

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-007

MEDICAL REVIEW(S)

CLINICAL TEAM LEADER MEMORANDUM

Date: March 15, 2007
To: NDA 22-007
From: Peter Starke, MD
Associate Director for Safety acting as Clinical Team Leader
Division of Pulmonary and Allergy Products (DPAP), HFD-570
Product: Formoterol fumarate inhalation solution 20mcg/2mL
Applicant: Dey, LP
Submission date: June 28, 2006
PDUFA date: April 29, 2007

Administrative and Introduction

This is a secondary review for a first-cycle 505(b)(2) application (NDA 22-007) submitted by Dey, LP for Formoterol Fumarate Inhalation Solution, 20 mcg/2 mL (hereafter referred to as FFIS). The application references Foradil[®] Aerolizer[®] (NDAs 21-279 and 20-831, Novartis) for the toxicology, pharmacology, clinical pharmacology of formoterol fumarate, and the Agency's previous findings of efficacy and safety of formoterol fumarate in patients with COPD. This drug product is not yet marketed in any other countries.

FFIS and Foradil Aerolizer (hereafter referred to as Foradil or FA) contain formoterol fumarate, a long-acting beta agonist (LABA) consisting of a racemic mixture of (R, R)- and (S, S)-enantiomers [redacted]. However, there are some notable differences between FFIS and FA. Whereas Foradil Aerolizer is an inhalation-driven, multidose, dry powder inhaler, FFIS is a unit-dose vial for nebulization. And 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. [redacted]

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[redacted]

The application is in Common Technical Document (CTD) format and includes information in Modules 1, 2, 3, 4, and 5. It was filed electronically as an eCTD application. The PDUFA date is April 29, 2007; the secondary review date is March 16, 2007.

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Regulatory Background, Review Consultations, and Audits

FDA met with Dey twice regarding the clinical development plan for FFIS for COPD. Previously, FDA had met with Dey regarding Dey's _____

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1. In April 2004, Dey provided a clinical development plan that included DL-059 as a single pivotal trial, with two supportive 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 the long-term, open-label safety extension of DL-059, in addition to efficacy and safety information from a new efficacy trial (201-065). Dey terminated the double-blind portion of study DL-059 early, with rollover to a lengthened open-label safety extension of one year. For more details, see the clinical trials section of this review.

Two consultations were made during the course of the review. The Division of Medication Errors and Technical Support (DMETS) provided a review incorporating comments from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The currently proposed trade name of "Perforomist" is considered acceptable. The Division of Surveillance, Research, and Communication Support (DSRCS) provided consultation on the submitted Medication Guide.

A DSI audit was requested for three sites from the pivotal efficacy and safety study, 201-065. The sites were chosen because they enrolled relatively large numbers of patients and efficacy was near maximal for FFIS at these sites. Results were available at the time of completion of the primary review. There were no significant findings that would invalidate the results of the study.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

Dr. John Hill performed the product review and recommends an Approval. There were no major CMC issues, and none remaining as of the completion of this review except that the establishment site inspection by the Office of Compliance is still pending.

FFIS is a sterile, clear, isotonic solution for oral inhalation by nebulization. Each 2 mL unit-dose vial contains an isotonic solution of 20 mcg of formoterol fumarate in _____ and sodium chloride (_____), _____ to a pH of 5.0 with citric acid _____ (_____) and sodium citrate (_____). It is packaged in 2.5 mL low-density polyethylene (LDPE) unit dose vials individually overwrapped with an _____, and packaged in cartons of _____ or 60 overwrapped vials.

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Stability data support 24-month expiry dating under refrigerated storage conditions (-°C), with up to 3 months post-dispensing storage at room temperature (25°C):

The drug substance is manufactured by either _____ or Merck Development Centre Private Limited in India. The drug product is manufactured by Dey, L.P. in Napa, California.

Pharmacology and Toxicology

Dr. Tim Robison performed the Pharmacology and Toxicology review and recommends an Approval. There were no major Pharm/Tox issues uncovered during the review of this application. No new pharmacology studies were performed. For preclinical toxicology, Dey relied on FDA's previous findings of safety and effectiveness of Foradil, but conducted a 14-day inhalation toxicology study with rats to bridge formulations: FFIS is a solution formulation for nebulization and Foradil Aerolizer is a dry powder inhaler formulation. The drug product does not contain any new or unusual excipients that required qualification.

Clinical Pharmacology and Biopharmaceutics

Dr. Partha Roy reviewed the Clinical Pharmacology and Biopharmaceutics data submitted with the application and recommends an Approval. One small clinical pharmacology / biopharmaceutics study was submitted to support this application, Study DL-056. The study supports the applicant's contention that FFIS does not result in higher systemic exposure [i.e. systemic safety] than the reference product, Foradil Aerolizer.

It should be noted that Dey is seeking to port much of the clinical pharmacology information from the Foradil Aerolizer label into the FFIS labeling. While some of the information is generic to formoterol, much of the PK/PD information was generated with FA, and not with FFIS. The specific FA study information should, therefore, be removed and replaced with general information about formoterol.

Study DL-056

This was an open-label, randomized, single-dose, 4-way crossover, pharmacokinetic study in 13 COPD patients (ATS criteria, 10 pack-year history, FEV₁ <80% but >30% predicted, FEV₁/FVC ratio <70%) comparing FFIS 10, 20, and 244 mcg with Foradil 12 mcg. Plasma and urinary concentrations of formoterol fumarate were assessed using high performance liquid chromatography/mass spectrometry methodology with a lower limit of quantitation of 2.5 pg/mL. The primary variables were: T_{max}, C_{max}, AUC₀₋₁₂, AUC₀₋₂₄, AUC_{0-t}, Ae₀₋₂₄, % dose excreted in urine, T_{1/2}.

Despite the sensitivity of the testing methodology, the plasma formoterol concentrations only indirectly support comparative systemic exposure of FFIS 20 mcg and FA 12 mcg doses. At FFIS doses of 10 and 20 mcg, formoterol fumarate concentrations were undetectable or sporadically detectable. With the exception of one patient, the same was true for the FA dose of 12 mcg. Therefore, only data from the suprathreshold FFIS 244 mcg dose could be used to determine systemic PK parameters, despite results reported for these doses. Historical data from the Foradil label imply less systemic exposure from 12 nebulized doses of FFIS than from 10 inhalations of Foradil Aerolizer.

Urinary data were the primary mechanism for comparison of systemic exposure between the two products. Urinary formoterol fumarate concentrations were available for all three doses. Excretion of unchanged urinary formoterol was used as an indirect measure of systemic exposure. The three FFIS doses showed linear kinetics, with 14% less excretion of urinary formoterol over 24 hours after FFIS 20 mcg than FA 12 mcg. Dr. Roy's review states that the mean percent dose excreted unchanged in the urine over 24 hours was about 2-fold higher for FA 12 mcg than FFIS 20 mcg, suggesting the possibility of lower bioavailability of FFIS

compared to FA. These data do not entirely match the limited systemic pharmacodynamic safety information [i.e., from 13 subjects] obtained in this study, discussed below.

Systemic effects on heart rate, blood pressure, ECG, serum glucose, and serum potassium were measured at various time points after exposure, including 1 hour post-dose. These data were reviewed by Dr. James Kaiser. All active treatments exhibited typical beta-agonist PD effects, with the expected more robust effects from the FFIS 244 mcg dose. Although there were no clinically meaningful differences between treatments in heart rate, blood pressure, ECG, or serum potassium (the highest dose of FFIS produced a small hypokalemic and heart rate-raising effect and a small effect on QTcB), there appeared to be a dose effect for FFIS on 1-hour mean serum glucose (higher FFIS doses were associated with higher mean serum glucose measurements; mean difference from pre-dose of 29 mg/dL with FFIS 20 mcg treatment), with minimal effect (7 mg/dL) seen with Foradil treatment (Figure 1). Since this was a very small single-dose study, the pharmacologic findings are not strong enough to make any absolute statements. Nevertheless, this raises the suspicion that despite the PK and urinary formoterol data, the systemic pharmacologic effects of FFIS 20 mcg may be higher than the corresponding effects from Foradil Aerolizer 12 mcg. These were the only immediate post-dose PD measures in the development program, the only other measures being pre-dose in the pivotal efficacy and safety study. In that study, no effects on pre-dose glucose were noted for any treatments after 12 weeks of dosing.

In summary, this study was considered acceptable by the biopharmaceutics and clinical teams to support comparative systemic exposure from FFIS 20 mcg and FA 12 mcg. Because of the limited PK information, PK/PD relationships were not explored and should not be represented as such in the labeling [as the applicant is requesting].

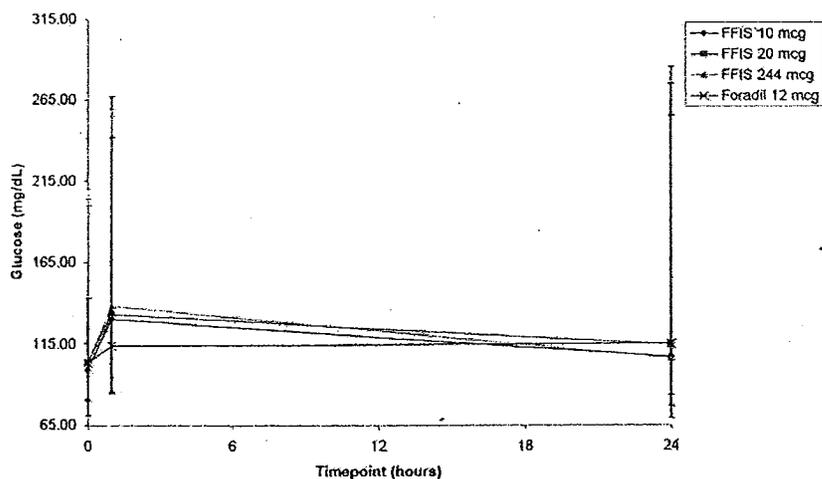


Figure 1. DL-056, Post-dose serum glucose, by time and treatment

Source: February 9, 2007 response to FDA request, Figure 3.1

Clinical and Statistical

Dr. James Kaiser performed the clinical review and recommends Approval. I concur with the recommendation for an Approval action.

The clinical program is shown in Table 1. It consisted of the one single-dose PK study (DL-056) discussed above, two single-dose dose-ranging (i.e. dose-finding) pharmacodynamic (PD) studies (DL-052, DL-057), one 12-week efficacy and safety study (201-065), and one 12-month open-label safety study (DL-059). Although the clinical development program was small, it was judged adequate to evaluate safety and efficacy for the proposed indication and estimate comparability with FA. All clinical trials used the Pari LC Plus nebulizer. Use of this nebulizer needs to be reflected in the labeling.

Dose selection for the development program was based on the two single-dose PD (i.e., bronchodilation) studies in COPD patients. **Study DL-052** was a preliminary PD study, which evaluated the FEV₁ dose-response relationship between two FFIS 40 and 80 mcg doses and two FA 12 and 24 mcg doses. However, the results of this study did not match either FFIS dose with FA 12 mcg (Table 2 and Figure 2); the two doses more closely matched that of FA 24 mcg, which had been studied in the Foradil program but was not approved because of safety findings in asthmatics. **Study DL-057** was the primary dose-finding study, which evaluated the dose-response for multiple doses of FFIS up to 40 mcg, including FFIS 2.5, 5, 10, 20, and 40 mcg, along with FA 12 mcg and placebos. This study showed a reasonable FEV₁ dose response relationship for different FFIS doses down to relatively low (but not necessarily ineffective) doses of FFIS in COPD patients, and showed comparable bronchodilation for FFIS 20 mcg and the known effective dose of FA 12 mcg in COPD patients (Table 3 and Figure 3). This dose was carried into the rest of the clinical program. It is of note that the next lower dose of 10 mcg also matched the FA 12 mcg, but was not chosen because the statistical evaluation plan for matching FFIS with FA 12 mcg used a descending order approach from highest to lowest FFIS dose.

Study DL-059 was originally intended to include both a 12-week safety and efficacy portion and a long-term safety extension. It studied FFIS 20 mcg, FA 12 mcg, and placebos administered BID. However, because of a drug allocation/randomization error in which patients did not receive the intended study drug nor were they continued on the same drug throughout the double-blind treatment period, it was impossible to salvage any efficacy data from the study. The open-label one-year safety extension of this study was acceptable, as patients were re-randomized for this section. Having lost the pivotal efficacy and safety study, Dey subsequently repeated the 12-week, double-blind efficacy and safety portion as **Study 201-065**. However, it should be noted that replacement study 201-065 had a smaller sample size than the original double-blind portion of study DL-059.

One drawback of the clinical program is the lack of corresponding PK data from any of the clinical studies, although the data from the small PK study (DL-056) were judged sufficient. Another drawback is the relative paucity of safety data from this program, which included limited single-dose data from 3 small PD studies in asthmatics, an open-label safety study with active but no placebo control, and a small 12-week pivotal efficacy and safety study. Despite these drawbacks, the data in the submission were judged sufficient with which to make a regulatory decision.

Another concern is the fact that this solution for nebulization will be marketed for COPD but readily available for use in asthma patients, including young children. The formulation is exactly the formulation conducive to use in the acute asthma Emergency Department or inpatient setting, and also conducive to use in a pediatric asthma population. The concern about an increase in mortality with use of LABAs in asthma is also an issue that was

considered. Although this extends to all LABAs, there is no data with regard to whether this concern extends to patients with COPD. These concerns resulted in carryover of the LABA asthma boxed warning, request for a Medication Guide, and request for Dey to commit to perform 3 postmarketing studies.

The table of COPD clinical studies performed by Dey follows, followed by summaries of the pivotal clinical studies. Studies in **bold** are those considered pivotal to the review. Studies in ***bolded italics*** were considered pivotal to the determination of efficacy and safety for this application.

Table 1. Clinical COPD Studies

Study / Location	Design / Population	Dose / Dosage strength	N
DL-052 US	<ul style="list-style-type: none"> • Double-blind, double-dummy, randomized, single-dose, 5-way crossover PD • 39 Adults ≥ 50 yrs with COPD by ATS definition, 10 pack-year history, FEV₁ <70% but >30% predicted, FEV₁/FVC ratio <70% • 1° endpoint: FEV₁ 0-12 hours 	FFIS 40 mcg FFIS 80 mcg FA 12 mcg FA 24 mcg Placebo	39
DL-056 US	<ul style="list-style-type: none"> • Open, randomized, single-dose, 4-way crossover PK • 13 Adults ≥ 59 yrs with COPD by ATS definition, 10 pack-year history, FEV₁ <80% but >30% predicted, FEV₁/FVC ratio <70% • 1° endpoint: T_{max}, C_{max} AUC₀₋₁₂, AUC₀₋₂₄, AUC_{0-t}, Ae₀₋₂₄, % dose excreted in urine, T1/2 • Safety: heart rate, blood pressure, ECG, serum glucose, potassium 	FFIS 10 mcg FFIS 20 mcg FFIS 244 mcg FA 12 mcg	13
DL-057 US	<ul style="list-style-type: none"> • Double-blind, double-dummy, randomized, single-dose, 7-way crossover dose-finding PD • 47 Adults ≥ 50 yrs with COPD by ATS definition, 10 pack-year history, FEV₁ <70% but >30% predicted, FEV₁/FVC ratio <70% • 1° endpoint: FEV₁ 0-12 hours 	FFIS 2.5 mcg FFIS 5 mcg FFIS 10 mcg FFIS 20 mcg FFIS 40 mcg FA 12 mcg Placebo	47
DL-059 Double-blind US	<ul style="list-style-type: none"> • Double-blind, double-dummy, randomized, 12-week efficacy and safety – this portion of the study was invalidated by a drug allocation/randomization error • 694 Adults ≥ 40 yrs with COPD 	FFIS 20 mcg BID FA 12 mcg BID Placebo BID	516 500 315
Open-label US	<ul style="list-style-type: none"> • Open-label, re-randomized 52-week safety extension • 569 Adults ≥ 40 yrs with COPD 	FFIS 20 mcg BID FA 12 mcg BID	463 106
201-065 US	<ul style="list-style-type: none"> • Double-blind, double-dummy, randomized, 12-week efficacy and safety • 351 Adults ≥ 40 yrs with COPD • 1° endpoint: AUC FEV₁ 0-12 hours at 12 weeks 	FFIS 20 mcg BID FA 12 mcg BID Placebo BID	123 114 114

T5.2.1, Tabular Listing.pdf

Dey also performed 4 single-dose, dose-ranging crossover studies in asthmatics. **DL-048** studied FFIS doses of 40, 80, 163, and 243 mcg, FA doses of 12 and 24 mcg, and placebo in 32 adults and adolescents. **DL-050** studied FFIS doses of 40, 80, 163, and 243 mcg, FA doses of 12 and 24 mcg, and placebo in 32 children 5-11 years of age. **DL-053** studied FFIS doses of 40 and 80 mcg, and FA doses of 12 and 24 mcg in 21 patients (10 patients 12 years

and older, 11 patients 5-11 years of age). DL-055 studied FFIS doses of 2.5, 5, 10, and 20 mcg, FA 12 mcg, and placebo in 45 children 5-11 years of age.

Study DL-052

This was a randomized, double-blind, double-dummy, active- and placebo-controlled, 5-way crossover, single-dose pharmacodynamic study conducted at 7 centers in the US in 39 COPD patients (ATS criteria, 10 pack-year history, FEV₁ <70% but >30% predicted, FEV₁/FVC ratio <70%) ≥50 years of age. Patients were randomized placebo(s), Foradil Aerolizer 12 and 24 mcg (Batch: 019E4038), or FFIS 40 and 80 mcg administered with a Pari LC Plus Nebulizer. The primary endpoint was the mean percent change in FEV₁ over 12 hours. Secondary endpoints included: percent change from pre-dose in FEV₁ at each time point, peak percent change from pre-dose FEV₁, peak percent change from pre-dose FEV₁ for each treatment, peak percent change from pre-dose in FVC. Safety was evaluated by adverse events, clinical laboratory tests, vital signs (including heart rate), tremor, ECGs and physical examinations. Primary results are shown in Table 2 and Figure 2. Thirty-nine patients were enrolled and 35 completed all treatment arms. There were no notable safety or review issues. Findings from this study suggested that the proposed FFIS doses of 40 and 80 mcg were not comparable to FA 12 mcg. Hence, a second dose-finding study, DL-057, was performed using lower FFIS doses.

Table 2. DL-052, Percent change in FEV₁ AUC 0-12 hr (%*hr), Evaluable pop

Mean % change in FEV ₁ AUC 0-12 hr	Treatment				
	Placebo	FA		FFIS	
		12 mcg	24 mcg	40 mcg	80 mcg
N	35	35	35	35	35
Mean (SD)	73.3 (147.5)	131.1 (126.7)	164.6 (148.5)	191.0 (163.8)	227.8 (255.7)
Min, Max					

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Source: Study DL-052, T11.4.1.1.1.1, p73; section-1-15-report-body.pdf

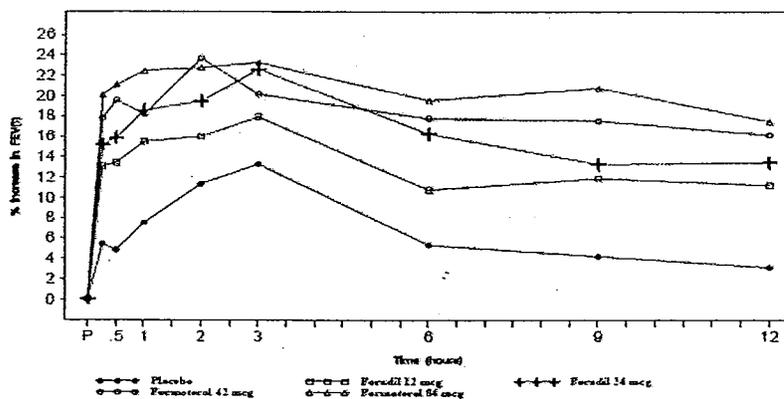


Figure 2. DL-052, Dose-response curve of mean percent change in FEV₁ (L), Time-avaluable pop

Source: Study DL-052, F11.4.1.1.1.1, p74; section-1-15-report-body.pdf

Study DL-057

This was a randomized, double-blind, double-dummy, active- and placebo-controlled, 7-way crossover, single-dose pharmacodynamic study conducted at 7 centers in the US in 47 COPD patients (ATS criteria, 10 pack-year history, FEV₁ <70% but >30% predicted, FEV₁/FVC ratio <70%) ≥50 years of age. Patients were randomized placebo(s), Foradil Aerolizer 12 mcg (Batch: 022G7030), or FFIS 2.5, 5, 10, 20, and 40 mcg administered with a Pari LC Plus nebulizer. The primary endpoint was FEV₁ over 12 hours (FEV₁ AUC_{0-12h}). Secondary endpoints included: percent change in trough FEV₁ from pre-dose, absolute and percent change from pre-dose FEV₁ at each post-dose time point for each treatment, peak percent change from pre-dose FEV₁ for each treatment, peak percent change from pre-dose in FVC for each treatment, and absolute and percent change in time-normalized FEV₁ AUC_{0-12h}. Safety was evaluated by adverse events, vital signs, clinical laboratory tests, physical examinations, and heart rate. All 47 patients completed all treatment arms. There were no notable safety or review issues. Primary results are shown in Table 3 and Figure 3.

