 2.69	0.57, 3.35

* This is the AUC of FEV₁ divided by the number of hours of observation
 [Source: section-1-15-report-body.pdf, Table 11.4.1.1.1]

In Dey's primary efficacy analysis (Table 45), the difference in FEV₁ between each active group and placebo exceeded 0.15 liters, and the p-value for each treatment against placebo was <0.001. The active treatment groups did not differ statistically.

One standard used to determine noninferiority of a treatment to a known active standard is a determination of whether at least half of the treatment effect is preserved by the new treatment. In trial 201-065, the lower limit of the confidence interval around the difference of the mean treatment effects of FFIS and FA is less than half of the overall treatment effect produced by (Foradil®) against placebo (that is, 0.085 is less than half of 0.205). This supports the comparability of the treatments in terms of efficacy.

Table 45. Trial 201-065: Primary efficacy results: Postbronchodilator standardized AUC_(0-12h) of FEV₁ at 12 weeks (last-observation-carried forward, ITT population)

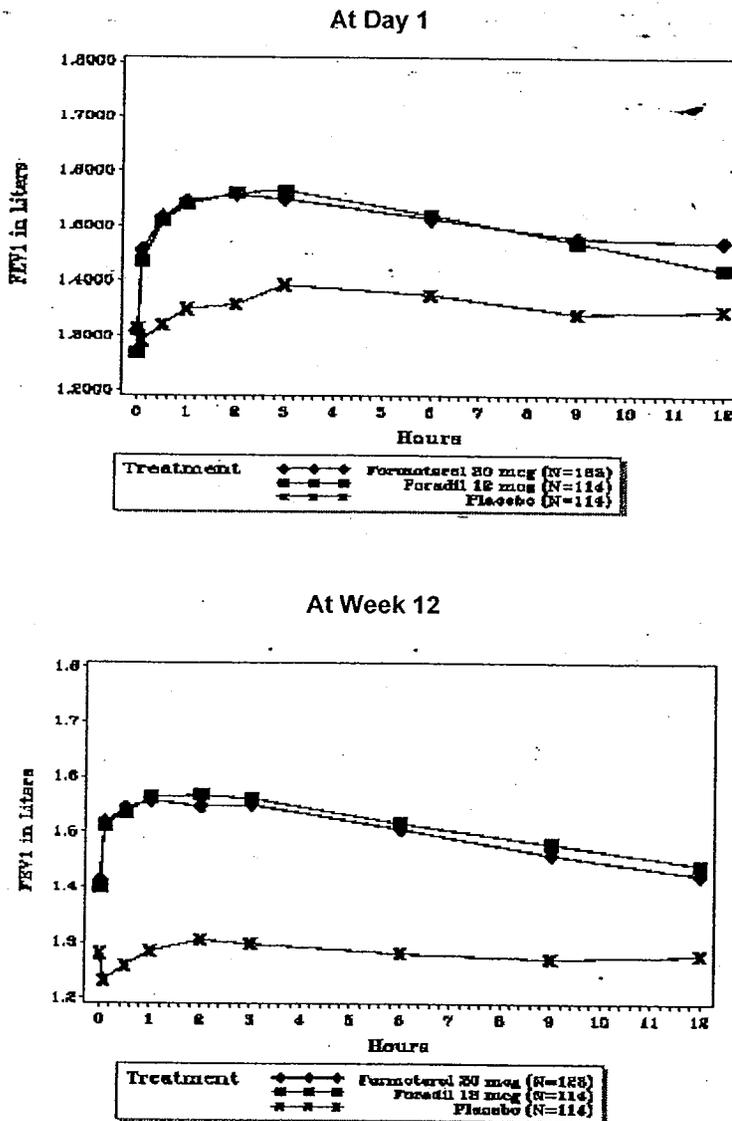
Treatment Comparison	LS Means (liters)		LS Mean Difference	95% Confidence Interval	p-value*
Formoterol vs. Placebo	1.492	1.306	0.185	0.120, 0.251	<0.0001
Foradil® vs. Placebo	1.511	1.306	0.205	0.138, 0.272	<0.0001
Formoterol vs. Foradil®	1.492	1.511	-0.020	-0.085, 0.046	0.5546

* ANCOVA model with treatment and center as fixed effects and baseline FEV₁ as the covariate
 [Source: section-1-15-report-body.pdf, Table 11.4.1.1.2]

For the primary analysis Dey "standardized" areas-under-the-curve of FEV₁ by the amount of time of observation (the area was divided by the amount of time observed). The amount of data missing as a result of subjects not receiving FEV₁ measurements out to 12 hours was small (about 80-90% of subjects had data at 12 hours). The FDA statistical reviewer performed an analysis of nonstandardized AUC data and concluded, "These results are consistent with those based on standardized AUC of FEV₁ as presented in the sponsor's study report."

Figure 3 shows plots of post-treatment FEV₁ (least squares means, based on an ANCOVA model with treatment and center as fixed effects and Day 1 Pre-Dose FEV₁ as the covariate) at baseline and at week 12.

Figure 3. Trial 201-065: Least-Squares mean FEV₁ changes over 12 hours after treatment



[Source: summary-clin-efficacy-copd.pdf, Figure 2.7.3.2.1 and Figure 2.7.3.2.2]

The magnitude of the peak post-treatment FEV₁ change from baseline for either active treatment is somewhat less than what Foradil[®] 12 mcg BID produced in that drug's pivotal trials (peak FEV₁ change from baseline approached 0.5 liters). However, in this trial both FFIS and FA produced similar bronchodilation clearly better than placebo. Post-treatment bronchodilation fell by the second visit (week 4, not shown) for both active treatments. Both at baseline and at week 12, both active treatments were better than placebo at all post-baseline time points.

The estimate of the difference between FFIS (20 µg) and placebo in AUC FEV_{1(0-12h)} in this trial using observed FEV₁ data (nonstandardized AUC) is 2.57 l·hr (see FDA statistical review).

This difference is similar to the difference between FFIS 20 µg and placebo previously seen in trial DL-057 after a single dose (19.9 for FFIS 20 µg and 17.5; difference of 2.4 l-hr).

Sensitivity analyses

FEV₁ results for the completer population (Table 46) are similar to those for the primary efficacy population.

Table 46. Trial 201-065: Baseline FEV₁ and end-of-trial (week 12) postbronchodilator FEV₁ AUC_(0-12h) (Completer analysis)

	FFIS 20 µg	FA 12 µg	Placebo
Baseline FEV ₁			
<i>n</i>	91	84	67
Mean (SD)	1.28 (0.437)	1.26 (0.380)	1.37 (0.436)
Median	1.24	1.21	1.28
Range	0.47, 2.61	0.54, 2.54	0.59, 2.47
Week 12 FEV ₁ AU ₍₀₋₁₂₎			
<i>n</i>	91	84	67
Mean (SD)	1.47 (0.528)	1.47 (0.434)	1.37 (0.499)
Median	1.37	1.40	1.30
Range	0.50, 3.52	0.56, 2.69	0.68, 2.79

[Source: section-1-15-report-body.pdf, Table 11.4.1.1.1]

Dey compared the effect of FFIS on the endpoint AUC compared to placebo (Table 47). The results are similar to those of the primary analysis.

Table 47. Trial 201-065: Comparison of FFIS to placebo at endpoint (completer population)

Treatment Comparison	LS Means		LS Mean Difference	95% Confidence Interval	p-value*
FFIS vs. Placebo	1.495	1.288	0.207	0.127, 0.287	<0.0001

* ANCOVA model with treatment and center as fixed effects and baseline FEV₁ as the covariate
 [Source: section-1-15-report-body.pdf, Table 11.4.1.1.1]

Dey concluded that the FEV₁ results do not fall into a normal distribution, and performed an ANCOVA on a rank-ordered distribution. This analysis (not shown) resulted in the same statistical conclusion as the primary analysis.

The relatively large proportion of discontinuers raises the question whether the method of imputation was critical to the findings of the trial. Upon request, Dey performed analyses of the primary endpoint using various techniques of handling missing data (Table 48).

Table 48. Dey sensitivity analyses for primary endpoint analysis (modified ITT population): Comparison of FFIS to Placebo FEV₁ AUC(0-12h)

Analysis	Least-squares mean difference, FFIS vs. placebo (liters)	p-value
Primary: standardization of AUC, with imputation of the last measured AUC for missing visits	0.185	<0.0001
Imputation of the predose FEV ₁ for missing data during a visit, with imputation of the last measured AUC for missing visits	0.180	<0.0001
Imputation of the predose FEV ₁ for missing data during a visit, with imputation of the highest AUC value for placebo-treated subjects and lowest post-dose AUC value for active-treated subjects	0.153	<0.0001
Imputation of the median FEV ₁ at a timepoint (for all subjects) for missing data during a visit, with imputation of the highest AUC value for placebo-treated subjects and lowest post-dose AUC value for active-treated subjects	0.107	0.0022
Imputation of the best FEV ₁ value for placebo-treated subjects and worst post-dose FEV ₁ value for active-treated subjects, with imputation of the highest AUC value for placebo-treated subjects and lowest post-dose AUC value for active-treated subjects	0.138	<0.0001

[Source: Dey NDA 22-007 submission of 1/25/07]

All analyses yielded a statistical value well below 0.05 for the comparison of FFIS to placebo. While the actual value of the p-value is hard to interpret, the consistency shows that the results are robust. Dey performed an analysis of the primary endpoint using observed data only (no LOCF) as a secondary endpoint (see secondary endpoint review below).

Subgroup analyses

Table 49 shows Dey's analysis of the primary endpoint analyzed with respect to subgroups of age (<65 or ≥65 years old) and sex. There was no notable difference of the effect of FFIS with respect to age or sex. The age cutoffs chosen by Dey were reasonable. Since between only 12-17% of the subjects were nonCaucasian, and these were distributed among "blacks," Hispanics, and Asians (primarily "blacks"), subset analyses by race would not be expected to be helpful.