The analytical plan called for a step down approach to establish equipotent doses of FA 12 mcg and FFIS, i.e. sequential analysis used an analysis of variance for each FFIS dose from highest to lowest, until a p-value of greater than 0.05 was obtained. The first dose to obtain this p-value was FFIS 20 mcg. While a p-value was not calculated for the FFIS 10 mcg dose vs FA 12 mcg, it appears that this dose might have satisfied the requirements for an equipotent dose if a step-up approach had been taken, i.e. an analysis from lowest to highest dose.

Table 3. DL-057, FEV₁ AUC 0-12 hr (L*hr), Completer pop

FEV ₁ AUC 0-12 hr	Treatment						
	Placebo	FA 12 mcg	FFIS				
			2.5 mcg	5 mcg	10 mcg	20 mcg	40 mcg
N	47	47	47	47	47	47	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	-5.7, 10.1						

Completer pop = ITT. All patients participated in all treatments

Source: Study DL-057, F11.4.1.1.1.1, p73; section-1-15-report-body.pdf

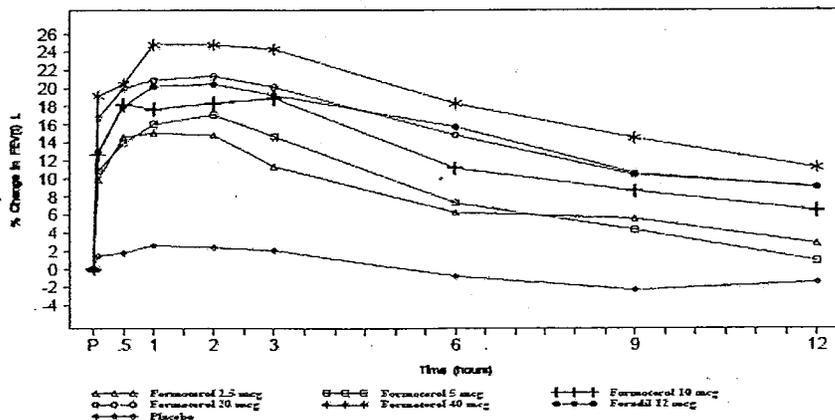


Figure 3. DL-057, Dose-response curve of mean percent change in FEV₁ (L), Completer pop

Source: Study DL-057, F11.4.1.2.1.1, p82; section-1-15-report-body.pdf

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Study DL-059

Study DL-059 was originally intended as the pivotal efficacy and safety study. It consisted of two periods: a 12-week double-blind phase, followed by a 40-week open-label safety extension. The double-blind phase of the study was similar in design to study 201-065, described below, except that the study proposed to enroll 690 COPD patients randomized 2:2:1 to FFIS 20 mcg, FA 12 mcg, and placebo. Two major issues invalidated the double-blind phase of the study: a major randomization error occurred, followed by switching of assigned treatments at post-baseline visits. The effect was to render the 12-week blinded efficacy comparison impossible and make to evaluation of safety findings in the double-blind period extremely problematic. Dr. Kaiser reviewed the safety for both phases of the study, and concluded that little safety information could be gleaned from the invalidated double-blind period.

Upon realization of the problem, Dey terminated the double-blind phase of the study, and re-randomized patients to an extended (52-week) open-label safety phase. The re-randomization has some bearing as patients on FFIS remained on FFIS, patients on placebo were switched to FFIS, and patients on FA were assigned randomly 1:1 to either FFIS or FA. This resulted in 463 patients randomized to FFIS and 106 to FA for up to 1 year. The data from this open-label, active-controlled, extension study constituted the full dataset for long-term safety of FFIS.

The two treatment groups were relatively similar in demographic and baseline characteristics, including FEV₁. There were 8 deaths, 6 in patients treated with FFIS and 2 in patients treated with FA. Four of the FFIS cases were due to cardiovascular disease. Serious cardiac disorders not resulting in death also occurred at a slightly increased rate in the FFIS group, including: MI (FFIS 5, FA 0), cardiac failure (FFIS 2, FA 0), coronary artery disease (FFIS 2, FA 2) unstable angina (FFIS 1, FA 0), and supraventricular tachycardia (FFIS 1, FA 0). All case report narratives were reviewed. However, the small number of patients in the FA treatment arm increases the uncertainty around the estimate of the relative proportion of cases between the treatment arms. In addition, given the ages of the patients, their medical histories, and underlying conditions [for most], none of the case reports were surprising. As a result, we did not consider any differences between treatment arms to be indicative of a safety signal for FFIS. There were no other notable safety or review issues.

Study 201-065

This was the pivotal efficacy and safety study, replacing the larger but terminated double-blind portion of study DL-059. It was a 12-week, randomized, double-blind, active- and placebo-controlled efficacy and safety study conducted at 38 centers in the US in 351 COPD patients (diagnosis of COPD, 10 pack-year smoking history, FEV₁ <70% but >30% predicted, FEV₁/FVC ratio <70%) ≥40 years of age). Patients were randomized 1:1:1 to FFIS 20 mcg (Batch: C062A) administered with a Pari LC Plus jet nebulizer and Pari ProNeb compressor, Foradil Aerolizer 12 mcg (Batch: S4A026E), or placebo(s), each administered twice daily. Spirometry was assessed pre-bronchodilator at baseline, day 1, and at weeks 4, 8 and 12. Safety was evaluated by adverse events, clinical laboratory tests [performed at baseline and after 12 weeks], physical examinations, vital signs, ECG [performed 2-3 hours post-dose at weeks 4, 8 and 12], and Holter monitoring [prior to day 1 and week 12 visits].

The primary endpoint was the standardized absolute FEV₁ over 12 hours (FEV₁ AUC_{0-12h}) at week 12, using an ANCOVA model including fixed effects for treatment and center. The primary contrast was to placebo. Secondary endpoints included: standardized AUC_{0-12h} for FEV₁ on day 1 and weeks 4, 8, and 12 (without LOCF); peak FEV₁ over 12 hours on day 1 and weeks 4, 8, and 12; trough FEV₁ at day 1 and weeks 4, 8, and 12; FEV₁ at each post-dose time point on day 1 and weeks 4, 8, and 12; standardized AUC_{0-12h} for FVC on day 1 and weeks 4, 8, and 12, use of albuterol rescue medication (number of puffs/day), and St Georges Respiratory Questionnaire (SGRQ) at Weeks 1 and 12. For the SGRQ, a difference of at least 4 points was considered clinically significant for the overall score and for the individual impact component score. A supplemental analysis included assessment of post-dose bronchodilation 5 minutes post-dose at each study visit. Dey wishes to include in the labeling for this study most of the secondary endpoints (including overall SGRQ), as well as the supplemental analysis of onset of action on Day 1.

The study randomized 351 patients, 123 to FFIS 20 mcg, 114 to FA 12 mcg, and 114 to placebo. The population included: 154 (43.9%) female, 197 (56.1%) male, 301 (85.8%) Caucasian, 36 (10.3%) Black, 13 (3.7%) Hispanic, 1 (0.3%) Asian, with a mean age of 62.8 years (range 40-86), 151 (43.0%) ≥65 years, of whom 182 (51.9%) were current smokers. The mean baseline pre-bronchodilator FEV₁ was 1.34 L, 49.9% predicted, and mean pre-bronchodilator FEV₁/FVC was 0.54. Treatment groups were relatively similar in demographic and baseline characteristics, including FEV₁, other pulmonary function measurements, and SGRQ scores.

Primary results are shown in Table 4. Both active treatments showed statistically significant differences from placebo, with results for the two actives being clinically comparable. The applicant's primary and certain secondary analyses were confirmed by the FDA statistician. Post-treatment FEV₁ over time curves for Day 1 and Week 12 are shown graphically in Figure 4 and Figure 5, respectively. Dey is seeking to include in the labeling figures depicting FEV₁ over time curves on Day 1 and Week 12 [using FEV₁ and not percent change in FEV₁ as is in the Brovana labeling]; this is acceptable. Dey is also seeking to include the FA arm in the CLINICAL STUDIES and ADVERSE REACTIONS sections; this is inappropriate.

Secondary analyses were consistent with and supportive of the primary results. Dey is seeking to place information on the secondary endpoints of FEV₁ for all post-dose timepoints, peak FEV₁, trough FEV₁, FVC, rescue medication use, and total SGRQ. The FA label includes AM pre-dose PEF and rescue albuterol use information; however PEFs were not carried out as part of this study. Each endpoint is discussed below.

1. Standardized FEV₁ AUC₀₋₁₂ at each visit and changes from baseline in standardized FEV₁ AUC₀₋₁₂ at Weeks 4, 8, and 12 for the ITT population (without LOCF) were comparable between the two actives. Peak FEV₁ was numerically slightly higher for FFIS on Day 1, but otherwise comparable throughout the treatment period. It should be noted that over the course of the treatment period, baseline FEV₁ for FFIS and FA increased but the peak FEV₁ remained about the same (Peak FEV₁ on Day 1 = 1.670 L, 1.655 L, and 1.497 for FFIS, FA and placebo, respectively; Peak FEV₁ at Week 12 = 1.663 L, 1.668 L, and 1.416 for FFIS, FA and placebo, respectively). Therefore, tachyphylaxis did not appear to be a major issue in this study, as might typically be expected from beta-agonists as a class. Trough FEV₁, percent change in FEV₁, and FVC AUC₀₋₁₂ data were also

comparable between actives. These data are supportive of the primary results, and add no further information than do the primary results and FEV₁ curves. Both peak and trough FEV₁ are readily apparent in the Figures. Therefore, specific information with regard to these results need not be depicted in the labeling. The issue of tachyphylaxis should be addressed by a class labeling statement.

2. Results of rescue use of albuterol between each set of study visits (other than baseline, which was slightly higher for FFIS than FA) were comparable between actives and higher than placebo by just over 1 puff/day. Since rescue medication use is considered useful information for the practitioner, this information should be included in the labeling.
3. Dey is also seeking to include the total SGRQ results in the labeling. For the total score, Dey chose a minimally important difference (MID) of 4 as clinically significant, a difference that is an accepted MID for total SGRQ. Results are shown in Table 5. The results for FFIS were statistically significant, exceeded the MID of 4 (for difference from placebo in change from baseline), and had 95% CIs excluding 0. Interestingly, the results for FA were not as favorable, with a difference from placebo in change from baseline that did not exceed 4, 95% CIs that did not exclude 0, and p-value that was not statistically significant. One could argue that if the two drugs were really comparable, this would not have happened. However, it is more likely that SGRQ is a poor way to distinguish between two active treatments, and that differences between active were due to chance. It is unreasonable to accept representation of SGRQ for this study because of two reasons: 1) although FFIS succeeded, FA failed, to some extent calling into question whether the results are as robust as desired; and 2) the results have not been replicated.

Because of the fact that the FA label carries a discussion of serious asthma (not COPD) exacerbations for the unapproved 24 mcg BID dose, we looked carefully at the issue of COPD exacerbations, SAEs, withdrawals, and other AEs during the review to discern if there was a difference between actives. Of note, the issue of serious asthma exacerbations for FA 24 mcg was seen in a study of about the same size and the same duration as this study. In the [labeled] FA COPD studies, dose ordering of seven AEs were noted for the 12 and 24 mcg doses, including: pharyngitis, fever, muscle cramps, increased sputum, dysphonia, myalgia, and tremor. In this study, there were no notable safety issues, no pattern of SAEs or AEs that raised safety concerns, and no discernable difference between FFIS 20 mcg and FA 12 mcg, except that the incidence of nasopharyngitis, gastroenteritis, nausea, dry mouth, diarrhea, stomach discomfort, rash, and insomnia was numerically higher for FFIS than other treatments. Foradil was slightly higher than other treatments in incidence of cystitis, sinusitis, dyspnea, and dizziness.

There are four issues of note with regard to labeling for this pivotal study:

1. Dey is seeking to include the FA arm in the CLINICAL STUDIES and ADVERSE REACTIONS sections, including the figures depicting FEV₁ over time and the table of adverse events. This is inappropriate. Dey will need to submit new figures without FA.
2. The adverse event table is restricted to AEs considered to be treatment-related. This is inappropriate. Dey will need to depict AEs without regard to treatment-relatedness.

3. The analysis of time to onset of action followed the format of the Foradil label and presents this information as the lead description of the clinical study. This is not appropriate. While it is acceptable to include information on onset of action, it should be presented similarly to that for Brovana at the end of the description of the study.
4. Dey wishes to include information with regard to many secondary endpoints in the labeling. Issues with regard to specific endpoints are discussed above. A general statement regarding the primary results being supported by the secondary results is reasonable, as is a mention of the results for rescue albuterol use. Also, a class-labeling statement regarding tachyphylaxis with continuous beta-agonist use should be included in the pharmacology section, but I would leave out mention of peak FEV₁ over the course of the study as this would incur a marketing advantage over other formoterol products, which pharmacologically should all act similarly. As a single study with conflicting SGRQ results for the two active drugs that Dey is seeking to reassure us as being comparable, the results for SGRQ are not robust enough to support placement in the labeling.

Table 4. 201-065, Primary Efficacy Results

Treatment	N	Standardized FEV ₁ AUC _{0-12h} (L), ITT					
		Baseline	Week 12		Comparison to placebo		
			Mean	LS mean	LS mean difference	95% CI	p-value
FFIS 20 mcg	123	1.32 (0.43)	1.51 (0.52)	1.492	0.185	0.120, 0.251	<0.0001
FA 12 mcg	114	1.28 (0.39)	1.49 (0.46)	1.511	0.205	0.138, 0.272	<0.0001
Placebo	114	1.32 (0.48)	1.33 (0.57)	1.306			

Source: Study 201-065, section-1-15-report-body.pdf, p91-2

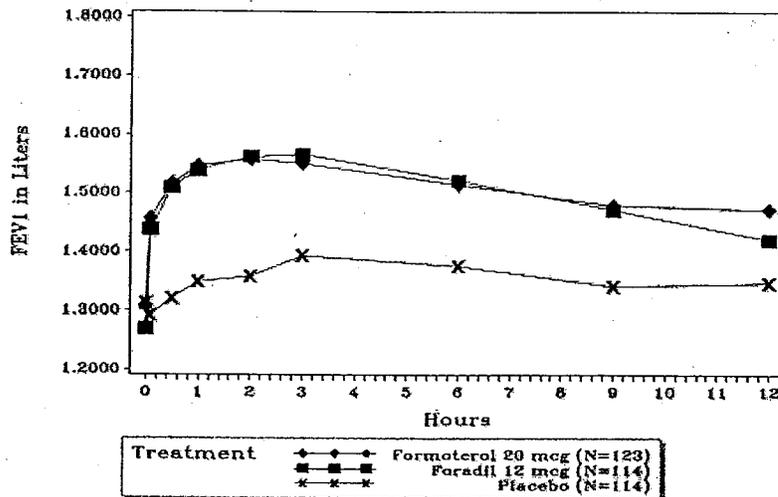


Figure 4. 201-065, LS mean FEV₁ (L)* over time by treatment, Day 1, ITT

* LS Means are based on an ANCOVA model with treatment and center as fixed effects and baseline FEV₁ (Day 1 Pre-Dose) as the covariate. LS Means at Day 1, Pre-Dose are based on an ANCOVA model with treatment and center as fixed effects.

Source: summaryofclin-efficacy-copd.pdf, p 16

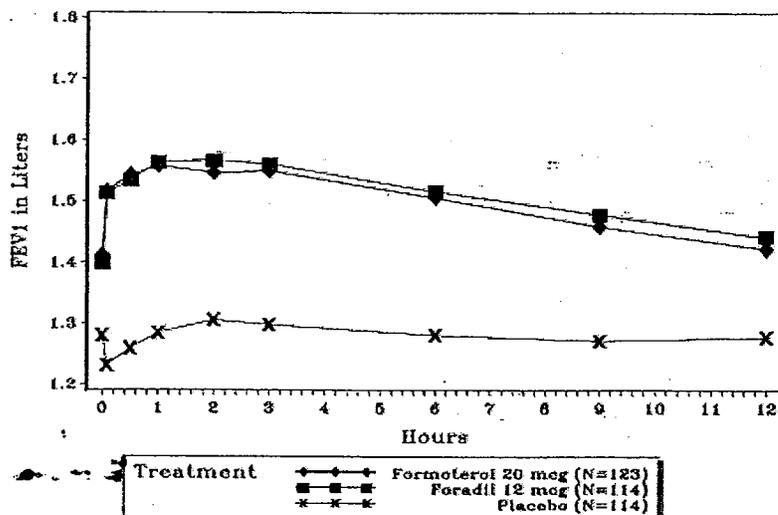


Figure 5. 201-065, LS mean FEV₁ (L)* over time by treatment, Week 12, ITT

* LS Means are based on an ANCOVA model with treatment and center as fixed effects and baseline FEV₁ (Day 1 Pre-Dose) as the covariate.

Source: summaryofclin-efficacy-copd.pdf, p 15

Table 5. 201-065, Total SGRQ Results, ITT pop

Treatment	N	Total SGRQ Scores, ITT pop, LS means				
		Baseline	Change from baseline at Week 12	Comparison to placebo		
				LS mean difference	95% CI	p-value
FFIS 20 mcg	123	47.85	-5.56	-4.91	-8.45, -1.37	0.0067
FA 12 mcg	114	49.70	-4.11	-3.46	-7.11, 0.19	0.0633
Placebo	114	48.53	-0.65			

Source: Study 201-065, section-1-15-report-body.pdf, p108

Product Name

Several trade names were submitted for consideration. Dey proposed the trade names "Perforomist," and "DMETS and DDMAC objected to" but found "Perforomist" acceptable. Dey has indicated that they are fine with the name Perforomist, which was there first choice. I have no objections to this proposed trade name.

b(4)

Labeling

Labeling negotiations were not completed prior to completion of this review. Therefore, this section is preliminary. Labeling comments from DMETS, DDMAC, and DSRCS will be considered for the final labeling. My comments with regard to pertinent labeling issues may be found within other sections of this review, and are not repeated here.

Labeling was submitted in PLR Word and PFD, but not SPL, format. The labeling is being reviewed, and compared with the last approved package inserts for Foradil (formoterol fumarate) Aerolizer and Brovana (arformoterol tartrate) Inhalation Solution, as well as other beta-agonist drug products. Brovana was approved during this review cycle for the same

indication as is sought in this application. During the review cycle, updated labeling with a boxed warning was requested and submitted, as was a Medication Guide.

Pediatric Considerations

PREA is triggered by this application. Dey has requested a waiver for children on the grounds that COPD is not a pediatric disease. This is acceptable, and a waiver of pediatric studies and should be granted.

Phase 4 Commitments

In a facsimile communication of December 13, 2006 the Division of Pulmonary and Allergy Products requested Dey to commit to the following postmarketing clinical trials. Dey's response follows the description of each study.

1. A multicenter, randomized, placebo-controlled, large, simple safety study to evaluate the effects of long term use of formoterol fumarate inhalation solution in patients with COPD. The objective of this trial would be to determine the risk of fatal and life-threatening respiratory events associated with the long term use of formoterol fumarate inhalation solution in patients with COPD. The study should be of adequate size and duration to meet the objective.

b(4)

2. A safety and tolerability study with one or more doses and one or more dose levels of formoterol fumarate inhalation solution in children with asthma and/or obstructive airway disease. The objective would be to assess the safety and tolerability of formoterol fumarate inhalation solution children 12 years of age and younger with asthma. Include a placebo or active control treatment group, as appropriate. Include children 12 years of age and younger so that the lower age limit would be based upon the age at which asthma/obstructive airway disease exists. The study should be of adequate size and duration to meet the objective.

b(4)

3. A safety and efficacy study with one or more doses and one or more dose levels of formoterol fumarate inhalation solution in children with asthma and/or obstructive airway disease presenting with an acute exacerbation. The objective would be to establish the safety and efficacy of formoterol fumarate inhalation solution in children 12 years of age and younger with an acute exacerbation of asthma. Include a placebo or active control treatment group, as appropriate. Include children 12 years of age and younger so that the lower age limit would be based upon the age at which asthma/obstructive airway disease exists. The study should be of adequate size and duration to meet the objective.

Recommendation

I recommend Approval of this NDA.

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/s/

Peter Starke
3/15/2007 04:13:23 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type New Drug Application
Submission Number 000
Submission Code NDA 22-007

Letter Date June 28, 2006

Stamp Date June 29, 2006

PDUFA Goal Date April 29, 2007

Reviewer Name James Kaiser
Review Completion Date February 28, 2007

Established Name [no established name]
(Proposed) Trade Name [no proposed trade name]
Therapeutic Class β_2 -adrenergic receptor agonist
Applicant Dey, L.P.

Priority Designation S

Formulation Inhalation solution
Dosing Regimen Twice daily
Indication maintenance treatment of broncho-
constriction
Intended Population patients with chronic obstructive
pulmonary disease including chronic
bronchitis and emphysema

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Dey L.P. submits NDA 22-007 for formoterol fumarate inhalation solution 20 µg/2ml (FFIS) under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This section of the Act allows three types of potential approvals, one of which is for a marketing application for which supporting information comes from studies not conducted by the applicant and for which the applicant has not obtained right of reference. Dey has provided sufficient evidence of the comparability of FFIS to Foradil® to allow for the safe and effective use of FFIS. Formoterol fumarate is a long-acting β_2 -agonist. The greatest concern at the current time regarding the use of long-acting β_2 -agonists is the potential for an increase in mortality in patients with asthma, and possibly COPD, taking these agents. There is a significant possibility that FFIS may be used in patients with asthma. Dey should generate information in the postmarketing setting regarding the long-term safety of FFIS in the asthma and COPD populations.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Long-acting β_2 -agonists (LABAs) may increase the incidence of severe exacerbations of asthma and asthma-related deaths, and data are insufficient to discern whether similar concerns exist in COPD patients taking LABAs. In addition, the clinical program for FFIS was conducted in a population that was to a large extent Caucasian. Postmarketing risk management should include an evaluation of fatal and life-threatening respiratory adverse events in patients with COPD, safety in racial and ethnic subgroups, cardiovascular adverse events in patients with COPD, potential low frequency adverse events associated with use, and safety in populations other than patients with COPD, especially patients with asthma.

1.2.2 Required Phase 4 Commitments

In a facsimile communication of December 13, 2006 the Division of Pulmonary and Allergy Products requested Dey to commit to the following postmarketing clinical trials:

1. A multicenter, randomized, placebo-controlled, large, simple safety study to evaluate the effects of long term use of formoterol fumarate inhalation solution in patients with COPD. The objective of this trial would be to determine the risk of fatal and life-threatening respiratory events associated with the long term use of formoterol fumarate inhalation solution in patients with COPD. The study should be of adequate size and duration to meet the objective.

b(4)

2. A safety and tolerability study with one or more doses and one or more dose levels of formoterol fumarate inhalation solution in children with asthma and/or obstructive airway disease. The objective would be to assess the safety and tolerability of formoterol fumarate inhalation solution children 12 years of age and younger with asthma. Include a placebo or active control treatment group, as appropriate. Include children 12 years of age and younger so that the lower age limit would be based upon the age at which asthma/obstructive airway disease exists. The study should be of adequate size and duration to meet the objective.

b(4)

3. A safety and efficacy study with one or more doses and one or more dose levels of formoterol fumarate inhalation solution in children with asthma and/or obstructive airway disease presenting with an acute exacerbation. The objective would be to establish the safety and efficacy of formoterol fumarate inhalation solution in children 12 years of age and younger with an acute exacerbation of asthma. Include a placebo or active control treatment group, as appropriate. Include children 12 years of age and younger so that the lower age limit would be based upon the age at which asthma/obstructive airway disease exists. The study should be of adequate size and duration to meet the objective.

b(4)

1.2.3 Other Phase 4 Requests

I do not recommend any other postmarketing commitments.

1.2.4 Pediatrics (PREA)

With submission of the application, Dey has requested a waiver of pediatric studies for this application. Since COPD is a condition that does not occur in the pediatric population, a waiver of pediatric studies is reasonable, and should be granted under PREA.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Dey originally studied FFIS in subjects with asthma, conducting four single-dose, dose finding trials. The program switched to COPD. All the trials studied the effects of the product when delivered with a standard nebulizer and compressor combination (Pari-LC nebulizer and compressor). They included a placebo (inactive) and Foradil[®] Aerolizer[®] (active) comparator arm, features that allowed a determination of the sensitivity of the trials to detect effects and a comparison of the effects to a product with a known record of safety and efficacy. Dey conducted two single-dose, dose-finding trials with FEV₁ as the primary outcome measure. The second of these trials, DL-057, established the dose that Dey would use for the further multiple-dose trials: 20 µg twice a day. Dey also conducted a single pharmacokinetic/pharmacodynamic trial, whose results showed that Dey's formoterol fumarate product does not produce greater systemic exposure, and thus would not be expected to have greater safety risk, than Foradil[®]. Dey initiated an efficacy trial, DL-059, which was invalidated for the assessment of efficacy (and to a large extent, safety), by incorrect treatment assignments and the switching of treatments by subjects. Subjects from this trial were switched over to a 52-week open-label safety trial, the only long-term experience of FFIS. Dey conducted a single trial for efficacy, trial 201-065. This was an adequately designed and conducted, randomized, double-blind, placebo-controlled trial with a Foradil[®] active comparator arm, in which subjects with COPD were treated for 12 weeks, a reasonable period of time after which to determine the bronchodilatory effects of the test treatment for chronic use in COPD. The primary endpoint was a measure of FEV₁ at the end of the treatment period. This trial showed that formoterol fumarate inhalation solution (20 µg/2m) was effective in producing bronchodilation. It is my judgment that the effect of Dey's product was comparable to that of Foradil[®] in this trial.

1.3.2 Efficacy

Efficacy for FFIS was shown in a single 12-week randomized, placebo-controlled, active comparator (Foradil[®]) trial that enrolled 351 subjects with COPD (trial 201-065). Subjects were given placebo, Foradil[®] 12 µg twice daily, or FFIS 20 µg twice daily for 12 weeks. The primary endpoint was a comparison between FFIS and placebo of the area-under-the-curve of FEV₁ determined for the 12 hours after the morning dose of trial medication at week 12. The statistical plan did not have a formal test for comparability of Dey's product to Foradil[®].

The clinical trial was adequately designed and conducted. FFIS was statistically superior to placebo. An examination of the confidence intervals of the differences among treatments shows that Dey's product preserved at least half of the treatment benefit (over placebo) produced by Foradil[®]. The extent of the treatment effect of FFIS in trial 201-065 was close to that seen at the same dose in a prior single-dose trial, DL-057.

1.3.3 Safety

The clinical safety data base is detailed in Table 5. In summary,

- The only long-term information on the safety of FFIS comes from the 463 subjects with COPD who received the proposed marketed formulation of formoterol fumarate inhalation solution at the proposed dose in a 52-week trial (DL-059 open-label period), 387 of whom were treated for at least 180 days, and 155 for at least 365 days.
- The only inactive-controlled information on the safety of multiple dose administration comes from the 123 subjects with COPD who received the proposed marketed formulation of formoterol fumarate inhalation solution at the proposed dose in the 12-week, placebo-controlled, active comparator (Foradil[®]) trial (201-065).
- Other, single-dose safety information include
 - 93 subjects with COPD treated in single-dose trials at varying doses of formoterol fumarate inhalation solution. This includes 59 subjects who received formoterol fumarate inhalation solution in single doses at the proposed dose.
 - 121 subjects with asthma treated with varying single doses of formulations of formoterol fumarate at varying concentrations.
- Serious adverse event data were submitted from ongoing trials in subjects with COPD with a different formulation of formoterol fumarate inhalation solution, using different means of nebulization.

Evaluations were adequate, including clinical events and laboratory evaluations. The causes and frequencies of deaths, serious adverse events, and adverse events generally did not raise concern for a new toxicity of FFIS compared to Foradil[®] in particular and long-acting β_2 -agonists.

The pharmacokinetics and pharmacodynamics of FFIS did not suggest an increase in exposure of the active moiety compared to Foradil[®]. Thus there is no concern that safety risk from systemic exposure would be increased compared to Foradil[®].

1.3.4 Dosing Regimen and Administration

Dey has provided adequate information to approve of the proposal for dosing FFIS at 20 μ g twice daily by nebulization. The clinical trials tested this regimen with one nebulizer and compressor combination. It is appropriate to state this limitation in labeling, as delivery by means of other nebulizer and compressor combinations may alter the delivery of the product to the airways.

1.3.5 Drug-Drug Interactions

FFIS does not contain any excipients expected to have interactions with drugs. Further information about the interaction of formoterol fumarate is not required, and was not provided by Dey.

1.3.6 Special Populations

Dey proposes FFIS for use in patients with COPD. Because it is a long-acting β_2 -agonist bronchodilator, there is a significant likelihood that it will be used off-label in patients with asthma, a population for which use of these agents may convey an increased mortality risk. Dey has only limited, single-dose experience in subjects with asthma. FDA requested that Dey commit to

postmarketing trials that will help to address the need for additional information (see section 1.1.2: Required Phase 4 Commitments). The clinical trial data base is comprised primarily of Caucasians. FDA has requested the conduct of a large, simple safety trial that will develop more information in various racial subpopulations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Dey LP proposes to market a new formulation of a long-acting beta₂ agonist (long-acting β₂ agonist, LABA), formoterol fumarate, which is currently marketed as Foradil[®] Aerolizer[®] and Brovana[®] Inhalation Solution. Both Dey's formoterol fumarate and Foradil[®] consists of racemic mixtures of (R, R)- and (S, S)-enantiomers; a formoterol preparation approved since the submission of the current NDA, Brovana[®], consists of only the R,R-enantiomer. Foradil[®] consists of formoterol fumarate on a lactose carrier powder, packaged in dry gelatin capsules that are to be used in an inhaler called the Aerolizer[®]. Dey submits this marketing application for formoterol inhalation solution, 20 mg/2ml, under regulation 505(b)(2), referencing toxicology, pharmacology, and pharmacokinetics of Foradil Aerolizer[®].

FFIS is a sterile, clear isotonic solution for oral inhalation by nebulization. It is formulated with sodium chloride to maintain _____, and citric acid _____ and sodium citrate _____ to buffer the formulation to a pH of 5.0. It is packaged in low-density polyethylene (LDPE) unit dose vials that are individually overwrapped with an _____

Dey has proposed the tradenames "_____" "Perforomist," and "_____" The Division of Medication Errors and Technical Support (DMETS) concurs with the Division of Drug Marketing, Advertising and Communications (DDMAC) in objecting to _____ but in finding "Perforomist" acceptable.

Dey's current formulation is at a concentration of 20 mg per ml. Dey is developing _____

2.2 Currently Available Treatment for Indications

Other LABA products available for use in chronic obstructive pulmonary disease (COPD) include Foradil[®] (formoterol fumarate inhalation powder), Serevent[®] (salmeterol xinafoate) and Advair[®] (salmeterol xinafoate with fluticasone propionate), all of which are in metered-dose inhaler (MDI) form. Brovana[®] (the R,R enantiomer of formoterol) was recently approved as a nebulization solution. Other bronchodilators are available for the treatment of COPD, for example anticholinergics, methylxanthines, and short-acting β-agonists such as albuterol.

2.3 Availability of Proposed Active Ingredient in the United States

Formoterol fumarate is available as Foradil[®] and Brovana[®], as discussed above. Notably, Foradil[®] is indicated for asthma and exercise-induced bronchospasm in addition to COPD.

The CMC review states the following regarding the drug substance, aerodynamic properties, and stability for FFIS:

Drug substance:

“The drug substance used in Formoterol Fumarate Inhalation Solution 20 mcg/2 mL is a racemic mixture (R,R and S,S). Formoterol fumarate dihydrate exists as a white to yellowish white solid. It is slightly soluble in water and its aqueous solubility is pH and temperature dependent. The solubility of Formoterol fumarate dihydrate at room temperature was found to be \sim mg/mL at pH 3 and \sim mg/mL at pH 5.0 and pH 7.0. The solubility of Formoterol fumarate dihydrate at refrigerated temperature was found to be \sim mg/mL at pH 5.0. As the therapeutic dose of Formoterol fumarate is in the order of tens of micrograms, Formoterol fumarate dihydrate was demonstrated to have sufficient aqueous solubility in the pH range of 3-7 to be developed as an inhalation solution for nebulization.”

b(4)

Aerodynamic properties of the solution

“Using a Pari LC Plus™ nebulizer/Proneb® Ultra compressor system [in accordance with the methods used in the clinical trials], the delivered dose, defined as the amount of formoterol fumarate emitted from the nebulizer was evaluated to be 7.33 ± 0.69 mcg. The average respirable dose, defined as the amount of Formoterol Fumarate contained in aerosols nebulized from two doses (2 x 2 mL) having aerodynamic diameters in the range of $1 \text{ } \mu\text{m}$, was 5.12 ± 0.55 mcg. These measured values represent about 37% of label claim. Finally, the volume based median diameter and the span, (D10-D90)/D50, of the Formoterol Fumarate Inhalation Solution 20 mcg/2 mL aerosols determined by $1 \text{ } \mu\text{m}$, respectively.”

b(4)

Stability

Although formoterol fumarate is known to undergo hydrolysis in aqueous solution, the CMC reviewer has determined that Dey has provided “appropriate stressed, supporting and real-time stability data to support the proposed expiry period of 24 months under the recommended refrigerated storage condition (\sim) including up to 3 months post-dispensing storage at $25^\circ\text{C} \pm 2^\circ\text{C}$ / \sim P.” The review further states, “The applicant has demonstrated lot-to-lot consistency in the manufacture and the quality of the drug product. As of the writing of this clinical review, the only outstanding CMC issue is the pending nature of pre-approval establishment inspections.”

b(4)

Product microbiology review revealed no issues.

3.2 Animal Pharmacology/Toxicology

The pharmacology/toxicology review states, “From a nonclinical perspective, safety of formoterol fumarate is primarily based upon a prior FDA finding of safety and effectiveness for Foradil® Aerolizer® (NDA 20-831 and NDA 21-279), as described in the drug’s approved labeling. The applicant conducted a 14-day inhalation toxicology study with rats to compare product performance of formoterol fumarate inhalation solution with the approved dry powder formulation of formoterol fumarate.” The reviewer found that this study determined no differences between FFIS and the approved dry powder formulation.

3.3 Division of Scientific Investigations Audit

The Division of Scientific Investigations conducted an audit of three sites involved with the critical efficacy trial 201-065. The Division of Pulmonary and Allergy Products selected the sites based on their relatively large size. In addition, one of the sites had a relatively large overall discontinuation rate, and subjects showed a small deterioration in the active comparator arm of the trial. In summary, the DSI audit did not uncover substantial data irregularities or misconduct.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Note: In the review of clinical trials Foradil® is denoted "FA."

4.1 Sources of Clinical Data

4.2 Tables of Clinical Trials

Table 1 is a summary of the critical studies for the dose-finding and determination of efficacy and safety in COPD.

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Table 1. Dey completed COPD trials (dose-finding, safety, and efficacy)

Trial	Study Objectives	Study Design	Test products; dosage regimen; route of administration	Number of Subjects	Nominal Duration of Treatment
DL-056	Evaluate the PK of FFIS compared with FA	Randomized, open-label, 4-way cross-over	FFIS (10, 20, 244 mcg), FA 12 mcg, inhalation	13	Single dose on 4 separate days
DL-052	Define a comparable dose of FFIS to 12 mcg FA and determine safety of FFIS	Randomized, double-blind, 5-way cross-over, placebo- and active-controlled, double-dummy	FFIS (40, 80 mcg), FA (12, 24 mcg), placebo, inhalation	39	Single dose on 5 separate days
DL-057	Determine the lowest dose of FFIS comparable to FA 12 mcg.	Randomized, double-blind, 7-way cross-over, placebo- and active-controlled, double-dummy	FFIS (2.5, 5, 10, 20, 40 mcg), FA 12 mcg, placebo, inhalation	47	Single dose on 7 separate days
DL-059*	Double-blind (DB) period: Efficacy and safety Open-label (OL) period: Long-term safety	DB: Phase III, randomized, double-dummy, parallel-group, placebo- and active-controlled OL: Randomized, open-label	DB: FFIS 20 mcg bid, FA 12 mcg bid, placebo bid, inhalation OL: FFIS 20 mcg bid, FA 12 mcg bid, inhalation	DB: 694 (516 FFIS, 500 FA, 315 placebo)* OL: 569 (463 FFIS, 106 FA)	DB: 12 weeks OL: 52 weeks
201-065	Efficacy and safety of FFIS 20 mcg compared to placebo	Randomized, double-blind, double-dummy, parallel-group, placebo- and active-	FFIS 20 mcg bid, FA 12 mcg bid, placebo bid, inhalation	351 (123 FFIS, 114 FA, 114 placebo)	12 weeks

FFIS = formoterol fumarate inhalation solution, 20 µg/2 ml; FA = Foradil[®]

*Errors in treatment assignments in the double-blind period did not allow efficacy to be evaluated and severely limited safety assessments

[Source: Dey tabular listing of all Clinical Studies; tabular_listing.pdf]

Table 2 shows the additional completed clinical trials, all in subjects with asthma, useful for the safety evaluation of FFIS:

Table 2. Additional completed trials for safety evaluation (asthma)

Trial	Study Objectives	Study Design	Test products; dosage regimen; route of administration	Number of Subjects	Nominal Duration of Treatment
DL-048 & DL-050	Safety of FFIS; define dose of FFIS comparable to FA 12 µg	Randomized, double-blind, double dummy, 7-way crossover	FFIS 40, 80, 162, 244 µg FA 12, 24 µg Placebo	DL-048: 32 Subjects 12-70 yrs DL-050: 32 Subjects 5-11 yrs	Single dose on 7 separate days; 2-7-d washout
DL-053	Evaluate dose-response of FFIS 40 & 80 µg to FA 12 µg	Randomized, double-blind, double dummy, 7-way crossover	FFIS 40, 80 µg FA 12 µg	21 Subjects 6-62 yrs	Single dose on 3 separate days; 2-7-d washout
DL-055	Define dose of FFIS comparable to FA 12 µg	Randomized, double-blind, double dummy, 6-way crossover	FFIS 2.5, 5, 10, 20 µg FA 12 µg Placebo	45 Subjects 5-12 yrs	Single dose on 6 separate days; 2-7-d washout

[Source: Dey tabular listing of all Clinical Studies; tabular_listing.pdf]

Table 3 shows the ongoing clinical trials, all in COPD, whose serious adverse event record was reported in the 120-day safety update.