Table 49. Trial 201-065: Comparison of FFIS to placebo at Week 12 by subgroups of age and sex

Subgroup	LS Means		LS Mean Difference	95% Confidence Interval	p-value*
	FFIS	Placebo			
<65	1.628	1.440	0.188	0.083, 0.292	0.0005
≥65	1.287	1.142	0.146	0.072, 0.219	0.0001
Male	1.668	1.487	0.181	0.074, 0.289	0.0011
Female	1.257	1.082	0.175	0.107, 0.243	<.0001

* ANCOVA model with treatment and center as fixed effects and baseline FEV₁ as the covariate

[Source: Trial 201-065 section-1-15-report Tables 14.2.2.8.2,4,6,8]

Secondary endpoints

Several of the secondary endpoints are different ways of looking at the effect of FFIS on FEV₁ and are more appropriately considered sensitivity analyses. The secondary endpoint examining FVC relies on the same spirometric data, and is minimal additional support. Albuterol use provides some nonspirometric, clinical support. The St. George's Respiratory Questionnaire data have uncertain clinical importance, but improvements on diary data is supportive of a benefit.

- Standardized FEV₁ AUC_(0-12h) based on observed data (no last-observation-carried forward)
 Dey analyzed standardized FEV₁ AUC_(0-12h) data without using the last-observation-carried forward, i.e., on observed data only. Table 50 shows selected (baseline and 12-week) data upon which the statistical tests were done. The numbers of subjects were notably lower at the last visit.

Table 50. Trial 201-065: FEV₁ AUC based on observed data (no LOCF), (modified ITT population)

		FFIS 20 µg n=123	FA 12 µg n=114	Placebo n=114
Day 1 (Baseline)	n	123	114	114
	Mean (SD)	1.52 (0.465)	1.48 (0.458)	1.37 (0.531)
	Median	1.45	1.41	1.27
	Min, Max			
Week 12	n	105	98	84
	Mean (SD)	1.49 (0.536)	1.47 (0.453)	1.33 (0.528)
	Median	1.42	1.39	1.25
	Min, Max			

[Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.1.1]

b(4)

Table 51 shows that the last-observation-carried forward technique was not critical to the outcome of the primary analysis. The results of the ANCOVA without LOCF mirrored those of the primary analysis.

Table 51. Trial 201-065: Week 12 FEV₁ AUC ANCOVA based on observed data (no LOCF)

Treatment Comparison	LS Means		LS Mean Difference	95% Confidence Interval	p-value*
Formoterol vs. Placebo	1.495	1.278	0.217	0.146, 0.288	<.0001
Foradil® vs. Placebo	1.513	1.278	0.235	0.162, 0.307	<.0001
Formoterol vs. Foradil	1.495	1.513	-0.018	-0.086, 0.050	0.6009

* ANCOVA model with treatment and center as fixed effects and baseline FEV₁ as the covariate.

[Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.1.2]

- Peak FEV₁

Table 52 is a summary of the observed peak post-dose FEV₁ values at baseline and Week 12. These results paralleled those of the AUC of FEV₁.

Table 52. Trial 201-065: Peak FEV₁, (modified ITT population)

		FFIS 20 µg n=123	FA 12 µg n=114	Placebo n=114
Day 1 (Baseline)	n	123	114	114
	Mean (SD)	1.69 (0.554)	1.63 (0.506)	1.52 (0.598)
	Median	1.63	1.58	1.37
	Min, Max			
Week 12	n	105	98	84
	Mean (SD)	1.65 (0.596)	1.62 (0.487)	1.47 (0.553)
	Median	1.61	1.56	1.40
	Min, Max			

[Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.2.1]

b(4)

Table 53 shows Dey's statistical analysis of the peak FEV₁ data, which parallels that of the AUC of FEV₁.

Table 53. Trial 201-065: Week 12 peak FEV₁

Treatment Comparison	LS Means		LS Mean Difference	95% Confidence Interval	p-value*
	Formoterol vs. Placebo	Foradil [®] vs. Placebo			
Formoterol vs. Placebo	1.663	1.416	0.247	0.174, 0.320	<.0001
Foradil [®] vs. Placebo	1.668	1.416	0.252	0.177, 0.327	<.0001
Formoterol vs. Foradil [®]	1.663	1.668	-0.005	-0.075, 0.065	0.8857

* ANCOVA model with treatment and center as fixed effects and baseline FEV₁ as the covariate.
 [Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.2.2]

• **Trough FEV₁**

Table 54 is a summary of trough FEV₁, defined as FEV₁ at approximately 12 hours after the morning dose, at baseline and Week 12.

Table 54. Trial 201-065: Trough FEV₁ (modified ITT population) at approximately 12 hours after the morning dose

		FFIS 20 µg n=123	FA 12 µg n=114	Placebo n=114
Day 1 (Baseline)	n	123	114	114
	Mean (SD)	1.46 (0.484)	1.39 (0.473)	1.34 (0.533)
	Median	1.37	1.31	1.22
	Min, Max	0.47, 2.95	0.55, 3.02	0.55, 2.73
Week 12	n	105	98	84
	Mean (SD)	1.41 (0.546)	1.41 (0.458)	1.32 (0.550)
	Median	1.32	1.35	1.24
	Min, Max			

[Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.3.1]

Table 55 is that statistical analysis of trough FEV₁. The analysis parallels that of the FEV₁ AUC.

Table 55. Trial 201-065: Baseline and Week 12 trough FEV₁ at approximately 12 hours after the morning dose

Visit	Treatment Comparison	LS Means		LS Mean Difference	95% Confidence Interval	p-value*
		Formoterol vs. Placebo	Foradil [®] vs. Placebo			
Day 1 (Baseline)	Formoterol vs. Placebo	1.444	1.319	0.125	0.058, 0.191	0.0003
	Foradil [®] vs. Placebo	1.414	1.319	0.094	0.026, 0.162	0.0067
	Formoterol vs. Foradil [®]	1.444	1.414	0.031	-0.036, 0.097	0.3664
Week 12	Formoterol vs. Placebo	1.412	1.270	0.143	0.067, 0.219	0.0003
	Foradil [®] vs. Placebo	1.453	1.270	0.183	0.106, 0.261	<.0001
	Formoterol vs. Foradil [®]	1.412	1.453	-0.040	-0.114, 0.033	0.2769

* ANCOVA model with treatment and center as fixed effects and baseline FEV₁ as the covariate.
 [Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.3.2]

Dey also summarized trough FEV₁, measured predose at the beginning of the dosing interval. Table 56 shows summary statistics at Day 1 and Week 12. These results are not notably different from the prespecified trough FEV₁ secondary endpoint.

Table 56. Trial 201-065: Supplemental analysis of trough FEV₁ (modified ITT population)

		FFIS 20 µg n=123	FA 12 µg n=114	Placebo n=114
Day 1 (Baseline)	n	123	114	114
	Mean (SD)	1.32 (0.431)	1.28 (0.393)	1.32 (0.484)
	Median	1.27	1.21	1.25
	Min, Max	0.47, 2.61	0.49, 2.54	0.45, 2.56
Week 12	n	104	97	84
	Mean (SD)	1.41 (0.511)	1.36 (0.426)	1.33 (0.512)
	Median	1.30	1.29	1.28
	Min, Max			

[Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.9.2]

• *Changes from predose FEV₁ over time at each visit*

Dey performed an ANCOVA with treatment and center as fixed effects and baseline FEV₁ (Day 1 pre-dose) as the covariate for each active treatment against placebo and each active treatment against the other. The p-value for the difference of FFIS to placebo in FEV₁ at baseline and each subsequent visit was less than 0.001 at each time point. The exact value of the p-value is difficult to interpret, as they are not adjusted for multiplicity, but they show a consistency of effect.

• *Standardized FVC AUC_(0-12h)*

The effects of the active treatments on the area-under-the-curve of FVC paralleled those on FEV₁ (Table 57 and Table 58). The effect of each active treatment was consistent with the Week 12 results at each visit (not shown).

Table 57. Trial 201-065: Standardized FVC AUC_(0-12h) (modified ITT population)

		FFIS 20 µg n=123	FA 12 µg n=114	Placebo n=114
Day 1 (Baseline)	n	123	114	114
	Mean (SD)	2.82 (0.775)	2.72 (0.825)	2.51 (0.827)
	Median	2.71	2.55	2.26
	Min, Max	1.58, 5.52	1.41, 5.03	0.99, 5.30
Week 12	n	105	98	84
	Mean (SD)	2.73 (0.784)	2.67 (0.791)	2.44 (0.763)
	Median	2.60	2.46	2.26
	Min, Max			

[Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.5.1]

Table 58. Trial 201-065: Statistical analysis of Week 12 standardized FVC AUC_(0-12h)

Treatment Comparison	LS Means		LS Mean Difference	95% Confidence Interval	p-value*
Formoterol vs. Placebo	2.739	2.398	0.341	0.191, 0.491	<.0001
Foradil [®] vs. Placebo	2.743	2.398	0.344	0.191, 0.497	<.0001
Formoterol vs. Foradil [®]	2.739	2.743	-0.003	-0.147, 0.140	0.9620

* ANCOVA model with treatment and center as fixed effects and baseline FEV₁ as the covariate.

[Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.5.2]

• *Use of albuterol*

Daily numbers of puffs of albuterol from a metered-dose inhaler are summarized in Table 59. Usage during the placebo screening period was similar among the groups, and remained stable in the placebo group while dropping by a little over 1 puff per day in each active group. The drop in albuterol usage was near maximal during the first 4-week period, and remained stable during subsequent periods.