Table 3. Ongoing clinical trials in COPD

Trial	Study Objectives	Study Design	Test products; dosage regimen; route of administration	Number of Subjects	Nominal Duration of Treatment
201-069	Safety and efficacy	Randomized, double-blind, parallel-group, placebo- and active-controlled, double-dummy	FFIS (20 µg/0.5 mL bid), FA 12 µg bid, placebo bid, inhalation ^{1,2}	347	12 weeks
201-070	Safety and efficacy	Randomized, double-blind, parallel-group, placebo- and active-controlled, double-dummy	Tiotropium 18 µg once daily, FFIS 20 µg bid, placebo bid, inhalation ²	Not reported	6 weeks
201-074	pharmacokinetics	Randomized, open-label, single- and multiple-dose, crossover,	FFIS 20 µg/0.5 mL bid for 10 days; FA 12 µg bid for 10 days ^{1,3}	Not reported	2 doses per day for 10 days in each of 2 periods

¹ These clinical trial use FFIS at a higher concentration (20 µg/0.5 ml) than the ones submitted for this NDA

² All these clinical trial used a different nebulizer (the nebulizer) from the one used in the clinical trials submitted in this NDA.

[Source: Dey tabular listing of all Clinical Studies; tabular_listing.pdf]

b(4)

4.3 Review Strategy

Dey's marketing application contains only one adequately-designed efficacy trial. However, in the presence of substantial pre-existing information about the active moiety and adequate dose finding in the clinical development of the product, this is sufficient information in principle upon which to base a decision about the efficacy of a product. Substantial information exists as to the safety and efficacy of long-acting β_2 agonists generally and formoterol fumarate specifically (marketed as an inhalation powder as Foradil®). The review of FFIS is first dependent upon the results of the pharmacokinetic/pharmacodynamic trial DL-056 to assess the potential for an increased safety risk due to increased exposure compared to Foradil®, and then on the bioactivity trial DL-057 whose intents was to establish a dose correspondence with Foradil® in terms of the effect on FEV₁. Subsequent trials (DL-059 and 201-065) were reviewed for 1 year of safety and 12 weeks of bioactivity information, respectively.

4.4 Data Quality and Integrity

The Division of Pulmonary and Allergy Products requested an inspection of three clinical sites involved with the critical efficacy trial 201-065. These sites were chosen because they had larger numbers of subjects compared to other sites in the trial and efficacy was near maximal at these sites. This combination of features would give these sites more influence than others on the outcome of the trial. In addition, one of the sites had the largest number of discontinuations among sites with more than 10 subjects and at this site the Foradil® treatment effect was less than placebo (in an unadjusted analysis), an unexpected finding. As of the writing of this review, the inspection by the Division of Scientific Integrity of these sites is not complete.

A major randomization error occurred during the double-blind period of trial DL-059, which had been intended to be a critical for the determination of efficacy (Dey subsequently conducted another efficacy trial). However, during my review of this marketing submission, I noted no issues with data integrity.

4.5 Compliance with Good Clinical Practices

Dey states that all clinical trials were conducted in accordance with Good Clinical Practices. I found no ethical issues with conduct of the trials in my review of this NDA.

4.6 Financial Disclosures

One investigator (Dr. Nicholas Gross) involved in the critical efficacy trial 201-065 claimed a financial interest. This investigator's data were included in analyses, as his site enrolled 7 subjects, comprising only 1.9% of total subjects in the trial. The impact of the financial interest is expected to be minimal.

5 CLINICAL PHARMACOLOGY

The critical pharmacology study submitted by Dey was trial DL-056. This was a multiple-period, crossover, single-dose trial comparing several doses of FFIS to Foradil® and placebo in

subjects with COPD. This section of the review will cite the summary of data and the conclusions of the pharmacology reviewer for NDA 22-007.

5.1 Pharmacokinetics

Table 4 is a summary of data from Trial DL-056 constructed by the FDA pharmacology reviewer.

Table 4. FDA Pharmacologist's summary of mean (sd) urine and plasma PK parameters of formoterol after single dose inhalation administration of FFIS and Foradil® Aerolizer®

	Treatment				
	FFIS 10 mcg	FFIS 20 mcg	FFIS 244 mcg	Foradil® 12 mcg	Ratio (FFIS 20 mcg: Foradil® 12 mcg)
Urine PK data					
Ae _(0-24h) (ng)	109.7 (56.0)	349.6 (190.3)	3317.5 (1733.0)	406.3 (116.5)	0.86
CL _R (mL/min)	NR	NR	157.0 (66.4)	NR	—
% dose	1.1 (0.6)	1.7 (1.0)	1.4 (0.7)	3.4 (1.0)	0.5
Plasma PK data					
C _{max} (pg/mL)	5.7 (8.1)	8.7 (9.3)	72.5 (35.3)	12.3 (4.2)	0.71
AUC _t (pg.hr/mL)	23.1 (30.2)	28.7 (38.3)	388.9 (173.8)	53.4 (44.6)	0.54
AUC _{inf} (pg.hr/mL)	NR	NR	449.8 (190.9)	NR	—
T _{max} * (hr)	7.5 (0.1-24.1)	0.6 (0.1-35.9)	0.2 (0.1-0.5)	0.5 (0.1-24.0)	1.2
T _{1/2} (hr)	NR	NR	7.0 (2.6)	NR	—

* Median (range); NR = Not reliably quantified; Ae(0-24h) = Amount of drug excreted from time 0 to 24 hrs post-dose; CL_R = renal clearance; % dose = percent dose excreted in urine over 24 hrs.

Dr. Roy concludes:

- “...the bioanalytical method was not sensitive enough to measure the majority of the drug concentrations in plasma, which were mostly near or below the [lower limit of quantitation]... Formoterol fumarate concentrations in urine were reliably measured for all three FFIS doses. Therefore, excretion of unchanged formoterol in urine was used as an indirect measure of systemic exposure. Limited plasma PK data was only used as supportive in reaching study conclusions.”
- “The mean amount of formoterol excreted in urine over 24 hrs following administration of FFIS 20 mcg was 14% lower compared to Foradil® Aerolizer®, 12 mcg [Table 4]. The mean percentage of dose excreted in urine was found to be consistent across all 3 FFIS groups suggesting linear pharmacokinetics. The mean percent dose excreted unchanged in urine over 24 hours was approximately 2-fold higher after patients were dosed with Foradil® Aerolizer® 12 mcg relative to the 20 mcg FFIS dose, indicating possibly lower bioavailability for FFIS compared to Foradil® Aerolizer®. These data, taken together,

support the conclusion that formoterol systemic exposure after the administration of 20 mcg FFIS via nebulizer Pari LC Plus[®] was slightly lower compared to that from Foradil[®] Aerolizer[®] 12 mcg.”

- “Plasma PK data, though limited, further supported these conclusions. The mean formoterol C_{max} and AUC_t from FFIS 20 mcg were found to be 29% and 46% lower compared to that obtained from Foradil[®] Aerolizer[®], respectively (Table 1). The systemic exposure from 244 mcg FFIS (i.e. 12-fold the intended therapeutic dose of FFIS) was comparable to that from 120 mcg Foradil[®] Aerolizer[®] (i.e. 10-fold the approved dose of Foradil[®] Aerolizer[®]). The study did not reveal any unexpected PK characteristics that differ significantly from what were known for Foradil[®] Aerolizer[®].”

5.2 Pharmacodynamics

This section of the review does not consider FEV₁, which is a pharmacodynamic endpoint studied in the clinical trials. It discusses systemic effects, which are related to the safety of FFIS.

Dey examined the effects of FFIS and Foradil[®] on serum chemistries and on various electrocardiographic parameters. This review will focus on the potential β -adrenergic effects of these products on serum glucose and potassium, and on the correct QT interval (these data are summarized in the Appendix to this review). In trial DL-056 FFIS at any dose (10, 20, or 244 μ g) had more of a hyperglycemic effect at 1 hour than Foradil[®]. The mean and median increase in serum glucose from predose at 1 hour in the FFIS 20 μ g group were 29 and 25 (mg/dl), as compared to 7.2 and 4.5 in the Foradil[®]-treated subjects. The differences were not present at the 24-hour time point post dose. A dose-dependent hypokalemic effect was seen in the FFIS groups; however, at the proposed dose of FFIS (20 μ g), the differences between FFIS and Foradil[®] in effects on serum potassium were negligible. Notable differences in glucose and potassium were not seen in the clinical program at the proposed dose with chronic use (the timing of laboratory determinations with respect to trial treatment at a visit was not specified). The differences in glucose and potassium in trial DL-056 do not indicate that FFIS is notably different from Foradil[®].

The maximum increase post-dose at any time point in the FFIS 10, 20, and 244 μ g groups and the Foradil[®] group were 41, 30, 52, and 42 msec, respectively (QTcB) and 24, 18, 31, and 29 msec. There was a very small mean effect of FFIS on the corrected QT only at the highest dose. No subject had a corrected QT greater than 500 msec.

5.3 Exposure-Response Relationships

In addition to the pharmacokinetics/pharmacodynamics trial DL-056 Dey conducted dose-finding with respect to efficacy. Trial DL-052 measured FEV₁ collected over a 12-hour period after the administration of single doses of FFIS at 40 and 80 μ g, Foradil[®] 12 μ g, and placebo (see the Appendix of this review). The Division of Pulmonary and Allergy Products stated that the doses chosen were unlikely to be sensitive enough to demonstrate a dose response, and recommended to Dey to explore doses lower than the lower dose used in this trial. In response, Dey conducted trial DL-057, which measured the same endpoint (area-under-the-curve of FEV₁ (AUC FEV₁(0-12h))) after the administration of single doses of FFIS at 2.5, 5, 10, 20, and 40 μ g, Foradil[®] 12 μ g, and placebo (see the Appendix of this review). FFIS at a dose of 20 μ g resulted in an AUC FEV₁(0-

12h) that was comparable to that produced by administration of Foradil® at its marketed dose (12 µg). Dey used the 20 µg dose in its further safety and efficacy trials.

6 INTEGRATED REVIEW OF EFFICACY

As stated above, because of the extent of the information regarding LABA products generally, and Foradil® in particular, information from one clinical trial of adequate design and conduct would be considered adequate for a regulatory decision on the approvability of FFIS, given corroboration on effect from the other dose-finding trials and a lack of concern over safety from the pharmacokinetic/pharmacodynamic trial. In this case, the trial was adequate, and other information in the submission (notably the results of dose-finding trials) was supportive.

6.1 Indication: COPD

Dey proposes 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.

This statement has the same content as the Foradil® COPD indication statement.

6.1.1 Methods

The efficacy of FFIS was established in one clinical trial. Dose finding was performed in the single-dose trials DL-052 and DL-057.

6.1.2 General Discussion of Endpoints

The critical efficacy trial for FFIS, trial 201-065 used the area-under-the-curve of FEV₁ determined over the 12 hours after morning treatment, after 12 weeks of twice-daily treatment, as the primary outcome measure. FEV₁ is a generally accepted outcome measure for a bronchodilator treatment in COPD. Twelve weeks was a reasonable period of time after which to determine the bronchodilatory effects of the test treatment for chronic use in COPD. The area-under-the-curve of FEV₁ determined over the 12 hours after treatment is a reasonable assessment of the effect of treatment over the treatment interval for a twice-daily treatment. Dey chose to standardize the area-under-the-curve of FEV₁ (a process of normalizing the data by the time observed) for this trial. FDA's statistical reviewer determined that this choice was not critical to the finding of efficacy. The primary endpoint comparison was between FFIS and placebo; a formal noninferiority test against Foradil® was not required by FDA. Dey's statistical testing was consistent with no difference between FFIS and Foradil®, and an analysis of the confidence interval around the difference between FFIS and Foradil® supports a lack of a difference between the two. Dey chose reasonable assessments to provide support for the primary endpoint. These included spirometry measures (FEV₁-related and FVC) and albuterol use during the trial.

6.1.3 Study Design

The dose-finding clinical trials were placebo-controlled and contained a Foradil® treatment arm. Inclusion of the Foradil® arm not only provided a means to assess the sensitivity of the trial to detect an effect, but provided a direct comparator to guide dose in the critical efficacy trial. Dose-finding was adequate, as described above.

Trial 201-065 was adequately designed to assess the effect of FFIS on bronchodilation. It included both a placebo treatment and an active comparator of known efficacy (Foradil®). Because the trial included both a nebulizer and a dry-powder inhaler, a double-dummy design was incorporated in which subjects received both types of treatment and each mode of delivery had a placebo. Labeling of treatments was blinded. The duration of the trial, 12 weeks, was adequate. Although the trial population was composed almost entirely of Caucasians, the results can be generalized to other racial groups. The trial included a prospective statistical analytical plan.

6.1.4 Efficacy Findings

Both the dose-finding trials and the critical efficacy trial used the area-under the curve of FEV₁ for the 12-hours after dosing (AUC FEV_{1(0-12h)}) as the primary efficacy measure. Dey conducted two dose-finding trials prior to initiating their efficacy program. Trial DL-052 inadequately explored the dose range, as its low dose was too high. This was followed by trial DL-057, a single-dose trial of FFIS 2.5, 5, 10, 20, and 40 µg, Foradil® 12 µg, and placebo that established a dose that was reasonably comparable to Foradil® (see Table 15 and Table 16 and Figure 2).

The efficacy of FFIS with repetitive use was shown in one clinical trial, 201-065 (see Appendix). In this trial 351 adult subjects with moderate COPD were randomized approximately equally to 12 weeks of treatment with either FFIS, Foradil® at its approved dose, or placebo. This trial was adequately conducted. The primary endpoint of the trial was a comparison of FFIS to placebo in the standardized area-under-the-curve of FEV₁ determined for 12 hours after the morning dose of trial agent at week 12. The other important comparison in the trial was FFIS to Foradil®. FFIS and Foradil® separated from placebo, each with a p-value less than 0.0001 (Table 44 and Table 45). (The effect of a single 20 µg dose of FFIS in the single-dose, dose-finding trial DL-057 was similar in magnitude to that produced at week 12 in trial 201-065, providing some near-replication of the FEV₁ finding in 201-065.) The two active treatments were not different from each other in Dey's statistical testing. Secondary spirometric endpoints (peak and trough FEV₁, FEV₁ at each post-dose time point compared to placebo, and FVC) were supportive of the efficacy primary endpoint. Albuterol use in the active treatment arms during the 12 weeks of the trial was a little greater than one puff a day less than that in placebo-treated subjects, also supporting the primary endpoint.

6.1.5 Clinical Microbiology

This section is not applicable to formoterol fumarate inhalation solution (20 µg/ml).

6.1.6 Efficacy Conclusions

Dey has shown that formoterol fumarate-inhalation solution (20 µg/ml) at a dose of 20 µg twice daily is effective as a twice-daily bronchodilator in patients with COPD.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Dey's clinical program included a double-blind, randomized, placebo- and active-(Foradil®)-controlled trial initially intended to demonstrate efficacy (see Table 1). Trial DL-059 was invalidated for the evaluation of efficacy, and to a large extent safety, due to large-scale errors in the assignment of treatments on the first day of treatment and by subsequent switching of treatments at subsequent visits. This clinical review includes discussion of safety data from this trial, mostly to illustrate that no new safety concerns came from it. However, the corruption of the treatment assignments made pooling of data from this trial with that from the other double-blind, placebo-controlled trial, 201-065, infeasible. There was little experience in overlapping doses in the single-dose trials, so combining these trials is not profitable in an integrated summary of safety. For these reasons, the integrated review of safety includes no pooled data.

Exposure

Table 5 shows the numbers of subjects who received at least one dose of FFIS at the indicated doses.

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Table 5. Summary of exposure to formoterol fumarate inhalation solution in completed trials

	Indication and nominal duration	Dose (µg)								Total
		2.5	5	10	20	40	80	162	244	
Multiple-dose trials										
201-065	COPD/12 weeks	—	—	—	123	—	—	—	—	123
DL-057 DB	COPD ¹	—	—	—	516	—	—	—	—	516
DL-057 OL	COPD/52 weeks	—	—	—	463	—	—	—	—	463
DL-057 combined	See note 1				620					620
Single dose trials										
DL-057	COPD	47	47	47	47	47	—	—	—	47
DL-052	COPD	—	—	—	—	37	36	—	—	37
DL-056	COPD	—	—	12	12	—	—	—	13	13
DL-048	Asthma	—	—	—	—	31	29	29	30	31
DL-050	Asthma	—	—	—	—	31	31	31	32	32
DL-053	Asthma	—	—	—	—	21	21	—	—	21
DL-055	Asthma	43	43	44	44	—	—	—	—	44

Notes:

1) The nominal duration of the double-blind period of DL-057 was 12 weeks; however, treatment switching resulted in most subjects not receiving any assigned treatment for the assigned time.

2) The bolded numbers are the subjects with COPD who received FFIS at the proposed marketed dose at least once. The total of these numbers is 802. The total number of COPD subjects who received FFIS at any dose is 840.

[Source: summary-clin-safety.pdf, Table 2.7.4.1.1.1]

Various concentrations of formoterol fumarate were used in the formulations studied in the clinical trials (for details, see the reviews of the reports in the Appendix to this review). All these formulations had the same concentrations of sodium chloride, sodium citrate _____ and were all formulated with _____ to the final volume. The proposed final concentration was used in the critical efficacy and safety trials (DL-059 and 201-065)

7.1.1 Deaths

The deaths that occurred in the clinical program for FFIS raised no concern about a toxicity not noted in β_2 -agonists generally. The principal cause of death in the clinical program was cardiovascular, occurred in subjects with predisposing features, and did not occur at a notably higher frequency than in subjects who took Foradil[®]. No deaths occurred in the single-dose trials.

Two deaths occurred in the double-blind period of DL-059:

- 70 year-old woman who died of a COPD exacerbation approximately 8 days after discontinuing from Foradil treatment.
- 76 year-old man who died as a result of metastatic liver disease. He had received treatment with placebo (about 1 month), FFIS (about 1 month), and finally FA (about 2 weeks).

Eight deaths occurred in the 52-week open-label period of DL-059:

FFIS

- 69 year-old man died of cardiac arrest on day 18. Medical conditions included hypertension, dyslipidemia, myocardial infarction.

- 78 year-old man died of exacerbation of COPD on day 272. He had had a treatment interruption for a prior COPD exacerbation. Medical conditions included thoracic scoliosis and a prior thoracotomy.
- 62 year-old man died of myocardial infarction on day 379, 15 days after completing the trial. Medical conditions included two myocardial infarctions and hypertension.
- 50 year-old man died of "coronary artery disease" on day 191, 3 days after stopping treatment. He had no prior related medical history.
- 65 year-old man died of congestive heart failure on day 345, 12 days after treatment was discontinued for the event. He had had a recent gastrointestinal bleeding event. Medical conditions included an abdominal aortic aneurysm on day 18 for which he had received a treatment interruption, hyperlipidemia, history of cardiac bypass surgery, ischemic cardiomyopathy, and deep venous thrombosis.
- 82 year-old man died of non-small cell lung cancer on day 403; he had completed the trial after a year of treatment

FA

- 69 year-old woman died of multi-organ failure that started on day 59. No relevant past medical history is reported.
- 66 year-old woman who died of an intracerebral hemorrhage on day 347. Medical conditions included obesity, cholecystitis, and pancreatitis.

Because the randomization of the trial resulted in approximately 4½ times as many subjects taking FFIS than FA, the numbers of deaths would be expected to be greater in the FFIS treatment arm even if the risk were similar.

Two subjects died during the run-in period of trial 201-065 (anaphylactic shock before receiving any run-in treatment and "probable atherosclerotic heart disease" after two weeks of placebo).

7.1.2 Other Serious Adverse Events

In the 52-week open-label trial DL-059, serious adverse events in the FFIS treatment arm were not notably different in frequency of nature from those in the Foradil® treatment arm. Cardiovascular events (myocardial infarction, cardiac failure, coronary artery disease, unstable angina, and supraventricular tachycardia) occurred in 15 (3.2%) of subjects taking FFIS (see Appendix for details). Two events (coronary artery disease) occurred in 2 (1.9%) of subjects taking Foradil®. Because there were approximately 4½ times as many subjects in the FFIS treatment arm, and the estimate of the rate in the Foradil® treatment arm is imprecise (just a few more subjects with serious adverse events would increase the rate significantly), the apparent imbalance is not concerning. Most of the subjects in the FFIS arm had predisposing features, and the events occurred in subjects of middle to elderly ages. Serious adverse events that were attributed to treatment occurred in only 3 subjects in the FFIS treatment arm (2 COPD exacerbations and 1 supraventricular tachycardia).

In the double-blind period of DL-059, whose analysis is severely limited by the switching of treatments, no new pattern of toxicity of FFIS compared to FA occurred. Three serious adverse events were considered related to treatment: 1) COPD exacerbation (1 subject in FFIS and 1 subject in placebo) and 2) supraventricular arrhythmia (FFIS).

In the double-blind, 12-week trial 201-065 there was no particular pattern of serious adverse events that raises a concern for the toxicity of FFIS:

- 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

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Few subjects discontinued due to adverse events in the clinical program generally. While in the 52-week open-label period of trial DL-059 proportionately more subjects withdrew consent and discontinued from trial participation from the FFIS treatment arm than from the Foradil[®] arm, the proportions of subjects withdrawing due to adverse events was slightly less in the group of FFIS-treated subjects. In addition, the reliability of the estimate of proportions of subjects withdrawing from the Foradil[®] arm in this trial was lower than the estimate in the FFIS arm due to the relatively small enrollment of only 106 subjects in the Foradil[®] arm.

In the controlled efficacy trial, more subjects dropped out due to adverse events from the placebo arm than from either active treatment arm (FFIS or Foradil[®]). Six subjects discontinued due to a COPD exacerbation from placebo as compared to one subject in each of the active treatment arms.

7.1.3.2 Adverse events associated with dropouts

In the long-term open-label experience, the largest categories of events associated with dropouts were in the cardiac disorders and respiratory, thoracic, and mediastinal disorders categories, which is expected given the age and disease condition of the subjects. The overall pattern of events associated with dropouts did not show a new toxicity from FFIS as compared to Foradil[®].

Some of the events associated with withdrawal from the FFIS arm in the double-blind trial 201-065 (notably nervousness, anxiety, headache, and dry mouth) are events that are seen with the administration of β_2 -agonists; however, there were few events overall.

7.1.3.3 Other significant adverse events

Administration of FFIS at the proposed dose did not result in notable increases in hypokalemia or hyperglycemia, which can occur with high doses of β -agonists. FFIS was associated with small increases in common β -agonist toxicities in the controlled trial.

7.1.4 Other Search Strategies

I did not use any additional search strategies to discover toxicities of treatment of FFIS.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were collected at a reasonable frequency, that is, at each clinical visit during the clinical trials. The exact question or questions used to elicit the possible occurrence of adverse events was not detailed in the protocols.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Dey encoded adverse events using a widely-used system, MedDRA (Medical Dictionary for Regulatory Activities). While there is occasional overlap of concepts in any coding system, in general the information in the current NDA was reasonably encoded.

7.1.5.3 Incidence of common adverse events

The clinical trials in COPD enrolled subjects generally of middle age and higher. The rate of cardiovascular, respiratory, and other adverse events would be expected to be higher than that of a younger or nondiseased population.

7.1.5.4 Common adverse event tables

Table 6 (from Table 64 in the review of trial 201-065 in the Appendix to this review) is a summary of adverse events noted in the controlled 12-week trial in at least two subjects in either the FFIS or Foradil[®] treatment arm and with at least a 1% greater incidence than in the placebo arm. The brevity of the trial and the relatively well nature of the subject population account in some measure for the low incidence of events. Because this is a small trial, small increases or decreases in numbers of subjects in any treatment arm would make notable differences in incidence rates. Severe events were uncommon, and showed no particular pattern of concern.

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Table 6. Subjects with adverse events by organ class and preferred term (Safety population), occurring in ≥2 subjects and ≥1% greater than placebo in the FFIS treatment arm in the controlled 12-week clinical trial*

MedDRA System Organ Class Preferred term	FFIS 20 µg (n=123)	FA 12 µg (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]
 * Bolded items are shown in the proposed package insert

The package insert proposed by Dey lists “treatment-related” adverse events nausea, dry mouth, and insomnia, generally at lower incidences than in Table 6. In the clinical trials the investigator judged the relation to treatment. The best way to determine a possible relation of adverse events to treatment is to compare active treatment to a nontreated (placebo) population. The package insert should be modified to reflect adverse events regardless of the investigator assessment of treatment-relatedness.

7.1.5.5 Identifying common and drug-related adverse events

The most compelling data suggesting a relatedness to treatment comes from nontreated controlled trials. Table 6 shows small increases in the FFIS treatment arm over placebo in the events nasopharyngitis, gastroenteritis viral, diarrhea, nausea, dry mouth, stomach discomfort, dizziness, myalgia, rash, and insomnia. The reliability of the estimates of the increases is not great, due to the small size of this trial.

In the open-label, 52-week trial DL-059, there were small increases in proportions of subjects with significant cardiac events over the Foradil® comparator arm. Due to the small size of the

Foradil[®] arm (106 subjects), a small number of additional subjects with cardiac events in the Foradil[®] treatment arm would have eliminated the apparent increases in the FFIS treatment arm.

7.1.5.6 Additional analyses and explorations

I performed no additional analyses or explorations of adverse event data.

7.1.6 Less Common Adverse Events

To detect differences in uncommon events a relatively large data base from a controlled trials is usually necessary. The controlled data for FFIS is quite small, and unsuitable for the examination of less common adverse events.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Hematology, serum chemistry, and urinalysis data were collected only at screening during the single-dose asthma trials, and only at screening and the end of trial during the single-dose COPD trials (which included varying treatments and doses), so these assessments are inadequate for the evaluation of safety. During the pharmacokinetic/pharmacodynamic trial DL-056, which studied a range of doses of FFIS including the proposed dose in a small number of subjects, these laboratory data were collected intensively, predose and mostly over the 24 hours post dose (Table 72, Appendix).

Trials 201-065 and the open-label period of DL-059 called for collection of a minimal amount of laboratory data: In trial 201-065 these data were collected at screening and at the end of the trial (Week 12). In trial DL-059, these data were collected at baseline (the end of the preceding double-blind period), at week 10 (also called week 22 of the overall DL-059 trial), and after 52 weeks (also called week 64 of the overall trial).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The acute effects of FFIS were studied only in trial DL-056. Trials 201-065 and DL-059 (open-label period) were useful for examining the potential effects of FFIS after weeks of use.

7.1.7.3 Standard analyses and explorations of laboratory data

I summarized selected laboratory data from DL-056 in the "Pharmacodynamics" section of this review above. Treatment with FFIS at the proposed dose resulted in a small increase in glucose over the marketed dose of Foradil[®], an increase that was no longer present at 24 hours. The effect on serum potassium was very small.

Review of summary statistics and shift data for trial 201-065 and both periods of trial DL-059 did not show a remarkable hyperglycemic, hypokalemic, or other effects on serum chemistries, nor did they reveal notable effects on clinical hematology or urinalysis (specific gravity and pH).

7.1.7.4 Additional analyses and explorations

I performed no additional analyses and explorations of the laboratory data.

7.1.7.5 Special assessments

Beta-agonist effects are discernible from the routine laboratories that were collected. Dey did not conduct special assessments, nor were they required.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were collected during the single-dose trials, but relatively few subjects received FFIS at the proposed dose during these trials. During the pharmacokinetic/pharmacodynamic trial DL-056, which studied a range of doses of FFIS including the proposed dose in a small number of subjects, respiratory rate, heart rate, and blood pressure were collected intensively (predose and at 5, 10, and 30 minutes and 1, 3, 6, 12, 16, 24, and 36 hours post dose).

Trial medication was administered at clinic visits in trial 201-065, and heart rate and blood pressure were determined predose and post-dose. Respiratory rate and body temperature were determined only predose, but these are not expected to be particularly sensitive to the sympathomimetic effects of β -agonists, so this was not critical.

Vital signs were collected at clinic visits during the open-label period of DL-059, but these visits were not designed to collect pre- and post-dose information. Dropouts occurred at a relatively high rate in this trial, so examination of trends in these data is also compromised.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Trial 201-065 was the most important source of controlled data on vital signs in subjects taking the proposed dose of FFIS.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 *Analyses focused on measures of central tendencies*

Review of vital sign summary statistics from trial 201-065 revealed no clinically meaningful differences from placebo in either treatment arm. Data from trial DL-059 showed no meaningful changes during the trial in either group in mean systolic or diastolic blood pressure or heart rate. In the double-blind period of trial DL-059, Dey categorized vital signs according to a set of criteria (Table 30), the basis of which is not established in the NDA submission. Given that these criteria are somewhat arbitrary (although prespecified), they may be used as an upper limit of tolerability by which to judge the two active treatment groups. Using these criteria, and analyzed by the last treatment received prior to vital sign measurement, there were no differences between FFIS and Foradil[®] treatment arms.

7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

I examined summary statistics that included means, medians, and ranges. There was no pattern suggesting a consistent difference from Foradil® in vital sign measurements when FFIS was administered at the proposed dose.

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

There were no dropouts for vital sign changes in the clinical trials.

7.1.8.4 Additional analyses and explorations

I performed no additional analyses and explorations of the laboratory data.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Nonclinical electrocardiographic data were not required nor submitted by Dey. The pharmacological effects of formoterol are reasonably well characterized.

ECGs were done only at screening during the single-dose COPD trials and in the asthma single-dose trial DL-055 (the other asthma trials did not obtain ECGs). During the pharmacokinetic/pharmacodynamic trial DL-056, ECGs were collected intensively (predose and at 1, 6, 12, and 24 hours post-dose). During trial 201-065, ECGs were done at screening and predose and 2-3 hours after visits at 4, 8, and 12 weeks. During the open-label trial, ECGs were done far less intensively, at 10 weeks (week 22 of the overall trial DL-059) and Week 52 (week 64 of the overall trial).

Holter monitoring in the clinical program is discussed in section 7.1.9.4 of this review.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The most important source of information regarding the influence of FFIS on the electrical activity of the heart comes from the controlled trial 201-065. Long-term use data comes from the open-label period of DL-059, but these data do not include any examination of the acute effects of a dose. Trial DL-056 gives intensive information on a limited number of subjects, and includes information on a dose far higher than the proposed dose.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 *Analyses focused on measures of central tendency*

In trial 201-065, there were no notable differences among the treatment groups in heart rate or PR, QT, QRS, RR, QTcB, or QTcF intervals.

In the open-label period of DL-059, there were no notable differences between treatment groups in mean PR, QT, QRS, RR, QTcB, or QTcF intervals.

7.1.9.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

In trial 201-065, 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. Examination of corrected QT interval using Bazett and Fridericia corrections showed a small number of subjects (2 in the Foradil[®]-treated group using the Bazett correction; 2 in the FFIS-treated and 1 in the Foradil[®] group) with increases above baseline of 60 msec or greater. These data are not concerning due to the small numbers of subjects and the size of the increases.

7.1.9.3.3 *Marked outliers and dropouts for ECG abnormalities*

There were no dropouts after enrollment for abnormalities of the ECG in the clinical trials.

7.1.9.4 *Additional analyses and explorations: Holter monitoring*

Holter monitoring was done in trial 201-065 prior to day 1 of treatment and the last scheduled visit (Week 12). Given the limitation that the numbers of subjects who received this test at Week 12 was somewhat less than that given the test on day 1 due to dropouts (approximately 14% dropouts in each active treatment group), 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.

7.1.10 Immunogenicity

Formoterol fumarate is not expected to be significantly immunogenic, as it is a small molecule. Dey did not study the immunogenicity of FFIS.

7.1.11 Human Carcinogenicity

Dey was not required to study the carcinogenicity of FFIS and did not submit data on this. As described in the labeling for Foradil[®], formoterol fumarate was not mutagenic or clastogenic in mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats. The label for Foradil[®] describes the results of 2-year drinking water and dietary studies of the carcinogenic potential of formoterol fumarate in rats and mice. Varying tumors have been noted, at doses from 25-fold higher than the expected maximal dose of Foradil[®] (24 µg) and higher.

7.1.12 Special Safety Studies

No special safety trials were required or submitted by Dey.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Long-acting β_2 -agonists are not associated with significant withdrawal effects. Adrenergic agonists would not be expected to be attractive agents for abuse.

7.1.14 Human Reproduction and Pregnancy Data

No new human reproductive or pregnancy data were required or submitted by Dey.

7.1.15 Assessment of Effect on Growth

Long-acting β_2 -agonists are not associated with significant effects on growth. Dey was not required to study the potential for a long-term effect on growth of FFIS and did not submit data on this.

7.1.16 Overdose Experience

No subjects in the clinical trials incurred an overdose.

7.1.17 Postmarketing Experience

FFIS is not marketed anywhere.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Dey conducted a clinical program adequate to satisfy the requirements of Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. That is, sufficient comparability to the reference product, Foradil[®], was demonstrated to allow approval of FFIS based on the size of the safety data base and the conduct of only one controlled efficacy trial. Although the population exposed to FFIS was predominantly Caucasian, there is no known safety issue for the use of LABAs in nonCaucasians patients with COPD. The long-term safety of FFIS in a larger population with COPD, which will include various racial subgroups, may be studied in the postmarketing environment (see section 1.2.2: Required Phase 4 Commitments).

Clinical trials did not include an adequate study of safety and efficacy in individuals with asthma. Because of the concern over the potential for an increased risk of severe exacerbations and death in patients taking LABAs, FDA has requested that Dey study the effects of FFIS in asthma patients in the postmarketing environment (section 1.2.2 of this review).

7.2.1.1 Study type and design/patient enumeration

I summarized the clinical trials and the subject numbers in sections 4.1 (Data Sources, Review Strategy, and Data Integrity: Sources of Clinical Data) and 7.1 (Integrated Review of Safety: Methods and Findings). I summarized the extent of the safety data base in section 1.3.3 (Summary of Clinical Findings: Safety).

7.2.1.2 Demographics

The clinical trials were conducted in the United States. Subjects in the COPD clinical program were generally middle-aged to elderly and were predominantly Caucasian. There were slightly more males than females. Baseline FEV₁ was characteristic of moderate COPD, between 1-2 liters. This clinical trial base is sufficiently representative of patients with COPD to allow a decision on approvability.

7.2.1.3 Extent of exposure (dose/duration)

The clinical trials included sufficient exposure, both in terms of duration and numbers of subjects. I summarized exposure in section 1.3.3 (Summary of Clinical Findings: Safety).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

I used no data sources other than the data submitted by Dey to evaluate the safety of formoterol fumarate inhalation solution (20 µg/2 ml).

7.2.2.1 Other studies

Dey submitted, and I used, no other trial data to evaluate the safety and efficacy of FFIS. However, the results of other studies (in asthma) have raised concern over the use of LABA products in patients with asthma, and these form the basis of postmarketing commitments and risk management.

7.2.2.2 Postmarketing experience

Formoterol fumarate inhalation solution (20 µg/2 ml) has not been marketed anywhere.

7.2.2.3 Literature

Formoterol fumarate inhalation solution is not the subject of any published trials.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience is adequate for this product, which is a new formulation of a marketed drug and for which there is extensive drug class experience.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No animal or *in vitro* testing were performed or required of this product.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate for FFIS.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No formal studies of the metabolism of FFIS or its interaction of FFIS with other drugs were performed or required.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This section of the review is not relevant; FFIS is a new formulation of a marketed drug, formoterol fumarate. In addition, there is extensive drug class experience for long-acting β_2 -agonists.

7.2.8 Assessment of Quality and Completeness of Data

The quality of the data was adequate. The clinical program was sparse, but adequate for a product for which there is extensive class experience, and for which there are data showing no greater systemic exposure than a marketed comparator product.

7.2.9 Additional Submissions, Including Safety Update

The 120-day safety update report contains a summary of serious adverse events occurring in trials that were ongoing at the time of the submission of the NDA. The designs of these trials are summarized in Table 3 (subject demographics are not submitted). All the trials differ from the currently submitted clinical trials in means of delivery of trial treatment, concentration of FFIS in the product, or required concomitant medication (see Table 3).

Report of serious adverse events

Study 201-069: Dey reports that "enrollment is complete," but does not state the amount of exposure time for the subjects in the trial. Twenty-four subjects reported a serious adverse event (Table 7). These events did not fall into a concerning pattern for either active treatment.

Table 7. Trial 201-069: Subjects with serious adverse events*

SYSTEM ORGAN CLASS Preferred Term	Formoterol fumarate 20 µg/0.5 ml N=116	FA 12µg N=115	Placebo N=116
CARDIAC DISORDERS	3	1	0
Acute myocardial infarction	1	0	0
Angina pectoris	1	0	0
Coronary artery disease	1	0	0
Myocardial infarction	0	1	0
NERVOUS SYSTEM DISORDERS	2	0	1
Cerebrovascular accident	1	0	0
Syncope	1	0	0
Dizziness	0	0	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	3	0
Chronic obstructive airways disease exacerbated	2	2	0
Pulmonary embolism	0	1	0
Respiratory failure	0	1	0
GASTROINTESTINAL DISORDERS	1	1	0
Small intestinal obstruction	1	0	0
Dysphagia	0	1	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	1	1
Chest pain	1	1	1
Infections and infestations	1	5	0
Gastroenteritis	1	0	0
Appendicitis	0	1	0
Bronchitis	0	1	0
Bronchitis acute	0	1	0
Pneumonia	0	3	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1	0	1
Fall	1	0	1
Hand fracture	1	0	0
Rib fracture	1	0	0
Humerus fracture	0	0	1
Patella fracture	0	0	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1	2	0
Osteonecrosis	1	0	0
Arthritis	0	1	0
Localised osteoarthritis	0	1	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED INCL CYSTS AND POLYPS	1	0	0
Small cell lung cancer stage unspecified	1	0	0
Vascular disorders	1	0	0
Hypotension	1	0	0
METABOLISM AND NUTRITION DISORDERS	0	1	0
Dehydration	0	1	0
Social circumstances	0	0	1
Exposure to communicable disease	0	0	1

*Subjects are counted once within each system organ class and once within each preferred term. Enrollment in the treatment arms is nearly identical, allowing direct comparison of incidences.
 [Source: NDA 22-007 120-day-safety-update.pdf, Table 1]

Trial 201-070: Three serious adverse events were reported. Dey does not report the nature of these events, but states, "Two of the events were unexpected and unrelated to study medication and one event was expected and unlikely related to study medication. Two of the patients discontinued from the study."

Study 201-074: This trial is complete. No serious adverse events were reported.

Dey's 120-day summary includes no animal studies nor does it include any published information specific to FFIS.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

I discuss the difficulties of pooling Dey's two double-blind trials or combining the dose-finding trials, in section 7.1 (Integrated Review of Safety: Methods and Findings).

7.4.1.1 Pooled data vs. individual study data

This section is not applicable.

7.4.1.2 Combining data

This section is not applicable.

7.4.2 Explorations for Predictive Factors

Adverse events generally occurred at a greater rate in subjects at 65 years of age and older, which is expected. However, there was no data to indicate that FFIS has a greater toxicity than Foradil® in the geriatric age group.

7.4.2.1 Explorations for dose dependency for adverse findings

In the dose-finding trials in COPD at single doses as high as 80 µg there were generally very few adverse events, and no clear dose dependence was found. The pharmacokinetic/pharmacodynamic trial DL-056 enrolled very few subjects and few adverse events occurred. However, there was a dose-dependent increase in glucose and decrease in potassium between 10-244 µg of FFIS (see Appendix).

7.4.2.2 Explorations for time dependency for adverse findings

Dey did not provide time analyses of adverse events, and I did not perform them.

7.4.2.3 Explorations for drug-demographic interactions

The adverse event data from the open-label period of DL-059 were subjected to analysis with respect to age and sex. There is no indication that FFIS is less tolerated than Foradil® in the geriatric age group, although there is a concern generally for β -sympathomimetic effects in particularly sensitive individuals. The serious cardiovascular events that occurred in DL-059 occurred mostly in subjects with predisposing clinical features.

7.4.2.4 Explorations for drug-disease interactions

Dey did not perform formal drug-disease interaction studies.

7.4.2.5 Explorations for drug-drug interactions

Dey did not explore drug-drug interactions, and I did not perform them.

7.4.3 Causality Determination

Section 7.1.5.5 (Identifying common and drug-related adverse events) shows the events occurring at a greater incidence in the placebo-controlled trial. In the open-label trial, causality was more difficult to determine, as there was no nontreated control to give a background rate. Events of concern, primarily cardiac, occurred in a background of older subjects with predisposing clinical features.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Dey has provided adequate dose-finding, pharmacokinetics, and clinical safety and efficacy at the proposed dose, to support its proposed dose strength and dose frequency.