Table 59. Trial 201-065: Daily albuterol puffs (modified ITT population)

		FFIS 20 µg n=123	FA 12 µg n=114	Placebo n=114
Screening Day 1	n	122	114	113
	Mean (SD)	2.82 (2.754)	2.45 (2.767)	2.80 (2.965)
	Median	2.00	1.38	2.00
	Min, Max	0.0, 10.1	0.0, 10.7	0.0, 14.6
Day 1 - Week 4	n	122	111	110
	Mean (SD)	1.63 (2.430)	1.57 (2.070)	2.86 (3.084)
	Median	0.56	0.64	2.00
	Min, Max	0.0, 13.1	0.0, 8.5	0.0, 15.7
Week 4 - Week 8	n	112	101	99
	Mean (SD)	1.53 (2.312)	1.53 (2.007)	2.91 (3.173)
	Median	0.48	0.64	2.09
	Min, Max	0.0, 11.5	0.0, 8.3	0.0, 16.9
Week 8 - Week 12	n	107	98	88
	Mean (SD)	1.50 (2.208)	1.48 (1.891)	2.71 (3.079)
	Median	0.34	0.42	1.93
	Min, Max	0.0, 10.1	0.0, 7.6	0.0, 17.1

[Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.6.1]

Table 60 shows, for albuterol use, the least-squares means and the statistical evaluation for screening to day 1 and for the last 4-week treatment period. The p-value for the difference from placebo for each active treatment was at or below 0.0002 for both the other post-day 1 periods (not shown). These results are supportive of efficacy, although the clinical impact of a just-over 1 puff-per-day decrease in albuterol use is not large.

Table 60. Trial 201-065: Daily albuterol puffs (modified ITT population)

Visit	Treatment Comparison	LS Means		LS Mean Difference	95% Confidence Interval	p-value*
Screening to Day 1	Formoterol vs. Placebo	2.722	2.698	0.024	-0.651, 0.700	0.9431
	Foradil [®] vs. Placebo	2.402	2.698	-0.295	-0.984, 0.393	0.3993
	Formoterol vs. Foradil [®]	2.722	2.402	0.320	-0.355, 0.995	0.3516
Weeks 8-12	Formoterol vs. Placebo	1.438	2.692	-1.254	-1.914, -0.594	0.0002
	Foradil [®] vs. Placebo	1.447	2.692	-1.245	-1.920, -0.570	0.0003
	Formoterol vs. Foradil [®]	1.438	1.447	-0.009	-0.652, 0.634	0.9776

* ANCOVA model with treatment and center as fixed effects.

[Source: Trial 201-065 section-1-15-report-body.pdf, Table 14.2.2.6.2]

• *St. George's Respiratory Questionnaire results*

Table 61 shows Dey's analysis of the total score on the SGRQ at baseline and the changes at week 12.

Table 61. Trial 201-065: Total score on St. George's Respiratory Questionnaire at baseline and change at 12 weeks (modified ITT population)

Visit	Treatment Comparison	LS Means		LS Mean Difference	95% Confidence Interval	p-value*
Baseline						
Screening to Day 1	Formoterol vs. Placebo	47.847	48.526	-0.679	-5.054, 3.696	0.7604
	Foradil [®] vs. Placebo	49.700	48.526	1.174	-3.297, 5.645	0.6057
	Formoterol vs. Foradil [®]	47.847	49.700	-1.853	-6.257, 2.552	0.4085
Change from baseline to Week 12 or early termination						
Weeks 8-12	Formoterol vs. Placebo	-5.558	-0.650	-4.908	-8.445, -1.370	0.0067
	Foradil [®] vs. Placebo	-4.109	-0.650	-3.459	-7.111, 0.193	0.0633
	Formoterol vs. Foradil [®]	-5.558	-4.109	-1.449	-4.982, 2.085	0.4202

* ANCOVA model with treatment and center as fixed effects and baseline FEV₁ as the covariate
 [Source: Trial 201-065 section-1-15-report-body.pdf, Table 11.4.1.2.7.1]

The least squares mean differences from placebo in the change from baseline to week 12 in the symptom score were 5.7 and 7.3 for FFIS and FA, respectively; for the activity score, 3.3 and 2.7 for FFIS and FA, respectively, and for the impact score, 5.4 and 3.7, respectively.

Dey did not provide details of the scoring methods for the St. George's Respiratory Questionnaire. Although the statistical analytical plan declared a difference of 4 points in the total score (or for the subscale score called the "impact" score) as clinically significant, the NDA does not contain support for declaration. These results support efficacy for both active products but are not independent, clinically meaningful measures of efficacy.

• *Post-dose immediate bronchodilation*

In an analysis not specified in the protocol, Dey summarized the FEV₁ results in terms of numbers and percents of subjects whose FEV₁ increased by 15% or more after trial treatment. This was based on the intent-to-treat population.

Table 62, based on an analysis of the SPIRO_D data set performed by the FDA statistical reviewer, shows the numbers and percents of FFIS and placebo groups whose FEV₁ increased by 5% from predose values 5 minutes after dosing at Day 1 and the Week 12 visit, based on observed data.

Table 62. Trial 201-065: FEV₁ increases by ≥15% at 5 minutes post-dose (observed subjects)

		FFIS	Placebo
Day 1	<i>n</i>	123	114
	Yes	38 (31%)	9 (8%)
	No	85 (69%)	105 (92%)
Week 12	<i>n</i>	106	84
	Yes	25 (24%)	4 (5%)
	No	81 (76%)	80 (95%)

Using the Fisher's exact test, the FDA statistical reviewer obtained a p-value of 0.00000547 for the Day 1 comparison to placebo and 0.0004 for the Week 12 results.

Based on my analysis of the SPIRO_D data set, the proportions of subjects with FEV₁ increases by ≥15% at 5 minutes post-dose were similar in the Foradil[®]-treated subjects (at Day 1 and

Week 12, 41/114 (36%) and 17/98 (17%), respectively) to the proportions in the FFIS groups shown in Table 62.

Comment

Despite showing a statistical difference from placebo in the numbers of subjects with criterion changes from baseline FEV₁, this analysis is insufficient to justify a label claim for early-onset bronchodilation.

Safety

Exposure

In the calculation of exposure, Dey considered the placebo to have the same dose as the matching active treatment (Table 63). The duration of exposure and doses of Aerolizer® were approximately equal between the two treatment groups, and greater than that for placebo. This is consistent with the greater number of discontinuers in the placebo group. Dey notes that 2 subjects were omitted from this analysis, as they were lost to monitoring prior to week 4, when data were collected. This omission would not have changed the analysis notably compared to the full data set.

Table 63. Trial 201-065: Exposure (Safety population)*

Statistics	FFIS 20mcg (n=123)		FA 12mcg (n=114)		Placebo (n=114)	
	Placebo Aerolizer®	Nebulizer	Aerolizer®	Placebo Nebulizer	Aerolizer®	Nebulizer
<i>n</i>	123	123	113	113	113	113
Cumulative Dose (mcg)						
Mean (SD)	1812.2 (489.55)	3024.4 (808.73)	1776.3 (544.11)	2965.7 (907.43)	1698.3 (586.14)	2831.5 (968.61)
Median	1992.0	3320.0	1980.0	3320.0	1980.0	3320.0
Range	72, 2232	120, 3760	12, 2268	20, 3660	60, 2412	100, 3760
Duration of exposure (days)						
<i>n</i>	123		113		113	
Mean (SD)	78.1 (20.22)		76.6 (23.01)		73.1 (23.87)	
Median	85.0		85.0		85.0	
Range	3, 97		1, 100		3, 92	

* Two subjects were omitted from this analysis

[Source: Trial 201-065 section-1-15-report-body pdf Table 12.1.1]

The proportions of the nominal dose received per day (40 µg per day for the FFIS group and 24 µg per day for the FA group), calculated as mean cumulative dose divided by days of exposure, were nearly 100% (approximately 96% and 97% for the FFIS nebulizer and FA Aerolizer®, and for the placebo group, 97% (for Aerolizer® placebo and nebulizer)).

Adverse events

Deaths

Two subjects died during the run-in period of the trial (anaphylactic shock before receiving any run-in placebo and “probable atherosclerotic heart disease” after two weeks of placebo).

Serious adverse events

The few serious adverse events occurred with no pattern of concern:

- FFIS: multiple traumatic injuries due to a road traffic accident in a subject
- FA: Subjects had cellulitis of the leg; acute renal failure; dislocation of hip; joint dislocation due to failed arthroplasty

- Placebo: exacerbation of COPD (n=2), surgical excision of meningioma; pancreatic carcinoma; appendicitis

Discontinuations due to adverse events

The few discontinuations that occurred due to adverse events exhibited no pattern of concern. Subjects treated with placebo discontinued for COPD exacerbation more frequently than those from either active treatment.

- FFIS: Subjects discontinued for chest discomfort and muscle cramps; nervousness, anxiety, headache, and dry mouth; chest pain; COPD exacerbation; multiple injuries related to auto accident
- FA: Subjects discontinued for chest pain; COPD exacerbation; visual disturbance; acute renal failure
- Placebo: Subjects discontinued for COPD exacerbation (n=6); QT prolongation; laryngospasm; dyspnea; meningioma

All adverse events

Adverse events that occurred in 2% or more of any treatment group are shown in Table 64, where subjects are counted once, even if they had more than one adverse event, within an adverse event category, and once in the system organ class (review of the rest of the adverse events does not show any other events of concern). The most remarkable finding is that active treatment of either drug was associated with fewer events in the category "Respiratory, thoracic and mediastinal disorders." However, the differences between the active treatment groups, and between either active group and placebo in specific events in this category, was not notable. There was no notable difference between either active treatment group and placebo in terms of the cardiac events reported (not shown in Table 64: palpitations, AV block first degree, and atrial fibrillation). Only 1 subject (FA) reported tremor.