8.2 Drug-Drug Interactions

Dey provided no information on drug-drug interactions in the NDA, and is not required.

8.3 Special Populations

Dey tested no special populations other than adults with COPD for safety and efficacy. Dey's exploration in single-dose trials in asthma populations resulted in an inadequate amount of information to support efficacy or safety claims in that population.

8.4 Pediatrics

With submission of the application, Dey has requested a waiver of pediatric studies for this application. Since COPD is a condition that does not occur in the pediatric population, a waiver of pediatric studies is reasonable, and should be granted under PREA.

8.5 Advisory Committee Meeting

This decision on the approvability of this product does not require an advisory committee meeting.

8.6 Literature Review

I found no literature regarding FFIS.

8.7 Postmarketing Risk Management Plan

FDA has requested Dey to commit to the conduct of three postmarketing clinical trials whose safety results will help guide risk management, and Dey has agreed to perform two, asking for consideration that pre-existing information in the asthma population obviate the need for one of two asthma trials. This request should be denied (see section 1.2.2).

In addition, FDA requires that FFIS be labeled with a boxed warning concerning its use in asthma patients, and has requested that Dey submit a Medication Guide. Dey has submitted a Medication Guide and revised labeling containing a boxed warning.

Dey states that it intends to "...monitor post-marketing SAEs and to provide 6 month and 12 month post-entry-to-market updates on these to the FDA. These updates will include an evaluation of fatal and life-threatening respiratory adverse events in patients with COPD, serious cardiovascular adverse events in patients with COPD, any potential low frequency adverse events associated with use of FFIS that are rare yet serious, and safety in populations other than patients with COPD, especially patients with asthma. These reports will include subgroup analyses by race and ethnicity. All SAE reports of fatal and life-threatening respiratory adverse events or fatal and life-threatening cardiovascular adverse events reported to Dey will follow a pre-formatted SAE report form designed to capture important information in a uniform way on each subject for these particular adverse events. It is hoped that this will result in an enhanced quality of SAE reports. A copy of this form will be submitted to the Agency for review and input."

8.8 Other Relevant Materials

I used information from the approval of Brovana[®] and the Foradil[®] label in the review of the NDA submission.

9 OVERALL ASSESSMENT

9.1 Conclusions

Dey has provided an adequate amount of pharmacokinetic, dose-finding, and safety and efficacy data to support the approval of formoterol fumarate inhalation solution (20 µg/2ml) for twice-daily administration by nebulization at a dose of 20 µg per dose for patients with COPD.

9.2 Recommendation on Regulatory Action

I recommend approval of Dey's formoterol fumarate inhalation solution (20 µg/2ml).

9.3 Recommendation on Postmarketing Actions

See section 1.2.2 (Recommendation on Postmarketing Action: Required Phase 4 Commitments) for a summary of my recommendations on postmarketing actions.

9.3.1 Risk Management Activity

See section 8.7: Postmarketing Risk Management Plan.

9.3.2 Required Phase 4 Commitments

See section 1.2.2 of this review.

9.3.3 Other Phase 4 Requests

See section 1.2.2 of this review.

9.4 Labeling Review

As of the writing of this review, labeling negotiations have not started. My general comments on labeling are in section 10.2 of this review.

9.5 Comments to Applicant

The following comments refer to postmarketing commitments for formoterol fumarate inhalation solution.

1. In your January 25, 2007 response to FDA you propose that the pediatric data presented in the NDA fulfill the FDA request of December 13, 2006 for you to conduct a safety and tolerability study with one or more doses and one or more dose levels of formoterol fumarate inhalation solution in children with asthma and/or obstructive airway disease. The data presented in NDA

22-007 in subjects with asthma consist of single-dose, dose-finding trials in a small number of subjects, including only 44 at the approved dose. These data are insufficient for the determination of safety or tolerability of FFIS at the approved dose.

2. In your January 25, 2007 response to FDA you propose that completion of a postmarketing trial in children presenting with an acute exacerbation of asthma (to fulfill a postmarketing commitment requested by FDA on December 13, 2006) would confer an additional 6 months of marketing exclusivity for your formoterol fumarate inhalation solution (20 mcg/2ml). Marketing exclusivity depends upon the adequate completion of a clinical development program designed to demonstrate efficacy and safety in an indicated population. We will be happy to discuss with you the elements of such a plan in asthma.

The following comments refer to the labeling for formoterol fumarate inhalation solution (20 mcg/2ml).

3.

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4. Submit revised labeling including a table of adverse events that does not include attribution of adverse events to the drug product. 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.

5.

b(4)

10 APPENDICES

Note: In the review of the clinical trials, Foradil® is denoted "FA."

For all of the COPD trials reviewed in this document, many aspects of investigational treatment were similar:

- Nebulization of treatment was by means of a Pari LC Plus nebulizer and a Pari Proneb compressor
- Placebo inhalation solution was manufactured by Dey. It consisted of citric acid USP (), sodium citrate USP (), sodium chloride, USP (), and (), i.e., the same constituents as the product without formoterol fumarate.
- The comparator active product, where used, was Foradil®. This consists of formoterol fumarate 12 µg with lactose 25 mg as a carrier.
- Placebo dry powder was manufactured by (). It consisted of lactose, 25 mg.
- Foradil® and placebo dry powder were administered by means of an Aerolizer®, manufactured by Novartis. b(4)

Blinding of clinical trials DL-052, DL-057, 201-065, and the asthma clinical trials included the following measures:

- Treatment with an Aerolizer® and nebulizer at each dose administration (double-dummy procedure)
- Both FFIS and placebo nebulization solutions are clear and colorless. They were filled into vials using the same mold and material (low-density polyethylene resin) and packaged into pouches of the same dimension using the same type of foil overwrap. The pouch labels were identical.
- Foradil® and its placebo are white powders. Dey removed the paper backing on the Foradil® and rounded the blister packaging at the edges to match it to the placebo blister. Labeling was identical for both trial agents.

10.1 Review of Individual Study Reports

10.1.1 Trial DL-052

Trial DL-052, "A Dose-ranging Study Comparing Dose-response Between Formoterol Fumarate Inhalation Solution and Formoterol Fumarate Dry Powder Inhaler in Patients With Stable COPD," was conducted between January 7, 2003 (first patient enrolled) and April 24, 2003 (the last patient completed). On May 13, 2003, FDA told Dey that the dose-finding for FFIS was inadequate. As a result, Dey performed DL-057, which is reviewed subsequently. The current review is restricted to a brief outline of the protocol and the findings of the trial, as its results have limited usefulness for the review of the proposed dose of 20 µg.

10.1.1.1 Protocol

This was a double-blind, 5-way crossover trial. Subjects were randomized equally to receive single doses of placebo, Foradil® (FA) at the approved dose of 12 µg or at 24 µg delivered via an Aerolizer®, or formoterol fumarate inhalation solution (FFIS) at 42 or 84 µg delivered via a nebulizers on separate days as shown in Table 8.

Table 8. Trial DL-052: Treatment arms

Treatment	Dose*
Placebo Aerolizer® + Placebo Inhalation Solution	not applicable
Foradil® Aerolizer® + Placebo Inhalation Solution	12 µg
Foradil® Aerolizer® + Placebo Inhalation Solution	24 µg
FFIS + Placebo Aerolizer®	42 µg
FFIS + Placebo Aerolizer®	84 µg

[Source: section-1-15-report-body.pdf, table 9.1.1]

*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).

Subjects

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

Inclusion criteria

- Either sex
- At least 50 years old
- Meeting American Thoracic Society definition of COPD
- Current or prior history of at least 10 pack-years of smoking
- $FEV_1 \geq 30\%$ predicted and $< 70\%$ predicted
- $FEV_1/VC < 70\%$

Exclusion criteria

- Clinical diagnosis of asthma
- Chest X-ray showing a significant disease other than COPD
- Hospitalization or emergency room visit for acute exacerbation of COPD within 4 weeks prior to screening
- Lower respiratory tract infection within 6 weeks of screening or a clinically significant upper respiratory tract illness within 2 weeks prior to screening
- Requirement for daily oxygen therapy
- Laboratory result not excluded by the protocol or abnormal and clinically significant ECG test at screening
- Abnormal and clinically significant laboratory test or ECG result at screening that could not be explained by a concurrent illness that was not excluded by the protocol
- Receipt of β -blockers for any indication

Comment

Eligibility criteria also included restrictions to avoid pregnancy, and requirements for willingness to follow protocol requirements with the expectation that they would do so, and exclusion for a history of hypersensitivity to beta₂-agonists or use of β -blockers, a medical condition that could place the subject at risk or interfere with participation, inability to withhold medications according to the concomitant medication restrictions, and use of an investigational drug within 30 days prior to screening.

Concomitant medications

Subjects on stable doses of theophylline, nedocromil, inhaled or intranasal corticosteroids, or oral or parenteral steroids (≤ 10 mg/day) for at least 1 month prior to screening were allowed to remain on fixed doses. Subjects were not to take long-acting β -agonists within 48 hours, short acting β -agonists within 6 hours, or caffeinated beverages within 8 hours of pulmonary testing.

Procedures

Procedures for the trial are shown in Table 9. Treatments were to be separated by a minimum of 3 days.

Table 9. Trial DL-052: Procedures

Procedure	Screening	Treatment period					Followup
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Day 14 to -1	Day 1	Day 4-9	Day 7-17	Day 10-25	Day 13-33	Day 16-41
Written Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
Physical Examination	X						X
Vital Signs	X	X	X	X	X	X	X
Sitting BP and HR		X	X	X	X	X	
Tremor		X	X	X	X	X	
Clinical Laboratory	X						X
Urine Pregnancy Test	X						X
Chest X-ray	X						
ECG	X						X
PFTs	X	X	X	X	X	X	
FEV1 Reversibility Test	X						
Study Drug Administration		X	X	X	X	X	
Review Prior/Concomitant Med	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X

[Source: section-1-15-report-body.pdf, table 9.5.1.1]

Analytical plan

The primary endpoint measure was the percent change in the $AUC_{(0-12h)}$. The primary analytical population was called the "evaluable" population, consisting of all subjects who completed all 5 treatments. Dey would declare two treatments comparable if the 90% confidence intervals of two treatments overlapped.

Changes to the protocol and analytical plan

Dey instituted no changes to the protocol after the start of subject enrollment. After the last subject was treated (May 19, 2003), Dey eliminated a secondary endpoint, inspiratory capacity. This was a minor change.

Comment

The trial was reasonably designed to measure the response to different doses of FFIS compared to FA in subjects with chronic pulmonary obstructive disease. However, the doses tested were high.

10.1.1.2 Results

Investigational treatments

The investigational agents were:

- Dey Formoterol Fumarate Inhalation Solution: Formulation Code/Batch Number: 42 mcg, C037 and C040; 84 mcg, C040
- Comparator Products: Foradil® Aerolizer® (manufactured by Novartis), Formulation Code/Batch Number: 019E4038
- Placebo Inhalation Solution (manufactured by Dey, L.P.): Formulation Code/Batch Number: C051
- Placebo Dry Powder (manufactured by _____): Formulation Code/Batch Number: 1253011-01

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Characteristics of the subjects and their disposition

The mean age of the population was 67.1 years, and approximately 66% of the population was male. Caucasians made up 86%, with 6% Hispanic and 6% "Black;" one subject's race was described as "Other." The mean FEV₁ prebronchodilator was 1.4 liters.

Four subjects discontinued from the trial (from three sequence groups), one each for a predose FEV₁ below range, a protocol violation (which was also an FEV₁ below range), for withdrawal of consent, and for an adverse event. This number of discontinuations would not be expected to have a notable effect on the trial.

Protocol violations

Most protocol violations were related to the timing of assessments or a post-dose FEV₁ below a predose value. The numbers and types of protocol violations would not have affected the interpretation of the trial's results.

Efficacy

Table 10 is a summary of the primary efficacy endpoint results. Because the variable is a change from baseline, it could be negative in value.

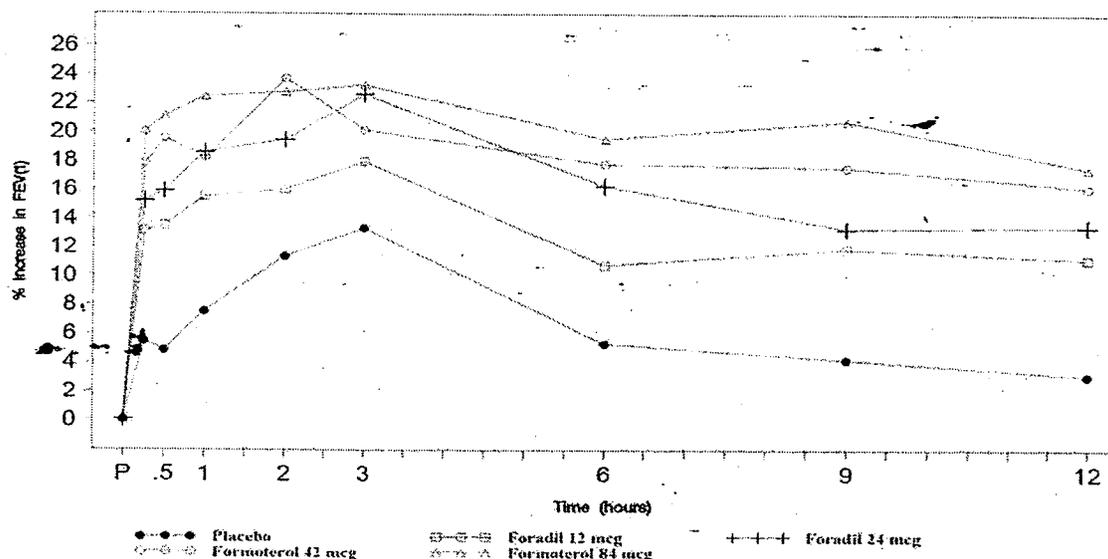
Table 10. Trial DL-052: AUC_(0-12h) of the Mean Percent Change in FEV₁ (Evaluable Population)

	Placebo N=35	FA 12 µg N=35	FA 24 µg N=35	FFIS 42 µg N=35	FFIS 84 µg N=35
Mean (SD)	73.3 (147.5)	131.1 (126.7)	164.6 (148.5)	191.0 (163.8)	227.8 (255.7)
Min, Max	-57.8, 680.3				

[Source: Trial DL-052 section-1-15-report-body.pdf, table 11.4.1.1.1]

These results are shown graphically in Figure 1.

Figure 1. Trial DL-052: Mean percent increase in FEV₁ with respect to dose and time after dose



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

Dey did not perform statistical comparisons of this endpoint. Importantly, the effect of each dose of FFIS was similar, showing little dose response.

Comment

In this trial, the proposed dose of FFIS was not studied.

This review does not discuss secondary efficacy endpoints for this trial, as they are of little relevance to the marketing approval decision of the proposed dose of FFIS.

Safety

Nearly all subjects received all treatments. Thirty-six subjects received placebo, Foradil[®] 12 µg, and FFIS 84 µg. Thirty-seven subjects received Foradil[®] 24 µg and FFIS 42 µg.

There were no deaths.

Three serious adverse events occurred:

- A 70 year-old woman with chronic atrial fibrillation experienced a CVA several hours after administration of FFIS 84 µg.
- A 75 year-old woman who experienced pneumonia; had received with FA 24 µg about 9 days prior.
- A 69 year-old man who experienced a myocardial infarction 3 days after a dose of FA (24 µg).

The temporal relationship of the CVA to the administration of the β₂-agonist formoterol makes it possible that the drug contributed to its pathogenesis (the investigator stated that the relationship to drug administration was unlikely). Overall, few serious adverse events occurred, which is not surprising in a single-dose trial.

As shown in Table 11, adverse events were uncommon (there were no adverse events associated with administration of FFIS at 42 µg), which is not unexpected given that a single dose only was given.

Table 11. Trial DL-052: Subjects with adverse events (Safety population)

	Placebo N=36	FA 12 µg N=36	FA 24 µg N=37	FFIS 42 µg N=37	FFIS 84 µg N=36
MI	0	0	1 (2.7%)	0	0
Scleral hemorrhage	1 (2.8%)	0	0	0	0
Scleritis NOS	0	1 (2.8%)	0	0	0
Diarrhea NOS	0	0	0	0	1 (2.8%)
Dyspepsia	1 (2.8%)	0	0	0	0
Nausea	0	1 (2.8%)	0	0	0
Influenza-like illness	0	0	0	0	1 (2.8%)
Edema peripheral	0	1 (2.8%)	0	0	0
Pneumonia NOS	0	0	1 (2.7%)	0	0
URTI NOS	0	1 (2.8%)	0	0	0
ALT increased	1 (2.8%)	0	0	0	0
AST increased	1 (2.8%)	0	0	0	0
Blood alk phos NOS increased	1 (2.8%)	0	0	0	0
Hyperkalaemia	0	0	1 (2.7%)	0	0
Back pain	1 (2.8%)	0	0	0	0
Muscle cramp	0	0	0	0	1 (2.8%)
CVA	0	0	0	0	1 (2.8%)
Hyporeflexia	1 (2.8%)	0	0	0	0
Tremor	0	1 (2.8%)	0	0	1 (2.8%)
Bronchospasm NOS	0	0	0	0	1 (2.8%)
COPD exacerbated	0	0	1 (2.7%)	0	0
Ecchymosis	0	1 (2.8%)	0	0	0

[Source: Trial DL-052 section-1-15-report-body.pdf, Table 12.2.2.1]

Laboratory and ECG evaluations

Since clinical laboratory evaluations and ECG were done only at screening and after all treatments had been administered, these cannot distinguish the effects of any treatment or dose level and are not reviewed here.

Summary of the results of DL-052

Trial DL-052 was a single-dose trial that failed to find a dose-response, as its dose levels were too high. This trial showed that high doses of FFIS could produce an effect greater than that of Foradil® at its marketed dose. There were few adverse events in the trial, not surprisingly, given the limited dosing.

The Division of Pulmonary and Allergy Products stated to Dey that this trial was an inadequate dose exploration of FFIS. As a result, Dey conducted trial DL-057, reviewed immediately below.

10.1.2 Trial DL-057

Trial DL-057, "A Dose-ranging Study Comparing Dose-response Between Formoterol Fumarate Inhalation Solution and Formoterol Fumarate Dry Powder Inhaler in Patients With

Stable Chronic Obstructive Pulmonary Disease," is the principle trial supporting Dey's choice of dose to study for efficacy (see the review of trial 201-065), and was conducted after trial DL-052 to provide dose exploration in a lower dose range. The trial was conducted between September 17, 2003 (first patient enrolled) and December 29, 2003 (the last patient completed).

10.1.2.1 Protocol

This was a double-blind, 7-way crossover trial designed to assess the effects of single doses of FFIS at several dose levels, lower than and up to all but the top dose in DL-052. Subjects were randomized to receive each of 7 single doses in a random order, separated from the rest by several days. The primary objective of the trial was to determine the lowest dose that produced an effect on the area-under-the-curve of FEV₁ over 12 hours after a dose that was comparable to that of the approved dose of Foradil®.

Subjects were to be assigned to each of the following in a random sequence, with a 3-8-day washout between each visit (Table 12).

Table 12. Trial DL-057: Treatment assignments (assigned in a random sequence)

Treatment	Dose
FFIS + Placebo Aerolizer®	2.5 mcg
FFIS + Placebo Aerolizer®	5 mcg
FFIS + Placebo Aerolizer®	10 mcg
FFIS + Placebo Aerolizer®	20 mcg
FFIS + Placebo Aerolizer®	40 mcg
FA Aerolizer® + Placebo Inhalation Solution	12 mcg
Placebo Aerolizer® + Placebo Inhalation Solution	Not applicable

An unblinded technician prepared treatments, but was not to participate in assessments during the trial.

Subjects were allowed to use short-acting β -agonists as needed but not within 8 hours of pulmonary testing, nor were not to take long-acting β -agonists for at least 48 hours of such testing. Caffeinated beverages were prohibited within 8 hours of pulmonary testing. Subjects on anti-inflammatory medications were to be on stable doses for at least 4 weeks prior to screening and remain on stable doses throughout the trial.