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Table 64. Trial 201-065: Subjects with adverse events by organ class and preferred term (Safety population), occurring in ≥ 2 subjects and $\geq 1\%$ greater than placebo in either active treatment group

MedDRA System Organ Class Preferred term	FFIS 20 μ g (n=123)	FA 12 μ g (n=114)	Placebo (n=114)
INFECTIONS AND INFESTATIONS	19 (15.4)	20 (17.5)	19 (16.7)
Nasopharyngitis	4 (3.3)	2 (1.8)	2 (1.8)
Gastroenteritis Viral	2 (1.6)	1 (0.9)	0
Cystitis	0	2 (1.8)	0
Sinusitis	0	4 (3.5)	2 (1.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	17 (13.8)	20 (17.5)	30 (26.3)
Dyspnoea Exacerbated	0	3 (2.6)	0
GASTROINTESTINAL DISORDERS	15 (12.2)	14 (12.3)	18 (15.8)
Diarrhoea	6 (4.9)	2 (1.8)	4 (3.5)
Nausea	6 (4.9)	4 (3.5)	3 (2.6)
Dry Mouth	4 (3.3)	2 (1.8)	2 (1.8)
Stomach Discomfort	2 (1.6)	0	0
NERVOUS SYSTEM DISORDERS	12 (9.8)	16 (14.0)	9 (7.9)
Dizziness	3 (2.4)	8 (7.0)	1 (0.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	9 (7.3)	10 (8.8)	3 (2.6)
Myalgia	2 (1.6)	0	0
Pain In Extremity	1 (0.8)	3 (2.6)	1 (0.9)
Intervertebral Disc Protrusion	0	2 (1.8)	0
SKIN & SUBCUTANEOUS TISSUE DISORDERS	6 (4.9)	4 (3.5)	3 (2.6)
Rash	2 (1.6)	0	0
PSYCHIATRIC DISORDERS	5 (4.1)	3 (2.6)	4 (3.5)
Insomnia	3 (2.4)	0	0
EAR & LABYRINTH DISORDERS	0	4 (3.5)	2 (1.8)
Cerumen Impaction	0	2 (1.8)	0

Note: Subjects are counted once within each system organ class and once for each preferred term
 [Source: Trial 201-065 section-1-15-report-body.pdf Table 14.3.1.1.1]

Due to the small numbers of events, it would not be particularly informative to examine the data by subgroups of age and sex.

Severe adverse events

There were few severe adverse events. The few severe events in the trial showed no pattern of concern (Table 65, constructed by this reviewer from data submitted by Dey).

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Table 65. Trial 201-065: Subjects with severe events (safety population)

MedDRA System Organ Class Preferred term	FFIS 20mcg (n=123)	FA 12mcg (n=114)	Placebo (n=114)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anaemia	0	0	1
Thrombocytopenia	0	0	1
EYE DISORDERS			
Cataract	0	0	1
Ocular icterus	0	0	1
GASTROINTESTINAL DISORDERS			
Abdominal pain	1	0	0
Abdominal pain upper	0	0	1
Diarrhoea	0	0	1
Faeces pale	0	0	1
Gastrooesophageal reflux disease	0	0	1
Vomiting	0	1	0
INFECTIONS AND INFESTATIONS			
Appendicitis	0	0	1
Bronchitis	0	0	1
Diverticulitis	0	1	0
Pharyngitis	0	1	0
Postoperative infection	0	0	1
Skin infection	0	0	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Animal bite	0	1	0
Joint dislocation	1	0	0
Post procedural pain	0	1	0
Road traffic accident	0	1	0
INVESTIGATIONS			
Blood glucose increased	1	0	0
Heart rate increased	0	1	0
METABOLISM AND NUTRITION DISORDERS			
Diabetes mellitus	0	0	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
Meningioma	0	0	1
Pancreatic carcinoma	0	0	1
NERVOUS SYSTEM DISORDERS			
Headache	0	1	0
PSYCHIATRIC DISORDERS			
Anxiety	0	1	0
Nervousness	0	1	0
Stress symptoms	1	0	0
RENAL AND URINARY DISORDERS			
Chromaturia	0	0	1
Renal failure acute	1	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Chronic obstructive airways disease exacerbated	0	1	2
Cough	0	1	0
Dyspnoea exacerbated	1	0	0
Pharyngolaryngeal pain	0	1	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Photosensitivity reaction	0	1	0

[Source: Trial 201-065 data set AE_D]

Vital sign evaluation

Blood pressure and heart rate were determined pre-dose, 30 minutes post-dose, and at hours 1, 6, and 12 post-dose at each post-baseline visit, excluding any early termination visit. Body

temperature and respiratory rate were taken at these visit only pre-dose. I reviewed summary statistics (means, medians, and ranges of these data. There were no notable changes in either active treatment on systolic or diastolic blood pressure or heart rate, either predose or after doses at weeks 4, 8, and 12 or at early termination of subject involvement with the trial (except for a subject with an increase in heart rate much greater than the rest of the FFIS group post-dose at week 12). Body temperature and respiratory rate summary statistics did not show any notable differences between treatment groups.

Clinical laboratories and ECG

The review of hematology data consisted of an examination of means, medians, and shifts from normal or high or low screening values at various time points. There were no notable differences between FFIS and FA or between either active group and placebo.

The review of serum chemistry data consisted of an examination of means, medians, and shifts from normal or high or low screening values at various time points. There were no notable differences between FFIS and FA or between either active group and placebo. This includes glucose and potassium, parameters of special relevance to β -agonists generally.

Urine pH and specific gravity, examined as mean and median data, showed no notable differences from screening for any treatment group.

Dey provided of ECG summary statistics for screening, and weeks 4, 8, and 12 pre- and post-dose. Examination of means and medians, there were no notable differences among the treatment groups in heart rate or PR, QT, QRS, RR, QTcB, or QTcF intervals. Maximal changes from baseline (expressed as the top of a range) tended to be similar among the groups, and there was no trend for them to be greater in FFIS-treated subjects. Table 66 summarizes the maximal change in QTcB and QTcF among subjects with post-baseline records. The maximum change resulted in a value over 500 msec for 1 subject in the FA group (although a comment accompanying the value states "Cannot comment on QT, QTcB due to Atrial bigeminy. Noisy").

Table 66. Trial 201-065: Maximal changes from baseline in corrected QT (Bazett and Fridericia correction)

Change Category (msec)	FFIS 20 μ g (N=122) N (%)	FA 12 μ g (N=112) N (%)	Placebo (N=111) N (%)
QTcB			
< 30	100 (82.0)	91 (81.3)	93 (83.8)
30 to <60	22 (18.0)	19 (17.0)	16 (14.4)
60 or greater	0 (0)	2 (1.8)	2 (1.8)
QTcF			
< 30	109 (89.3)	95 (84.8)	99 (89.2)
30 to <60	11 (9.0)	16 (14.3)	11 (9.9)
60 or greater	2 (1.6)	1 (0.9)	1 (0.9)

N= number of subjects with a post-baseline record
 [Source: Trial 201-065 section-1-15-report-body pdf, Table 12.5.3.1]

Holter monitoring:

The data from Holter monitoring should be interpreted with caution, as there was a marked fall in the numbers of subjects who received this test at week 12 compared to the numbers

randomized into the trial. At screening the numbers of subjects in the FFIS, FA, and placebo groups were 122, 112, and 111, respectively; at week 12, the numbers analyzed for changes were 105, 93, and 85-87. Given this notable limitation of the data, there was no increase in the duration of atrial fibrillation, maximum heart rate, mean heart rate, number of premature beats, number of episodes of supraventricular tachycardia, or episodes of ventricular tachycardia in association with the use of FFIS.

Summary of the results of 201-065

Trial 201-065 was a 12-week trial that was adequately conducted to determine the effect of FFIS on bronchodilation. It contained a placebo control and a comparator, Foradil[®] whose efficacy and safety have been documented. After twice daily treatments, A 20 µg morning dose of FFIS produced better bronchodilation than placebo, and comparable bronchodilation to Foradil[®] Aerolizer[®]. The result was robust to sensitivity analyses and was supported by other spirometric measures (peak and trough FEV₁ and FVC). Albuterol use also supported the primary endpoint, as it was decreased in either active treatment by a little over one puff per day during the 12 weeks of the trial. Safety concerns were minimal, and not notably different from Foradil[®].

10.1.5 Asthma trials

Dey conducted 4 single-dose trials in asthma. These are summarized here to illustrate the safety record. The designs of these trials are outlined in Table 2. Subjects in these trials were to have a baseline FEV₁ after withholding medication of between 40-85% predicted, with a bronchodilator response to a short-acting β-agonist. Subjects were to be without other pulmonary or other complicating diseases. Single doses of FFIS or FA were administered in random orders, with washout periods between the doses that were to be between 2 and 7 days. All subjects were to receive all treatments in a crossover design. FFIS was administered by means of a PARI-LC Plus nebulizer.

Simplified tables of safety procedures, with the schedule of treatment, for the asthma trials are shown in Table 67.

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Table 67. Safety procedures and schedule of treatment for trials DL-048, -050, -053, and -055

Trial 048 and 050

Procedure	Screen	Treatment Period							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Day -14 to -1	Day 1	Day 4-9	Day 7-17	Day 10-25	Day 13-33	Day 16-41	Day 19-49	Day 20-50
Physical Examination	X								X
Vital Signs	X	X	X	X	X	X	X	X	X
Clinical Laboratory	X								
AM PEFR		X							
Randomization		X							
FEV ₁	X	X	X	X	X	X	X	X	
Heart Rate		X	X	X	X	X	X	X	
Tremor		X	X	X	X	X	X	X	
PEFR		X	X	X	X	X	X	X	
Crossover Treatment			X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X	X	X

Trial 053

Procedure	Screening	Treatment Period		
	Visit 1	Visit 2	Visit 3	Visit 4
	Day -14 to -1	Day 1	Day 4-9	Day 7-17
Physical Examination	X			X
Clinical Laboratory	X			
Vital Signs: Temperature & Respiratory Rate	X			
Vital Signs: Heart Rate & Blood Pressure	X	X	X	X
Randomization		X		
Spirometry (pre and post)	X			
FEV ₁		X	X	X
Crossover Treatment		X	X	X
Review Concomitant Medication		X	X	X
Adverse Events Assessment		X	X	X

Trial 055

Procedure	Screening	Treatment period					
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7a
	Day -14 to -1	Day 1	Day 3-8	Day 5-15	Day 7-22	Day 9-29	Day 1-36
Physical examination	X						X
Clinical laboratory	X						
Vital signs	X	X	X	X	X	X	X
ECG	X						
Randomization		X					
Reversibility testing	X						
Spirometry (pre and post)	X						
FEV ₁		X	X	X	X	X	X
Crossover treatment		X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
AE assessment		X	X	X	X	X	X

[Sources: Trials 048, 050, 053, and 055, section-1-15-report-body.pdf, Tables 9.5.1.1]

Note that neither clinical laboratories nor ECG were done after screening.

Demographics for the trial populations as a whole are shown in Table 68. The age of the trial populations was substantially lower than that for the COPD trials. Proportionately more subjects were nonCaucasian in trials -050, -053, and -055 than in the COPD trials.

Table 68. Asthma single dose trials: Demographics*

		DL-048 N=32	DL-050 N=32	DL-053 N=21	DL-055 N=45
Age (yr)	Mean (SD)	39.7 (15.9)	9.4 (1.7)	19.6 (15.9)	9.5 (1.9)
	Median	39.5	10.0	11.0	10.0
	Min, max	13, 68	5, 11	6, 62	5, 12
Gender [n, (%)]	Male	13 (41)	14 (44)	12 (57)	29 (64)
	Female	19 (59)	18 (56)	9 (43)	16 (36)
Race (n [%])	Caucasian	27 (84)	15 (47)	12 (57)	25 (56)
	Hispanic	1 (3)	8 (25)	4 (19)	8 (18)
	Black	1 (3)	6 (19)	1 (5)	8 (18)
	Asian	-	2 (6)	3 (14)	3 (7)
	Other†	3 (9)	1 (3)	1 (5)	1 (2)

* Randomized subjects for trials 048, 0505, and 053; completers for trial 053
 [Sources: Trials 048, 050, 053, and 055, section-1-15-report-body.pdf, Tables 14.1.2.1]

Safety results (asthma trials)

DL-048

Exposure and discontinuations

Nearly all subjects received all treatments in the trial. No more than 3 subjects missed any randomized single dose per treatment arm. Overall, 4 subjects discontinued.

Deaths, serious adverse events, and discontinuations due to adverse event

No one died in this trial or discontinued due to an adverse event. There was one serious adverse event: A 16 year-old man experienced abdominal pain after receipt of FFIS 170 µg, and was later diagnosed with Crohn's disease.

Nonserious adverse events

Table 69 shows adverse events from DL-048. Note that the dose is expressed as the dihydrate form of formoterol (for example, 40 µg of the anhydrous form is equivalent to 42 µg of the dihydrate).

Table 69. Trial DL-048: Subjects with adverse events*

	Placebo (N=29)	FA 12 µg (N=30)	FA 24 µg (N=31)	FFIS 42 µg (N=31)	FFIS 84 µg (N=29)	FFIS 170 µg (N=29)	FFIS 254 µg (N=30)
Ear pain	0	0	0	0	0	1 (3.4%)	0
Conjunctival hyperemia	0	0	0	0	0	0	1 (3.3%)
Conjunctivitis	0	0	0	0	1 (3.4%)	0	0
Abdominal pain upper	0	0	0	0	0	1 (3.4%)	0
Crohn's disease	0	0	0	0	0	1 (3.4%)	0
Diarrhea NOS	0	1 (3.3%)	0	0	0	1 (3.4%)	0
Dry mouth	0	0	0	0	0	0	1 (3.3%)
Nausea	0	0	0	0	1 (3.4%)	0	0
Vomiting NOS	0	1 (3.3%)	0	0	0	0	0
Fatigue	1 (3.4%)	0	0	0	0	0	1 (3.3%)
Sinusitis NOS	0	1 (3.3%)	1 (3.2%)	0	0	0	0
URTI	0	1 (3.3%)	0	0	0	0	0
Pain in limb	0	0	0	0	0	0	1 (3.3%)
Headache	0	0	0	0	0	1 (3.4%)	2 (6.7%)
Migraine aggravated	1 (3.4%)	0	0	0	0	1 (3.4%)	0
Tremor	0	0	0	0	0	2 (6.9%)	1 (3.3%)
Nervousness	0	0	0	0	0	0	1 (3.3%)
Nasal congestion	0	0	0	0	1 (3.4%)	0	0
Pulmonary congestion	0	0	0	0	1 (3.4%)	0	0
Rhinitis NOS	0	0	0	0	0	1 (3.4%)	0
Sinus congestion	1 (3.4%)	0	0	0	0	0	0
Dry skin	0	0	0	0	0	0	1 (3.3%)
Hot flushes NOS	0	0	0	1 (3.2%)	0	0	0

*Doses of FFIS are expressed as the dihydrate form (for example, 40 µg of the anhydrous form is equivalent to 42 µg of the dihydrate).

[Source: DL-048 section-1-15-report-body pdf, Table 12.2.2.1]

In trial DL-048, single doses of FFIS up to 254 µg did not produce remarkable toxicities.

DL-050

Exposure and discontinuations

Nearly all subjects received all treatments in the trial. No more than 2 subjects missed any randomized single dose per treatment arm. Overall, 3 subjects discontinued.

Deaths, serious adverse events, and discontinuations due to adverse event

No one died in this trial or discontinued due to an adverse event. There was one serious adverse event: An 11 year-old girl experienced viral meningitis about a week after starting the trial; she had received FFIS 254 µg at the time of the event."

Nonserious adverse events

Table 70 shows adverse events from DL-050.

Table 70. Trial DL-050: Subjects with adverse events

	Placebo (N=32)	FA 12 mcg (n=30)	FA 24 mcg (n=30)	FFIS 42 mcg (n=31)	FFIS 84 mcg (n=31)	FFIS 170 mcg (n=31)	FFIS 254 mcg (n=32)
Meningitis viral NOS	0	0	0	0	0	0	1 (3.1%)
Sinusitis NOS	0	0	0	0	0	0	1 (3.1%)
Upper respiratory tract infection viral NOS	1 (3.1%)	0	1 (3.3%)	0	0	0	0
Tremor	1 (3.1%)	0	0	0	0	0	0
Asthma aggravated	1 (3.1%)	0	0	0	0	0	0
Bronchitis NOS	1 (3.1%)	0	0	0	0	0	0
Hoarseness	0	1 (3.3%)	0	0	0	0	0
Eczema	0	0	0	1 (3.2%)	0	0	0

[Source: DL-050 section-1-15-report-body.pdf, Table 12.2.2.1]

In trial DL-050, single doses of FFIS, up to 254 µg, did not produce remarkable toxicities.

DL-053

Exposure and discontinuations

All but 1 subject received each of the three treatments (FA 12 µg, FFIS 42 µg, and FFIS 84 µg). One subject discontinued from this trial.

Deaths, serious adverse events, and discontinuations due to adverse event

No deaths, discontinuations due to adverse events, or serious adverse events occurred in this trial.

Nonserious adverse events

One patient experienced 3 adverse events after administration of FFIS 42 mcg (gastroenteritis NOS [not otherwise specified], upper respiratory tract infection NOS, and aggravated asthma), and another patient experienced rhinitis NOS after administration of FA 12 mcg. All of the adverse events were mild or moderate in intensity.

DL-055

Exposure and discontinuations

No more than 2 subjects missed any randomized single dose per treatment arm. One subject discontinued from the trial.

Deaths, serious adverse events, and discontinuations due to adverse event

No deaths, discontinuations due to adverse events, or serious adverse events occurred in this trial.

Nonserious adverse events

Table 71 shows adverse events from DL-055.

Table 71. Trial DL-055: Subjects with adverse events

	Placebo N=45	FA 12 mcg N=44	FFIS 2.5 mcg N=43	FFIS 5 mcg N=43	FFIS 10 mcg N=44	FFIS 20 mcg N=44
Abdominal Pain Upper	0	3 (6.8%)	0	0	0	0
Abrasion NOS	0	0	1 (2.3%)	0	1 (2.3%)	0
Allergy Aggravated	0	0	1 (2.3%)	0	0	0
Asthma Aggravated	0	0	0	1 (2.3%)	0	0
Diarrhea NOS	0	0	0	0	0	1 (2.3%)
Ear Pain	0	0	1 (2.3%)	0	0	0
Hand Fracture	0	0	0	0	1 (2.3%)	0
Headache	0	1 (2.3%)	0	1 (2.3%)	0	1 (2.3%)
Hematuria	0	0	0	0	0	1 (2.3%)
Hypersensitivity NOS	0	1 (2.3%)	0	0	0	0
Injury NOS	1 (2.2%)	0	0	0	0	0
Micturition Disorder	0	0	1 (2.3%)	0	0	0
Nasopharyngitis	0	0	0	0	1 (2.3%)	0
Tremor	0	0	0	0	0	1 (2.3%)
Viral Infection NOS	0	0	0	0	0	1 (2.3%)
Vomiting NOS	1 (2.2%)	1 (2.3%)	0	0	1 (2.3%)	0

[Source: DL-055 section-1-15-report-body.pdf, Table 12.2.2.1]

In trial DL-055, single doses of FFIS up to 20 µg did not produce remarkable toxicities.