Subjects

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

Inclusion criteria

- Either sex
- At least 50 years old
- Meeting American Thoracic Society definition of COPD
- Current or prior history of at least 10 pack-years of smoking
- FEV₁ \geq 30% predicted and <70% predicted
- FEV₁/FVC < 70%

Exclusion criteria

- Clinical diagnosis of asthma
- Chest X-ray showing a significant disease other than COPD
- Hospitalization or emergency room visit for acute exacerbation of COPD within 4 weeks prior to screening

- Lower respiratory tract infection within 6 weeks of screening or a clinically significant upper respiratory tract illness within 2 weeks prior to screening
- Requirement for daily oxygen therapy
- Qtc >0.46 seconds or abnormal and clinically significant ECG test result at screening
- Medical illness that could place the subject at risk of complications (other than COPD)
- Abnormal and clinically significant laboratory test or ECG result at screening that could not be explained by a concurrent illness that was not excluded by the protocol
- Receipt of β -blockers for any indication

Comment

Eligibility criteria also included restrictions to avoid pregnancy, and requirements for willingness to follow protocol requirements with the expectation that they would do so, and exclusion for a history of hypersensitivity to beta₂-agonists, inability to withhold medications according to the concomitant medication restrictions, and use of an investigational drug within 30 days prior to screening.

Procedures

Table 13 shows the procedures mandated by the protocol. Trial drugs were administered at visits 2-7.

Table 13. Trial DL-057: Procedures

PROCEDURE	Screening	Treatment period							Followup
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9a
	Day -14 to -1	Day 1	Day 5-10	Day 9-19	Day 13-28	Day 17-37	Day 21-46	Day 25-55	Day 29-64
Written Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Physical Examination	X								X
Clinical Laboratory	X								X
Urine Pregnancy Test	X								X
Chest X-ray	X								
Vital Signs	X	X	X	X	X	X	X	X	X
ECG	X								
Randomization		X							
Spirometry (pre&post bronchodilator)	X								
FEV ₁		X	X	X	X	X	X	X	
Reversibility Test	X								
Crossover Treatment		X	X	X	X	X	X		
Dispense Non-study Treatment Medication		X	X	X	X	X	X	X	
Concomitant Meds	X	X	X	X	X	X	X	X	X
Device Demonstration	X								
AE Assessment		X	X	X	X	X	X	X	X

Analytical plan

The primary analytical plan was intended to establish "equipotent" doses of FFIS and FA, using a completer population. Testing of the effect of FFIS compared to FA on mean FEV₁ AUC_(0 to 12h) was to proceed sequentially using analysis of variance from top dose down until a p-value greater

than 0.05 was found between the treatments. In addition, 90% confidence intervals were to be established on the ratio of the effects of the treatments to each other. The last-observation-carried-forward technique was used to impute missing data in the event of dropping out at or after a 2-hour post-dose time point.

Secondary endpoints included other spirometric measures:

- percent change in trough FEV₁ from baseline, defined as the FEV₁ approximately 12 hours after trial drug administration
- percent change from pre-dose FEV₁ at each post-dose time point for each treatment
- peak percent change from pre-dose FEV₁ for each treatment
- peak percent change from pre-dose FVC for each treatment

Comment

The lack of statistical significance is not sufficient for establishing equivalence between two groups. However, identifying a dose to study in subsequent critical efficacy trials does not require meeting a statistical criterion.

Changes to the protocol

The original protocol was dated August 7, 2003. The protocol was amended once prior to the completion of subject involvement, on December 16, 2003. This amendment called for an interim analysis, which was to be specified in the statistical analytical plan, prior to data validation and database lock. An amended statistical analytical plan was signed on January 29, 2004, after completion of the last subject. This change to the protocol and its analytical plan is not expected to have influenced the conclusions of the trial.

10.1.2.2 Results

Investigational treatments

The investigational agents were:

- Dey Formoterol Fumarate Inhalation Solution: Formulation Code/Batch Number: 2.5 mcg, C051 and C052; 5 mcg, C052; 10 mcg, C053; 20 mcg, C054, 40 mcg, C056
- Comparator Products: Foradil[®] Aerolizer[®] (manufactured by Novartis), Formulation Code/Batch Number: 022G7030
- Placebo Inhalation Solution (manufactured by Dey, L.P.): Formulation Code/Batch Number: C051
- Placebo Dry Powder (manufactured by): Formulation Code/Batch Number: 1253016 – 01

b(4)

Subjects

One site enrolled 5 subjects, four sites enrolled 7 subjects, and one site enrolled 14 subjects. All subjects met eligibility criteria, and no subject discontinued. Table 14 shows the baseline characteristics of the completer population, the primary endpoint population. Subjects who received sequence 2 (of the 7 sequences) were slightly different from the others in terms of age, gender distribution, and age at onset of COPD, but these differences (not shown) would not be expected to alter the results of the trial significantly. Overall, the trial population was primarily male and Caucasian, with a mean age of 63 and a mean prebronchodilator FEV₁ of 1.5 liters.

Table 14. Trial DL-057: Baseline characteristics (Completer population, n=47)

Age (years)	Mean (SD)	63.0 (8.5)	Age of COPD Onset (years)	Mean	56.1 (10.7)
	Range	50, 83		Range	31, 80
Gender n(%)	Male	29 (61.7)	Actual FEV ₁ Pre-bronchodilator	Mean (SD)	1.5 (0.6)
	Female	18 (38.3)		Median	1.3
Race N(%)	Caucasian	43 (91.5)		Actual FEV ₁ Post-bronchodilator	Min, Max
	Black	2 (4.3)	Mean (SD)		1.7 (0.6)
	Hispanic	2 (4.3)	Median		1.7
				Min, Max	—

b(4)

Protocol violations

The only dosing error was that one subject received 2 doses out of sequence. Other violations included visits outside of time windows and predose FEV₁ changed >15% from baseline screening. The numbers of these violations was not large and their effect is expected to be minor.

Efficacy

Primary endpoint

Table 15 shows the predose FEV₁ and the endpoint AUC_(0-12h) of FEV₁ for the treatment groups. All actively-treated groups had a greater AUC of FEV₁ than placebo.

Table 15. Trial DL-057 predose FEV₁ and endpoint AUC_(0-12h) of FEV₁ (Completer population*)

		FFIS 2.5 µg	FFIS 5 µg	FFIS 10 µg	FFIS 20 µg	FFIS 40 µg	FA 12 µg	Placebo
Predose FEV ₁ (l)	Mean (SD)	1.5 (0.6)	1.5 (0.6)	1.5 (0.6)	1.5 (0.6)	1.5 (0.5)	1.4 (0.5)	1.5 (0.6)
	Median	1.3	1.4	1.3	1.4	1.3	1.3	1.3
	Range	0.6, 3.1	0.6, 3.0	0.6, 3.0	0.6, 3.1	0.7, 2.8	0.7, 3.0	0.7, 3.1
Total FEV ₁ AUC (l x hr)	Mean (SD)	18.9 (7.4)	18.9 (6.9)	19.5 (7.2)	19.9 (7.2)	20.5 (7.2)	19.5 (7.0)	17.5 (7.3)
	Median	17.6	17.4	17.4	20.1	18.7	18.5	16.3
	Range	8.2, 39.3	8.7, 36.9	9.0, 38.5	8.9, 38.7	9.4, 38.8	8.7, 37.5	7.7, 37.5

*n=47 for all measures except Total FEV₁ AUC, placebo group
 [Source: section-1-15-report-body.pdf, table 14.2.1.1]

The primary analysis was conducted on log-transformed AUC data. Using a step-down procedure, the FFIS 20 mcg dose was the first dose to demonstrate a p-value greater than 0.05 compared to FA 12 mcg. Treatment with any dose of FFIS resulted in effects close to that of FA, as shown by the closeness of the mean ratios (and confidence intervals) of FFIS¹ effect to FA.

Table 16. Trial DL-057: Between-Treatment Comparisons of Log-Transformed FEV₁ AUC (0-12): Completer Population

Comparator	Treatment	Exponentiated mean ratio (%)	90% confidence interval	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	not done
FA 12 mcg	FFIS 5 mcg	96.6	94.2, 99.0	not done
FA 12 mcg	FFIS 2.5 mcg	95.7	93.4, 98.1	not done

[Source: DL-057 section-1-15-report-body.pdf, Table 11.4.1.1.2]

Comment

As stated before, the lack of statistical significance does not establish equivalence. However, this was not a requirement for studying the dose in further trials.

Secondary endpoints

Percent change in trough FEV₁ from baseline (completers)

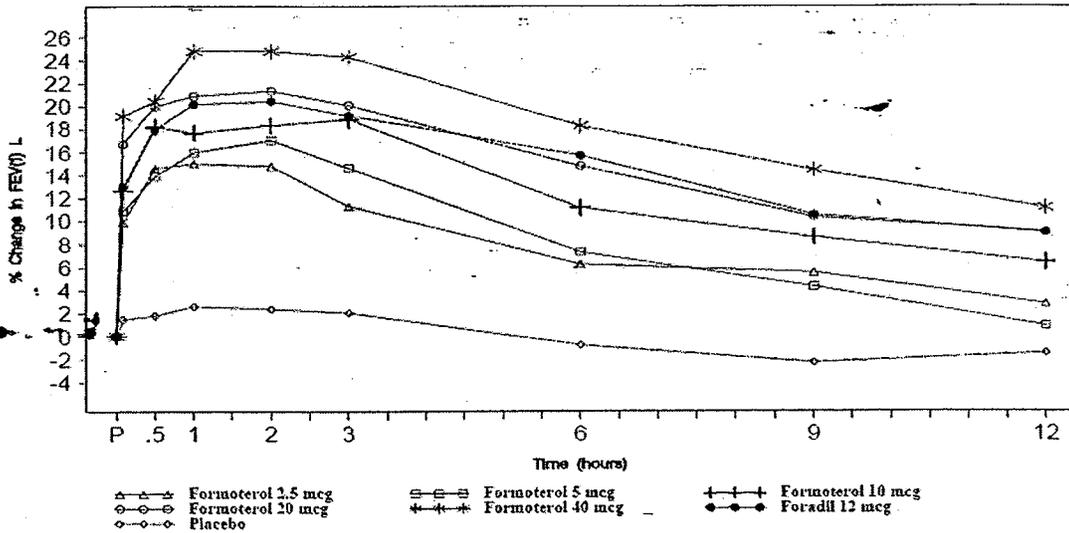
Pre-dose FEV₁ was similar among the active dose groups (1.4 to 1.5 liters). The percent change at 12 hours in the FFIS group was dose-dependent (from 2.8 in the 2.5 µg group to 11.1 in the 40 µg group).

Percent change from pre-dose FEV₁ at each post-dose time point for each treatment

Dey performed no statistical analysis on these data, which are illustrated in Figure 2. All doses produced a monotonic rise, followed by a monotonic fall in FEV₁ over the 12 hours post-treatment. The response to FFIS was dose-dependent. The response to FFIS 40 µg was noticeably greater than that for FA at its marketed dose, and visually the FFIS 20 µg dose most closely approximated the approved FA dose.

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Figure 2. Trial DL-057: Mean percent change in FEV₁ with respect to dose and time after dose (Completer population)



[Source: section-1-15-report-body.pdf, figure 11.4.1.2.1.1]

Dey also calculated the absolute change from pre-dose in FEV₁. The results were consistent with the mean percents change.

Peak percent change from pre-dose FEV₁ for each treatment

Peak percent change from pre-dose FEV₁ (Table 17) was consistent with the data on FEV₁ AUC previously presented. Mean peak FEV₁ at the FFIS dose of 20 µg most closely approximated that of the approved dose of FA.

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Table 17. Trial DL-057: Percent change in peak FEV₁ (Completer population)

	Placebo N=47	FA 12 mcg N=47	FFIS 2.5 mcg N=47	FFIS 5 mcg N=47	FFIS 10 mcg N=47	FFIS 20 mcg N=47	FFIS 40 mcg N=47
FEV ₁ Pre-dose (n)	47	47	47	47	47	47	47
Mean (sd)	1.46 (0.58)	1.43 (0.54)	1.46 (0.56)	1.47 (0.56)	1.46 (0.58)	1.47 (0.56)	1.46 (0.54)
Min, max							
Peak FEV ₁ (n)	46	47	47	47	47	47	47
Mean (sd)	1.63 (0.65)	1.80 (0.59)	1.76 (0.66)	1.79 (0.64)	1.78 (0.61)	1.83 (0.62)	1.88 (0.65)
Min, max							
Change From Pre-dose (%) n	46	47	47	47	47	47	47
Mean (sd)	11.25 (16.51)	27.55 (14.65)	21.29 (16.71)	23.22 (15.12)	24.49 (14.41)	27.49 (19.13)	30.80 (20.63)
Min, max	-12.75	0.63	-2.55	-2.90	3.43	-0.98	-0.42

b(4)

[Source: section-1-15-report-body.pdf, table 11.4.1.2.4.1]

Peak percent change from pre-dose FVC

Peak FVC followed roughly the same pattern as FEV₁ (Table 18) in showing a dose-response. Mean FVC at the FFIS dose of 40 µg most closely approximated that of the approved dose of FA.

Table 18. Trial DL-057: Percent change in peak FVC (Completer population)

	Placebo N=47	FA 12 mcg N=47	FFIS 2.5 mcg N=47	FFIS 5 mcg N=47	FFIS 10 mcg N=47	FFIS 20 mcg N=47	FFIS 40 mcg N=47
FVC Pre-dose (n)	47	47	47	47	47	47	47
Mean (SD)	1.46 (0.58)	1.43 (0.54)	1.46 (0.56)	1.47 (0.56)	1.46 (0.58)	1.47 (0.56)	1.46 (0.54)
Min, Max							
Peak FVC (n)	46	47	47	47	47	47	47
Mean (SD)	2.93 (0.95)	3.27 (0.96)	3.15 (0.90)	3.19 (0.89)	3.22 (0.91)	3.27 (0.91)	3.31 (0.92)
Min, Max							
Change from pre-dose (%) (n)	46	47	47	47	47	47	47
Mean (SD)	0.24 (0.33)	0.61 (0.36)	0.44 (0.29)	0.51 (0.41)	0.52 (0.32)	0.56 (0.35)	0.62 (0.37)
Min, Ma							

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[Source: section-1-15-report-body.pdf, table 11.4.1.2.5.1]

Time-normalized FEV₁ AUC_{0-12h} and percent change in time-normalized FEV₁ AUC_{0-12h}

Dey performed these analyses on areas under the curve of FEV₁ normalized for time missed during the post-treatment 12-hour measurement period. The results (not shown here) were consistent with those for the primary endpoint.

Summary of efficacy

DL-057 was a trial limited in scope to the demonstration of spirometrically-derived measures of lung function. These data showed a dose-responsiveness to single-doses of FFIS in the dose range from 2.5-40 µg. Statistical testing did not establish the equivalence of FFIS 20 µg to Foradil® 12 µg; however, based on various parameters of lung function, the effects of the treatment products at these doses were reasonably comparable. The effect on lung function was consistent across various different FEV₁ parameters and FVC.

Safety

There were no deaths or serious adverse events. Adverse events were uncommon and showed no notable pattern (Table 19). Sporadic events (a rash in FFIS and FA, a headache at the highest dose of FFIS, and decreased breath sounds after placebo) were considered probably related to treatment. These events did not establish a pattern of concern for the safety of administration of FFIS.

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Table 19. Trial DL-057: Subjects with adverse events occurring after treatment (safety population*)

	Placebo N=47	FA 12 mcg N=47	FFIS 2.5 mcg N=47	FFIS 5 mcg N=47	FFIS 10 mcg N=47	FFIS 20 mcg N=47	FFIS 40 mcg N=47
Abdominal pain upper	0	0	0	1 (2.1%)	0	0	0
Breath sounds decreased	1 (2.1%)	0	0	0	0	0	0
Cerumen impaction	1 (2.1%)	0	0	0	0	0	0
Chest pain	0	0	0	1 (2.1%)	0	0	0
Cough	0	0	1 (2.1%)	0	0	0	0
Dyspnea NOS	0	0	0	1 (2.1%)	0	0	0
Epistaxis	0	0	0	0	0	0	1 (2.1%)
Headache	0	0	0	0	0	0	1 (2.1%)
Liver function tests NOS abnormal	0	0	0	0	1 (2.1%)	0	0
Nasal congestion	0	0	0	0	0	0	1 (2.1%)
Occult blood NOS positive	0	0	1 (2.1%)	0	0	0	0
Rash NOS	0	1 (2.1%)	0	1 (2.1%)	0	0	0
Skin laceration	0	0	0	0	0	0	1 (2.1%)
Upper RTI NOS	0	1 (2.1%)	0	0	1 (2.1%)	1 (2.1%)	0
Upper RTI viral NOS	0	1 (2.1%)	1 (2.1%)	0	0	0	0

[Source: section-1-15-report-body.pdf, table 12.2.2.1]

*The completer (efficacy) and safety populations were the same.

Laboratory and ECG evaluations

Since clinical laboratory evaluations were done only at screening and after all treatments had been administered, and ECGs were done only at baseline, these cannot distinguish the effects of any treatment or dose level and are not reviewed here.

Summary of the results of DL-057

DL-057 was adequately conducted. It showed a dose-responsiveness of post-dose FEV₁ effect using FFIS doses from 2.5 to 40 µg. The dose (20 µg) Dey chose to study in the critical efficacy trial was comparable in effect to that of FA; secondary spirometric measures suggest that this dose was a reasonable choice. There were no notable safety concerns from the trial.

Based on these results, Dey chose the 20 µg dose level to study in critical safety and efficacy trials.

10.1.3 Trial DL-059

Trial DL-059 was originally designed to incorporate a 12-week, randomized, double-blind treatment period comparing FFIS, Foradil®, and placebo, followed by 40 weeks of open-label treatment with Foradil® or FFIS. A major randomization error occurred; in addition, subjects switched treatments at post-baseline visits during the double-blind portion of the trial, rendering the 12-week blinded comparison impossible. In addition, the switching of treatments by numerous subjects makes comparison of safety findings in the double-blind period problematic. This review will describe the design of trial DL-059, followed by a description of the notable safety findings of the double-blind period trial and a more detailed description of safety from the open-label period.

DL-059 was originally given a title denoting a 40-week open-label treatment period. Because the double-blind period of the trial was corrupted, the open-label period of the trial was

lengthened to provide 52 weeks of safety data. The final title of the protocol is "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, Followed by a 52-Week Open-Label Safety Extension."

The first subject was enrolled into the double-blind part of the trial on May 12, 2004 and the last subject completed involvement with the double-blind portion on January 6, 2005. The first subject enrolled in the open-label period of the trial on August 17, 2004, and the last subject completed the open-label part of the trial on December 14, 2005.

10.1.3.1 Protocol

This was a trial intended to generate evidence of efficacy during a double-blind treatment period, then generate evidence of safety after a prolonged open-label treatment period. The trial was comprised of three periods:

1. Screening: 7-14 days during which all subjects were to receive single-blinded placebo Aerolizer® and placebo nebulizer solution, both twice daily
2. Double-blind treatment: The double-blind portion of the trial was double-dummy and placebo-controlled; 690 subjects were to be randomized 2:2:1 to 12 weeks of twice daily treatment with formoterol fumarate inhalation solution (FFIS), 20 µg, Foradil® (FA) at the approved dose of 12 µg, or placebo, respectively (Table 20). Aerolizer® treatment was to be first, followed by treatment with the nebulizer and compressor combination (Pari LC Plus jet nebulizer and Pari ProNeb compressor).

Table 20. Trial DL-059: Treatments during the double-blind period

Treatment	Dose of formoterol
Placebo Aerolizer® + FFIS	20 µg twice daily
FA Aerolizer® + Placebo Inhalation Solution	12 µg twice daily
Placebo Aerolizer® + Placebo Inhalation Solution	Not applicable

[Source: appendix-16-1-01-protocol.pdf, table 1.1]

3. Open-label treatment: 52 weeks of treatment with twice-daily FFIS or FA (Table 21). The last day of the 12-week double-blind period was considered the first day of the open-label period. Randomized treatment in this period was determined upon original randomization.
 - Subjects on FFIS in the double-blind period were to remain on FFIS
 - Subjects on placebo were to be switched to FFIS
 - Subjects on FA were to be assigned randomly in a 1:1 ratio to FA or FFIS

This assignment scheme would be expected to result in a ratio of subjects on FFIS:FA of 5:1, given equal randomization from the double-blind period.