Summary of the safety in asthma trials

The asthma trials, in which subjects were administered single doses of FFIS from 2.5 µg to 254 µg, did not produce notable toxicities. The single-dose nature of the trials was certainly contributory to the low incidence of adverse events. In addition, the overall trial populations were generally younger than those in the COPD trials.

10.1.6 Trial DL-056

Trial DL-056 was designed to compare the pharmacokinetics of single doses of FFIS (10, 20, and 244 µg) to those of FA at its marketed dose (12 µg) in subjects at least 50 years old with COPD. A screening period of between 1 and 14 days was followed by 5 visits (Table 72). Visits were to be separated by between 5 and 14 days.

Table 72. Trial DL-056 Procedures

	Screening visit 1 (day -1 to -14)	Visit 2		Visit 3		Visit 4		Visit 5	
		Day 1	Day 2						
Written informed consent	X								
Medical history / BMI	X								
Physical examination	X								X
Clinical laboratory tests	X	X		X		X		X	X
Pulmonary function test	X								
Vital signs	X	X	X	X	X	X	X	X	X
Blood for PK analysis		X	X	X	X	X	X	X	X
Urine for PK analysis		X	X	X	X	X	X	X	X
ECG	X	X	X	X	X	X	X	X	X
Randomization		X							
Crossover treatment		X		X		X		X	
Review concomitant med	X	X	X	X	X	X	X	X	X
AE assessment		X	X	X	X	X	X	X	X

--Clinical laboratory tests: hematology, serum chemistry, and urinalysis will be conducted at screening (Visit 1) and 1 hour post-dose on each treatment day (Day 1 of Visits 2, 3, 4, 5). Glucose will also be measured pre-dose and 24 hours post-dose at each treatment visit (Visits 2, 3, 4, 5). Potassium will be measured pre-dose, and 12 and 24 hours post-dose on each treatment visit (Visits 2, 3, 4, 5).

--During each treatment visit, body temperature will be obtained pre-dose. Respiratory rate, heart rate, and blood pressure will be obtained pre-dose and at approximately the following time points post-dose: 5, 10, and 30 minutes, and 1, 3, 6, 12, 16, 24 and 36 hours. Vital signs will be collected prior to blood draws at all time points.

--During each treatment visit, blood samples for PK analysis will be taken just prior to dosing on Day 1 of each of the 4 treatment visits (Visits 2, 3, 4, 5) at the following time points post-dose: 5, 10, and 30 minutes, and 1, 3, 6, 12, 16, 24 and 36 hours.

--During each treatment visit, all urine voided will be collected as follows: 0-3, 3-6, 6-12, and 12-24 hours post-dose, a pre-dose urine sample must also be collected immediately before each dose is administered.

--During each treatment visit, a 12-lead ECG will be performed pre-dose and at the following time points post-dose: 1, 6, 12, and 24 hours.

[Source: DL-056 appendix-16-1-01-protocol.pdf, table 7 1]

Investigational treatments

The investigational agents and modes of delivery were:

- Dey Formoterol Fumarate Inhalation Solution: Formulation Code/Batch Number: 10 mcg, C053; 20 mcg, C054; 244 mcg, C043
- Comparator Products: Foradil[®] Aerolizer[®] (manufactured by Novartis), Formulation Code/Batch Number: 022G7030, 006H0421

Subjects

Thirteen of the 16 planned subjects were randomized into treatment and took at least 1 dose of trial medication. Subjects were almost 60 years old (two subjects did not meet the age criterion of being greater than 50 years old), evenly divided between males and females, and mostly Caucasian. Mean FEV₁ was 1.5 liters (Table 73). One subject (who was less than 50 years old) did not meet the criterion for FEV₁.

Table 73. Trial DL-056: Demographics and characteristics (all subjects randomized, n=13)

Age (years)	Mean (SD)	58.5 (8.9)	FEV ₁ /FVC	Mean (SD)	58.8 (10.1)
	Median	58.0		Median	61.0
	Range	46.0, 74.0		Range	34.4, 75.0
Gender n(%)	Male	6 (46.2%)	FEV ₁ (L)	Mean (SD)	1.5 (0.5)
	Female	7 (53.8%)		Median	1.4
Race n(%)	Caucasian	12 (92.3%)		Range	1.0, 2.6
	Other	1 (7.7%)			

[Sources: DL-056 section-1-15-report-body Table 11.2.1 and Table 14.1.2.1]

Exposure

Twelve subjects received all 4 treatments; one subject discontinued after receipt of his first treatment, FFIS 244 µg.

Safety

Adverse events

No serious adverse events were reported in this trial. One subject discontinued due to fracturing ribs 5, 6, 7, and 8 six days after receiving a dose of FFIS (244 µg).

Few adverse events occurred (see bulleted list below). For all groups except FFIS 244 µg (n=13) the number of subjects is 12.

- FFIS 10 µg: pain in the extremity (1 subject)
- FFIS 20 µg: nausea (1 subject)
- FFIS 244 µg: noncardiac chest pain, sympathomimetic effect, rib fracture, hypokalemia, muscle cramp, pain in extremity, headache (1 subject each)
- FA 12 µg: vomiting, influenza, sinus headache, chronic obstructive airways disease (1 subject each) and venipuncture site hemorrhage (2 subjects each)

Two subjects in the FFIS 244 µg group had events considered related to treatment: 1) a subject with hypokalemia and sympathomimetic effect and 2) a subject with noncardiac chest pain and pain in the extremity. A subject in FFIS 20 µg had nausea that was considered related to treatment.

Vital signs

I examined group means and medians.

- Systolic and diastolic blood pressure were approximately balanced predose for all treatments. There were no notable changes from pre-dose, in any treatment group post-dose. Ranges of the data do not suggest a safety concern.
- Heart rate was approximately balanced predose for all treatments. The largest increase in heart rate occurred in the FFIS 244 µg treatment group, where the maximal mean increase occurred between 30 minutes and 6 hours after dosing (mean increase ranged between 5.2-6.2 bpm over baseline). This is not a clinically important change. Ranges of the data do not suggest a safety concern.
- Respiratory rate was approximately balanced at baseline. One subject, who had a respiratory rate of 12 breaths per minute predose, experienced an increase in respiratory rate to 24 breaths per minute at 12 and 16 hours after his only dose in the trial (244 µg). Ranges of the data do not suggest a safety concern.

Laboratory data

Table 74 is a summary of the pre- and post-dose glucose and potassium data from trial DL-056 (mean and range data are shown graphically in Figure 4).

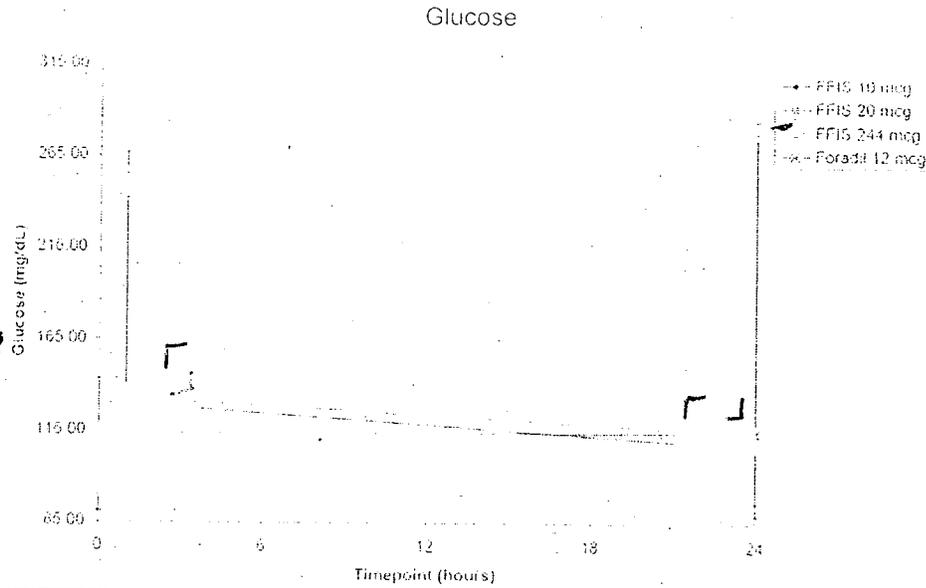
Table 74. DL-056: Summary of pre-dose serum glucose and potassium and changes from baseline

		Glucose (mg/dl)			
		FFIS 10 µg	FFIS 20 µg	FFIS 244 µg	FA 12 µg
predose	n	13	12	12	13
	mean	98.9	104	104	103
	median	91	98	96	103
	max				
	min				
1 hr change	n	12	12	13	12
	mean	26.3	29.3	38.2	7.2
	median	10	25	30	4.5
	max				
	min				
24 hr change	n	11	11	13	12
	mean	2.4	8.2	2.8	8.3
	median	2	0	5	4.5
	max				
	min				
		Potassium (mEq/l)			
		FFIS 10 µg	FFIS 20 µg	FFIS 244 µg	FA 12 µg
predose	n	13	10	11	12
	mean	4.35	4.04	4.71	4.23
	median	4.3	4.1	4.4	4.1
	max				
	min				
1 hr change	n	12	12	13	12
	mean	0.06	-0.35	-0.68	-0.2
	median	0.05	-0.2	-0.8	-0.05
	max				
	min				
12 hr change	n	12	12	13	12
	mean	0.12	-0.22	-0.28	0.03
	median	-0.1	-0.25	-0.4	0.1
	max				
	min				
24 hr change	n	12	12	13	12
	mean	0.34	-0.42	-0.08	-0.2
	median	0.35	-0.4	-0.1	0
	max				
	min				

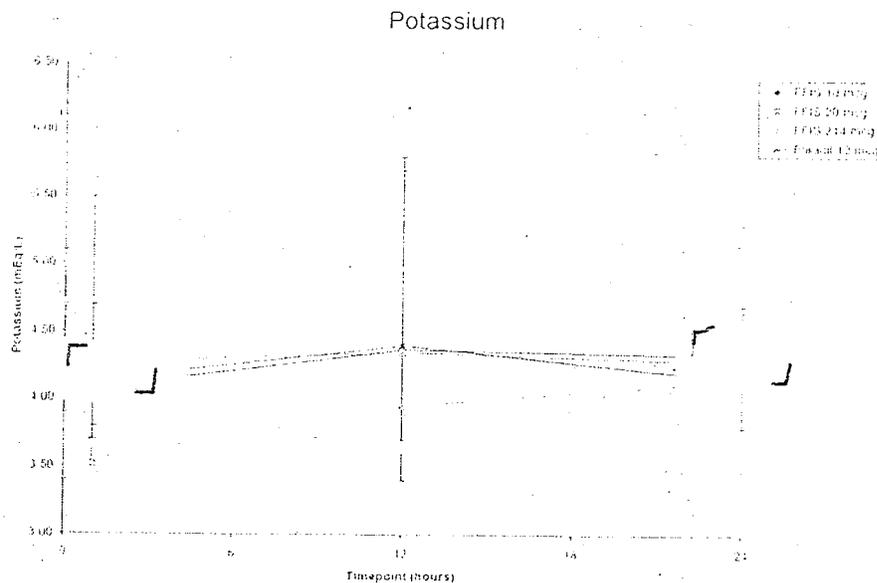
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[Sources: Dey NDA 22-007 February 9, 2007 response to FDA request, Tables 3.1 and 3.2 and Parm_D data set]

Figure 4. DL-056 serum glucose and potassium predose and post dose (mean and range)



b(4)



b(4)

[Sources: Dey NDA 22-007 February 9, 2007 response to FDA request, Figures 3.1 And 3.2]

The glucose data, which show large ranges, show a small baseline imbalance. There is a dose effect in the FFIS groups at one hour, as shown by the median data. The effect on glucose of FFIS at any dose at one hour was a little higher than that of Foradil[®]. At 24 hours, groups were approximately back to baseline.

FFIS at the marketed dose had little effect on serum potassium, as did Foradil[®]. There was a distinct hypokalemic effect of FFIS at the highest dose, however, which was evident at 1 and 12 hours post dose. All groups had serum potassium over 4 again at 24 hours.

ECG

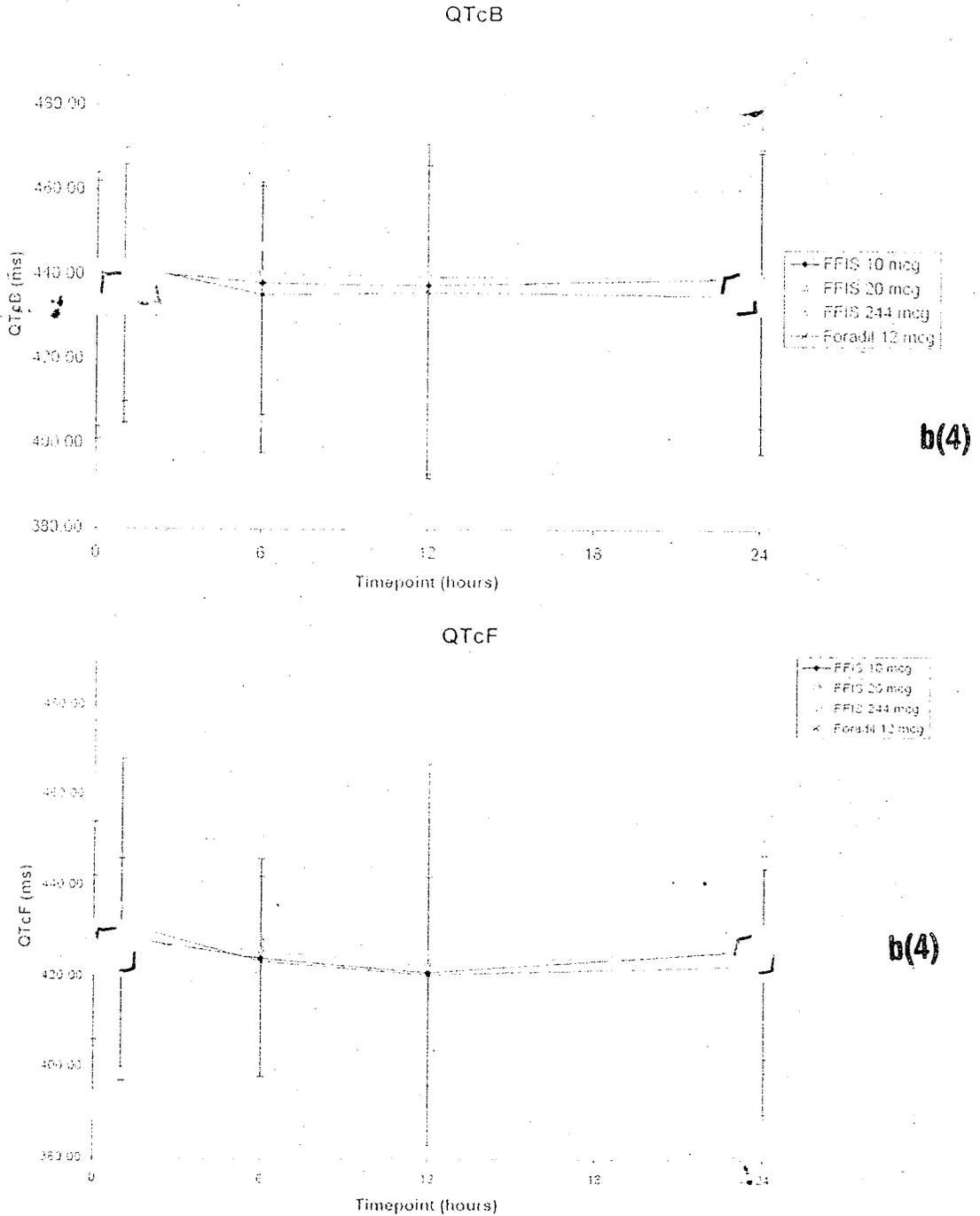
Heart rate was balanced across treatments predose, and was elevated at 1 hour in the highest FFIS dose group. Groups were balanced again at 12 hours.

Corrected QT intervals

Predose QTcB and QTcF among the treatment group was 435-440 msec and 425-429 msec, respectively. The maximum increase post-dose at any time point in the FFIS 10, 20, and 244 µg groups and the Foradil[®] group were 41, 30, 52, and 42 msec, respectively (QTcB) and 24, 18, 31, and 29 msec. Summary data are shown graphically in Figure 5.

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Figure 5. DL-056QTcB and QTcF predose and post dose (mean and range)



[Sources: Dey NDA 22-007 February 9, 2007 response to FDA request, Figures 3.1 And 3.2]

The data show a very small effect of FFIS at the highest dose. No subject had a corrected QT greater than 500 msec.

Adverse events

One subject discontinued about 6 days after receiving one dose in the trial (FFIS, 244 µg). The highest dose of FFIS, 244 µg, was associated with an adverse event termed "sympathomimetic effect" and "hypokalemia;" otherwise, there was no remarkable pattern of toxicities of either Foradil[®] or FFIS in this trial.

10.2 Line-by-Line Labeling Review

This review document does not include complete line-by-line comments on the label. Dey should modify the clinical sections of the proposed labeling in the following general ways:

- 1) The proposed labeling for formoterol fumarate inhalation solution (20 mcg/2ml) contains specific safety and efficacy comparisons to Foradil[®] Aerolizer[®]. These specific comparisons are not appropriate in labeling for formoterol fumarate inhalation solution, and should be removed.
- 2) The adverse event table contains events considered treatment-related by investigators in the clinical trial 201-065. Relationship to treatment is best judged overall by comparisons to nontreated contemporaneous controls. Dey should replace the adverse event table with one that does not restrict its display to treatment-related events only.

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/s/

James Kaiser
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MEDICAL OFFICER

Peter Starke
2/28/2007 04:26:28 PM
MEDICAL OFFICER

I concur.

NDA 22-007

Clarification in Medical Officer NDA filing planning memorandum
September 6, 2006

There is a typographical error in item I in section 8, "Comments to the Applicant." The correct date of approval of the Foradil Aerolizer label should be stated as June 19, 2006.

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James Kaiser
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MEDICAL OFFICER

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Abbreviation: FFIS = formoterol inhalation solution (20 mcg/ 2ml)

1. Regulatory Background

Dey submits the application under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, referring to Foradil[®] Aerolizer[®] NDA 21-279 and NDA 20-831 for the toxicology, pharmacology, and pharmacokinetics of formoterol fumarate. Whereas Foradil has indications for COPD, asthma, and exercise-induced bronchospasm, Dey has specifically limited this application to the indication of COPD. Studies for this indication were performed under IND 68,782.

FDA met with Dey twice regarding the clinical development plan for FFIS for COPD.

1. In April 2004 Dey provided a clinical plan that included DL-059 as a single pivotal trial, with two dose-finding trials (DL-052 and DL-057) and a single PK trial (DL-056). For details of these trials see the summary of clinical trial data below. FDA stated that in principle the submission of data could be adequate for NDA review.

2. As a result of a randomization error, DL-059 became unsuitable to provide efficacy information. In September 2005, FDA told Dey that in principle it would be adequate to use safety data from DL-059, in addition to efficacy information from a new efficacy trial. For more details, see the clinical trials section of this review.

See Section 3 for a brief summary of the clinical trials used to support the marketing application.

2. Summary Of The Contents Of The Submission

Required elements of an NDA submission

The submission contains the essential elements of an NDA submission (with exception of the elements noted below the table):

Essential elements of an NDA submission according to 21 CFR 314.50

21 CFR 314.50 essential element	Present y/n
Application form	y ¹
Index to summary, technical, and case report forms and tabulations	y
Summary	y
Technical section	y
Samples	n ¹
Labeling	y
Case report forms	y
Case report tabulations	y
Patent information	y
Patent certification	y
Claimed exclusivity (If applicant believes the product is entitled to it)	y
Financial certification or disclosure	y

¹ The following items are not submitted, according to Form 356h:

- Index
- Samples
- Clinical microbiology
- Safety update report

Dey states, "All clinical studies performed in support of this NDA were conducted in compliance with the requirements set forth in 21 CFR Parts 50 and 56, International Conference on Harmonisation (ICH E6) guidelines..."

Dey also provides in the submission:

- A prescription drug user fee form, with confirmation from FDA of receipt of fee
- A notice of transfer of obligations
- A field copy certification
- A debarment certification
- A request for waiver of pediatric studies.
- A request for categorical exclusion from environmental assessment because of a very limited expected concentration upon release into environment.
- A risk management plan. Dey commits to the following steps to prevent use of the product in patients with asthma:
 - Prominent labeling for use in COPD, with statement that safety and efficacy in asthma have not been established
 - Prominent display of COPD indication in advertising
 - Training of sales representatives and medical communication personnel

3. Clinical trials

Submitted trials

201-065

The primary evidence of efficacy comes from trial 201-065, a 351-subject, randomized, double-blind, double-dummy, 12-week trial comparing FFIS 20 mcg by inhalation twice daily, Foradil 12

mcg twice daily, and placebo treatment (123 subjects received FFIS). Subjects of either sex at least 40 years of age were enrolled. They had to have COPD with persistent cough, sputum production, or shortness of breath on effort, a history of at least 10 pack-years of cigarette smoking, a screening post-bronchodilator FEV₁ 30-70% of predicted normal with an FEV₁/FVC ratio <70%. Baseline FEV₁ had to be within 15% of the screening value. FFIS and placebo nebulizations were administered with the Pari-LC-Plus nebulizer and PRONEB compressor/nebulizer. Study visits were at baseline (randomization) and at weeks 4, 8, and 12. The primary efficacy variable was the standardized absolute AUC₀₋₁₂ (L) for FEV₁ measured following the morning dose of study medication at Week 12, determined in randomized patients who took double-blind study medication and had a baseline evaluation and at least 1 post-baseline evaluation (called the ITT population by Dey). It was analyzed statistically by ANCOVA. Secondary outcomes included other FEV₁ and FVC measures, use of albuterol, and a measure of the St. George's Respiratory Questionnaire. Table 1 shows results as portrayed by Dey.

Table 1. Primary efficacy results (Trial 201-065)

Treatment Comparison	LS Means		LS Mean Difference	95% Confidence Interval	p-value*
FFIS vs. Placebo	1.492	1.306	0.185	0.120, 0.251	<0.0001
Foradil vs. Placebo	1.511	1.306	0.205	0.138, 0.272	<0.0001
FFIS vs. Foradil	1.492	1.511	-0.020	-0.085, 0.046	0.5546

Source: Table 11.4.1.1.2, Trial 201-065 clinical trial report

Dey submits no other multiple-dose efficacy trials.

This trial was conducted by the same contract research organization that conducted DL-059 (see below), in which a randomization error occurred.

DL-056

The pharmacokinetics of FFIS in comparison to Foradil is submitted in trial DL-065, a randomized, open-label, 4-way crossover study comparing 3 single doses of FFIS (10, 20, and 244 mcg) with Foradil 12 mcg by inhalation in 13 subjects with COPD.

DL-059

The primary evidence of long-term safety comes from trial DL-059. This was conceived of as combining a 12-week, randomized, double-blind treatment period comparing FFIS, Foradil, and placebo (like trial 201-065), followed by 52 weeks of open-label treatment with Foradil or FFIS (subjects randomized to placebo or FFIS, and half the subjects randomized to Foradil would receive FFIS in the open-label portion of the trial; half of the subjects randomized to Foradil would continue to receive Foradil). A major randomization error occurred and subjects switched treatments at post-baseline visits, rendering the 12-week blinded comparison unsuitable for efficacy purposes. Subjects in the double-blind period were given the option to either immediately enter the open-label period or to withdraw entirely. In the open-label period subjects were treated according to the randomization plan (see above). In the 52 week open-label period, 463 were treated with FFIS. Because of the randomization problem, only the long-term safety section of the study could be used to support the application. The Division also requested Dey to submit safety data from patients randomized to treatment in the 12-week placebo-controlled section of the study, based on what the patients actually received.

Other trials

Single-dose, completed trials in COPD

Two single-dose dose-ranging pharmacodynamic studies were performed to select a dose of FFIS comparable to Foradil Aerolizer, 12 mcg, in COPD patients. The studies identified a dose of 20 mcg as the dose to be carried into Phase 3 COPD studies.

- DL-052: 39-subject, randomized, double-blind, 5-way crossover, placebo and active-controlled, double-dummy trial studying FFIS (40, 80 mcg), Foradil (12, 24 mcg), and placebo. The primary outcome was $AUC_{(0-12h)}$ of the mean percent change in FEV_1 from pre-dose for each treatment following single-dose administration of study medication.
- DL-057: 47-subject, randomized, double-blind, 7-way crossover, placebo and active-controlled, double-dummy trial, studying FFIS (2.5, 5, 10, 20, 40 mcg), Foradil 12 mcg, and placebo. The primary outcome was $FEV_1 AUC_{(0-12h)}$. Using a step-down procedure, Dey obtained the following results:

Table 2. DL-057: Dose-ranging results (DL-057)

Comparator	Treatment	Exponentiated mean ratio (%)	90% CI	p-value
FA 12 mcg	FFIS 40 mcg	105.1	102.5, 107.7	0.0011
FA 12 mcg	FFIS 20 mcg	102.1	99.6, 104.6	0.1721
FA 12 mcg	FFIS 10 mcg	99.5	97.1, 102.0	NA
FA 12 mcg	FFIS 5 mcg	96.6	94.2, 99.0	NA
FA 12 mcg	FFIS 2.5 mcg	95.7	93.4, 98.1	NA

Source: Table 11.4.1.1.2, Trial DL-057 clinical trial report

Single-dose, completed trials in asthma

Four single-dose crossover trials in asthma subjects are submitted: DL-048, -050, -053, and 055, studying doses of FFIS from 2.5 mcg to 244 mcg. The total number of subjects is 124.

Non-submitted, ongoing trials in COPD

Safety summaries

Because of the complexities of the analysis of safety stemming from the randomization error, Dey has submitted safety data as follows:

- 1) Trial 201-065 (12-weeks, double-blind)

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- 2) DL-059 double-blind 12-week period, by treatment actually received
- 3) DL-059 double-blind 12-week period and 201-065 integrated
- 4) DL-059 (open-label 52-weeks)

Safety data are also submitted from COPD trials DL-052, -056, and -057 and asthma trials DL-048, -050, -053, and -055 individually.

4. Proposed Labeling

Of note, a trade name has not yet been selected for this drug.

The proposed package insert includes the following indication statement:

TRADE NAME 20 mcg/2 mL is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.

The submission contains a draft package insert, annotated and non-annotated, and draft carton labels.

5. Acceptability for filing

The application is acceptable to be filed. It contains all the requisite components and is technically able to be reviewed. The clinical plan was adequate in principle, and the principal efficacy trial met its primary endpoint according to the applicant's analysis. The dose was chosen on a rational basis. Because the submission relies on certain pre-existing information about the formoterol, Dey is not required to submit two efficacy trials. The quantity of exposure is adequate nominally, in the absence of a safety signal detected upon detailed review.

6. PREA

The submission includes a request for waiver of pediatric studies. A waiver is requested for the following reasons:

- COPD is a nonpediatric condition.
- The product is not intended for pediatric use.
- Dey does not intend to _____

This request is reasonable for a COPD indication.

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7. Referrals

DMETS referral will be made for a trade name consult, when submitted. FDA will select sites from the pivotal efficacy and safety study (Study 201-065) for a DSI audit. The DSI audit may be more important because the same contract research organization was used for the pivotal efficacy trial (Study 201-065) as was used for the trial in which a major randomization error occurred (Study DL-059).

8. Comments to the Applicant

The following comments will be sent to the applicant:

1. While we recognize your commitment to a risk management plan to minimize use in patients with asthma, formoterol fumarate inhalation solution (FFIS) is a bronchodilator, and off-label use of the

product in asthma is likely. Since evidence suggests that long-acting beta agonists may increase the risk of asthma-related death, we have determined that all formoterol products will carry a boxed warning for these risks. Modify your labeling to include a boxed warning for FFIS. Follow the wording on the current Foradil Aerolizer label, approved June 196 2006.

2. Although studies have been conducted suggesting that long-acting beta agonists may increase the risk of asthma-related death, corresponding safety studies have not been performed in COPD patients. We note that you have not conducted a large simple safety study of sufficient size to address this important safety issue in COPD patients. We strongly encourage you to consider performing such a study.

3. Because of the configuration of FFIS as a solution for nebulization, use in urgent and emergency room settings as a treatment for acute bronchospasm in children with asthma is likely. We note that you have not conducted clinical trials to generate safety information for use in these settings. We strongly encourage you to consider performing such a study.

4. We grant your request for a waiver of pediatric studies for COPD.

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/s/

James Kaiser
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Peter Starke
8/31/2006 02:58:06 PM
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