Table 21. Trial DL-059: Treatments during the open-label period*

Treatment	Dose of formoterol
Placebo Aerolizer® + FFIS	20 µg twice daily
FA Aerolizer® + Placebo Inhalation Solution	12 µg twice daily

*See review for details of the randomization to these treatments
[Source: section-1-15-report-body.pdf, table 9.1.1]

Subjects

Subjects with the following characteristics were to be enrolled in the trial. Eligibility was not reassessed for enrollment into the open-label period of the trial.

Inclusion criteria

- Either sex
- At least 40 years old
- Medical diagnosis of COPD including persistent presence of cough, sputum production, and/or shortness of breath on effort
- Current or prior history of at least 10 pack-years of smoking
- Screening postbronchodilator: $FEV_1 \geq 30\%$ predicted to $<70\%$ predicted and $FEV_1/FVC < 70\%$
- Day 1 predose $FEV_1 \pm 15\%$ screening prebronchodilator FEV_1 and $<70\%$ predicted

Exclusion criteria

- Medical diagnosis of asthma
- Chest X-ray within 12 months showing a significant disease other than COPD
- History of lobectomy or receipt of radiation or chemotherapy within the previous 12 months
- Exacerbation of COPD in the 30 days prior to screening, where exacerbation is defined as an increase in symptoms requiring
 - an increase in use or the addition of one or more of the following therapies: corticosteroids, antibiotics, or oxygen for >3 days; and/or
 - hospitalization or an extension of a hospitalization
- Respiratory tract infection in the 30 days prior to screening
- Requirement for prednisone >10 mg every day or >20 mg every other day or equivalent dose or unstable oral steroid dose for 30 days prior to screening
- Requirement for daily use of supplemental oxygen for >12 hours a day, within 30 days of the screening visit
- ECG with a QTc >0.46 seconds
- Myocardial infarction within 6 months of screening
- Abnormal and clinically significant laboratory test not explained or related to a concurrent illness excluded by the protocol

Comment

Eligibility criteria also included the ability to understand the requirements of the study and provide written informed consent to participate in this study, restrictions to avoid pregnancy, and requirements for willingness to follow protocol requirements with the expectation that they would do so, and exclusion for a history of hypersensitivity to beta₂-agonists or use of beta-blockers, a medical condition that could place the subject at risk, interfere with participation, or confound trial objectives, inability to withhold medications according to the concomitant medication restrictions,

requirement for the use of MAO inhibitors, history of illegal drug use or substance or alcohol abuse within the past 5 years, and use of an investigational drug within 30 days prior to screening.

Concomitant medications

During the screening and double-blind periods, the protocol allowed subjects to remain on oral, parenteral, inhaled or intranasal corticosteroids that were at fixed doses of ≤ 10 mg/day or ≤ 20 mg every other day for at least 1 month prior to screening. Nedocromil or cromolyn sodium and tiotropium were prohibited. Inhalational and oral β -agonists, xanthines, anticholinergics (other than tiotropium), tricyclic antidepressants, and β -blockers were not to be used within specific time limits of spirometry.

During the open-label period, subjects were to be advised not to take medications containing another long-acting β -agonist, and medication restrictions consistent with the labeling of Foradil[®] were in place.

Procedures

Procedures for the trial, including the double-blind and open-label periods are shown in Table 22.

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Table 22. Trial DL-059: Procedures

	Day -14 to -7	Double-blind period					Open-label period						ET*
		Day 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 22	Wk 32	Wk 42	Wk 52	Wk 64	
visit→	1	2	3	4	5	6	telephone	7	8	9	10	11	
Consent	X												
Inclusion/Exclusion Criteria	X												
Medical History	X												
Physical Examination	X					X		X				X	X
Vital Signs	X	X	X	X	X	X		X	X	X	X	X	X
ECG	X			X	X	X		X				X	X
Holler Monitoring (subset only)	X					X							
Chest X-Ray	X												
Hematology, Serum Chemistry, Urinalysis	X					X		X				X	X
Spirometry Pre-and Post-BD	X												
Spirometry (12 hour)		X		X	X	X							
SGRQ		X				X		X				X	X
Demonstrate Study Med&Delivery	X	X											
Randomization		X											
Dispense diary	X	X	X	X	X	X		X	X	X	X		
Dispense trial med	X	X	X	X	X	X		X	X	X	X		
Dispense rescue med	X	X	X	X	X								
Collect/review diary		X	X	X	X	X		X	X	X	X	X	X
Collect/review trial medication		X	X	X	X	X		X	X	X	X	X	X
Collect/review rescue medication		X	X	X	X	X							
Review smoking status	X	X	X	X	X	X	X	X	X	X	X	X	X
Review AEs		X	X	X	X	X	X	X	X	X	X	X	X
Review conc. meds	X	X	X	X	X	X	X	X	X	X	X	X	X

*ET= early termination.

Pregnancy was monitored (not shown)

[Source: appendix-16-1-01-protocol.pdf, table 4.1]

Discontinuations

The use of <15 days of oral corticosteroids or oxygen for a COPD exacerbation or respiratory tract infection up to twice during the double-blind period (separated by >14 days) would not require the discontinuation of a subject. The protocol stated that subjects who required “a more aggressive treatment regimen” or who had “an increased number of exacerbations” would be reviewed for discontinuation by Dey.

Analytical plan

The double-blind period of the trial was intended to provide evidence for the evaluation of the post-treatment FEV₁ over 12 hours. The occurrence of major randomization errors makes the discussion of the analytical plan moot. See “Results” for a discussion of the safety analysis that was conducted.

Changes to the protocol

The original protocol was dated February 20, 2004. Dey changed the protocol twice. The first amendment was dated April 15, 2004, prior to the enrollment of the first subject. Since the first amendment could not have altered the results of an ongoing trial, it will not be discussed here.

Amendment 2 was dated February 22, 2005. It increased the duration of the open-label phase after the double-blind phase from 40 weeks to 52 weeks and added analyses of safety to examine the effects of the randomization errors that occurred. These were minor changes that are not expected to have had a notable effect on the interpretation of the trial's results.

The original protocol called for transfer of all FA and placebo subjects to FFIS in the open-label period. Dey states that in response to comments from FDA in April 2004 the code for randomization of subjects into FA was regenerated so that these subjects would be treated as two distinct groups. One of the groups would be transferred to FFIS as originally planned; the other would continue on FA. This change was reflected in the statistical analytical plan dated August 20, 2005.

Comment on the design of the trial

The double-blind portion of the trial was reasonably designed to measure the FEV₁ response to FFIS compared to FA in subjects with chronic pulmonary obstructive disease. However, this period was unable to provide efficacy data due to the corruption of randomization and the switching of treatments during the trial. The open-label period had infrequent visits (every 10 weeks).

10.1.3.2 Safety results

This review will discuss the safety results of the double-blind period first, followed by a discussion of the open-label safety results. Because of the inconsistency of treatment during the double-blind phase, efficacy was impossible to judge. The St. George's Respiratory Questionnaire was administered during the open-label period as a measure of efficacy. Questionnaire data are particularly subject to knowledge of treatment assignment, and there was no washout period to re-establish baseline. For these reasons, this review will not discuss the questionnaire data, but concentrate on the safety findings only.

Results in double-blind period

Investigational treatments

The investigational agents were:

- Dey Formoterol Fumarate Inhalation Solution: Formulation Code/Batch Number: C062A
- Comparator Products: Foradil® Aerolizer® (manufactured by Novartis), Formulation Code/Batch Number: 037H0436; 028H0434
- Placebo Inhalation Solution (manufactured by Dey, L.P.): Formulation Code/Batch Number: C059A; C070
- Placebo Aerolizer® (manufactured by _____): Formulation Code/Batch Number: 1253025-02; 1253023-08; 1253023-10; 1253023-11; 1253023-12

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Randomization of subjects

Six hundred and ninety-four subjects were randomized approximately 2:2:1 to treatments, the ratio specified in the protocol. However, most subjects did not receive their scheduled treatments (Table 23, constructed by this reviewer from data provided by Dey).

Table 23. DL-059 double-blind period: Receipt of scheduled treatment (yes or no) by visit

	FFIS		FA		Placebo		Total n
	yes	no	yes	no	yes	no	
Visit 1/Day 1	n=276		n=279		n=139		694
	107	169	116	163	33	106	
Visit 3/ week4	n=257		n=262		n=126		645
	94	163	115	147	14	112	
Visit 4/ week 8	n=229		n=216		n=107		552
	99	130	77	139	23	84	
Visit 5/ week 12	n=1		n=2		n=2		5
	0	1	1	1	1	1	

[source: DL-059 DB dataset ACT_TRT.xpt]

Demographics and baseline characteristics

The characteristics of the populations enrolled in the double-blind period are shown in Table 24. Subjects were generally considerably older than the lower limit of eligibility and there was a slight preponderance of men. About half the subjects currently smoked, the great majority of subjects were Caucasians, and FEV₁ was a little over a liter.

The subsetting of these data by treatment received on day 1 is primarily useful for the analysis of safety events that occurred during the first 30 days prior to switching of many of the treatments in many of the subjects (see below). However, the overall trial population characteristics can be inferred generally, since the treatment arms were balanced in terms of these characteristics.

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Table 24. Trial DL-059 double-blind period: Demographic and baseline subject characteristics (actual treatment received on Day 1, safety population)

		FFIS 20 µg n=277	FA 12 µg n=268	Placebo n=149
Age (y)	Mean (SD)	64.3 (10.41)	63.8 (9.69)	63.8 (9.82)
	Median	65.0	64.0	64.0
	Min, Max	40, 90	40, 83	43, 86
Gender (n [%])	Male	144 (52.0%)	150 (56.0%)	78 (52.3%)
	Female	133 (48.0%)	118 (44.0%)	71 (47.7%)
Race (n [%])	Caucasian	242 (87.4%)	230 (85.8%)	128 (85.9%)
	Hispanic	6 (2.2%)	5 (1.9%)	3 (2.0%)
	Black	25 (9.0%)	30 (11.2%)	17 (11.4%)
	Asian	4 (1.4%)	2 (0.7%)	0
	Other	0	1 (0.4%)	1 (0.7%)
Currently Smokes (N [%])	Yes	142 (51.3%)	143 (53.4%)	80 (54.1%)
	No	135 (48.7%)	125 (46.6%)	68 (45.9%)
FEV ₁ (L)Pre-Bronchodilator	n	275	264	148
	Mean (SD)	1.27 (0.481)	1.32 (0.480)	1.30 (0.479)
	Median	1.17	1.23	1.17
	Min, Max	0.45, 2.85	0.51, 2.99	0.48, 2.78

[Source: DL-059 double-blind section-1-15-report-body.pdf, table 11.2.1 and 11.2.2]

Disposition of subjects

Table 25 shows the disposition of subjects in the double-blind period. Eighteen percent of subjects discontinued. More subjects discontinued from the double-blind period (and more due to adverse events) with placebo as their last treatment than from either active treatment.

Table 25. Trial DL-059 double-blind period: Disposition by final treatment received in period

	Final treatment received			
	FFIS 20 µg (n=291)	FA 12 µg (n=250)	Placebo (n=153)	Total (n=694)
Patients completed	244 (83.8)	210 (84.0)	115 (75.2)	569 (82.0)
Patients discontinued	47 (16.2)	40 (16.0)	38 (24.8)	125 (18.0)
Reason for discontinuation				
Adverse event	12 (4.1)	14 (5.6)	18 (11.8)	44 (6.3)
Protocol violation	2 (0.7)	1 (0.4)	0	3 (0.4)
Lost to follow-up	3 (1.0)	6 (2.4)	2 (1.3)	11 (1.6)
Withdrawal of consent	23 (7.9)	15 (6.0)	12 (7.8)	50 (7.2)
Other	7 (2.4)	4 (1.6)	6 (3.9)	17 (2.4)

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

Protocol violations

Few subjects were enrolled in violation of eligibility criteria; these violations tended to be minor.

Exposure

Less than one quarter (157) of the subjects were dosed with the same treatment throughout the trial, 437 were dosed with 2 different treatments, and 100 were dosed with all 3 treatments. The median duration of exposure to any treatment was nearly equal between the active treatment groups at approximately 30 days.

Adverse events

Note: In the tables of adverse events, numbers of subjects in each treatment group add up to more than the total of subjects in the trial, as many subjects were on more than one treatment at some point.

Deaths

Two deaths occurred in the double-blind period:

- 70 year-old woman who died of a COPD exacerbation approximately 8 days after discontinuing from Foradil[®] treatment.
- 76 year-old man who died as a result of metastatic liver disease. He had received treatment with placebo (about 1 month), FFIS (about 1 month), and finally FA (about 2 weeks).

Serious adverse events and discontinuations due to safety events

The numbers of events in any system organ class were small. Three serious adverse events were considered related to treatment: 1) COPD exacerbation (1 subject in FFIS and 1 subject in placebo) and 2) supraventricular arrhythmia (FFIS).

Table 26 shows serious adverse events with respect to the treatment received at the time of the event. No safety concern is raised by this summary, keeping in mind that this analysis is severely limited by the switching of treatments during the trial.

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Table 26. Trial DL-059 double-blind period: Subjects with serious adverse events by treatment received at the time of the event

SYSTEM ORGAN CLASS Preferred Term	FFIS 20 µg (N=516)	FA 12 µg (N=500)	Placebo (N=315)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (0.8)	4 (0.8)	2 (0.6)
Chronic obstructive airways disease exacerbated	4 (0.8)	4 (0.8)	2 (0.6)
CARDIAC DISORDERS	3 (0.6)	1 (0.2)	0
Acute myocardial infarction	1 (0.2)	0	0
Arrhythmia supraventricular	1 (0.2)	0	0
Sick sinus syndrome	1 (0.2)	0	0
Angina pectoris	0	1 (0.2)	0
VASCULAR DISORDERS	2 (0.4)	0	1 (0.3)
Aortic aneurysm	1 (0.2)	0	0
Atherosclerosis	1 (0.2)	0	0
Arterial occlusive disease	0	0	1 (0.3)
GASTROINTESTINAL DISORDERS	1 (0.2)	0	1 (0.3)
Hiatus hernia	1 (0.2)	0	0
Pancreatitis	0	0	1 (0.3)
INFECTIONS AND INFESTATIONS	1 (0.2)	0	1 (0.3)
Cellulitis	1 (0.2)	0	0
Pyelonephritis	0	0	1 (0.3)
NERVOUS SYSTEM DISORDERS	1 (0.2)	0	0
Carotid artery stenosis	1 (0.2)	0	0
PSYCHIATRIC DISORDERS	1 (0.2)	0	0
Suicide attempt	1 (0.2)	0	0
HEPATOBIILIARY DISORDERS	0	0	1 (0.3)
Cholecystitis	0	0	1 (0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS)	0	1 (0.2)	0
Metastases to liver	0	1 (0.2)	0
RENAL AND URINARY DISORDERS	0	1 (0.2)	0
Nephrolithiasis	0	1 (0.2)	0

Individual subjects are counted once in each preferred term and once in each System Organ Class
[Source: DL-059 DB section-1-15-report-body.pdf, Table 12.3.1.2.1]

Discontinuations due to adverse events (Table 27) also did not raise a safety concern, keeping in mind the limitations of this analysis due to the switching of treatments.

Table 27. Trial DL-059 double-blind period: Subjects who discontinued due to adverse events by treatment received at the time of the event

SYSTEM ORGAN CLASS Preferred Term	FFIS 20 µg (N=516)	FA 12 µg (N=500)	Placebo (N=315)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (0.8)	9 (1.8)	11 (3.5)
Chronic obstructive airways disease exacerbated	3 (0.6)	4 (0.8)	7 (2.2)
Dyspnoea exacerbated	1 (0.2)	1 (0.2)	2 (0.6)
Aspiration	0	1 (0.2)	0
Cough	0	1 (0.2)	1 (0.3)
Dyspnoea	0	0	1 (0.3)
Pharyngolaryngeal pain	0	1 (0.2)	0
Respiratory distress	0	1 (0.2)	0
CARDIAC DISORDERS	2 (0.4)	1 (0.2)	1 (0.3)
Arrhythmia supraventricular	1 (0.2)	0	0
Ventricular extrasystoles	1 (0.2)	0	0
Atrial fibrillation	0	0	1 (0.3)
Angina pectoris	0	1 (0.2)	0
NERVOUS SYSTEM DISORDERS	2 (0.4)	1 (0.2)	0
Dizziness	1 (0.2)	0	0
Syncope	1 (0.2)	0	0
Tremor	0	1 (0.2)	0
HEPATOBIILIARY DISORDERS	1 (0.2)	0	0
Bile duct obstruction	1 (0.2)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.2)	0	0
Hyperhidrosis	1 (0.2)	0	0
VASCULAR DISORDERS	1 (0.2)	0	0
Hypertension	1 (0.2)	0	0
GASTROINTESTINAL DISORDERS	0	2 (0.4)	2 (0.6)
Diarrhoea	0	1 (0.2)	0
Dyspepsia	0	0	1 (0.3)
Gastrointestinal discomfort	0	0	1 (0.3)
Oral pain	0	1 (0.2)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (0.2)	1 (0.3)
Chest discomfort	0	0	1 (0.3)
Chest pain	0	1 (0.2)	0
INFECTIONS AND INFESTATIONS	0	0	2 (0.6)
Gastroenteritis viral	0	0	1 (0.3)
Upper respiratory tract infection	0	0	1 (0.3)
INVESTIGATIONS	0	1 (0.2)	0
Heart rate increased	0	1 (0.2)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (0.2)	0
Muscle cramp	0	1 (0.2)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS)	0	1 (0.2)	0
Metastases to liver	0	1 (0.2)	0

Individual subjects are counted once in each preferred term and once in each System Organ Class
 [Source: DL-059 DB section-1-15-report-body.pdf, Table 12.3.1.3.1]

Table 28 is a summary of adverse events, expressed as numbers of subjects per treatment group with respect to the treatment they received at the time of the event. As with all the safety information for this period, this analysis is flawed by possible carryover effects of the other treatments received. It shows no notable safety concern, however.

Table 28. Trial DL-059 double-blind period: Subjects with adverse events by treatment received at the time of the event

SYSTEM ORGAN CLASS Preferred Term	FFIS 20 µg (N=516)	FA 12 µg (N=500)	Placebo (N=315)
INFECTIONS AND INFESTATIONS	67 (13.0)	59 (11.8)	43 (13.7)
Upper respiratory tract infection	14 (2.7)	16 (3.2)	6 (1.9)
Sinusitis	12 (2.3)	5 (1.0)	3 (1.0)
Bronchitis acute	9 (1.7)	4 (0.8)	2 (0.6)
Nasopharyngitis	8 (1.6)	12 (2.4)	6 (1.9)
Oral candidiasis	5 (1.0)	3 (0.6)	0
Urinary tract infection	3 (0.6)	2 (0.4)	3 (1.0)
Viral infection	2 (0.4)	0	4 (1.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	52 (10.1)	65 (13.0)	48 (15.2)
Chronic obstructive airways disease exacerbated	23 (4.5)	24 (4.8)	20 (6.3)
Cough	10 (1.9)	13 (2.6)	9 (2.9)
Dyspnoea exacerbated	7 (1.4)	3 (0.6)	7 (2.2)
Dyspnoea	3 (0.6)	3 (0.6)	5 (1.6)
Pharyngolaryngeal pain	3 (0.6)	11 (2.2)	3 (1.0)
GASTROINTESTINAL DISORDERS	29 (5.6)	27 (5.4)	17 (5.4)
Diarrhoea	9 (1.7)	7 (1.4)	4 (1.3)
Nausea	4 (0.8)	5 (1.0)	2 (0.6)
Constipation	3 (0.6)	1 (0.2)	3 (1.0)
Abdominal pain upper	1 (0.2)	1 (0.2)	3 (1.0)
NERVOUS SYSTEM DISORDERS	26 (5.0)	32 (6.4)	10 (3.2)
Headache	15 (2.9)	19 (3.8)	7 (2.2)
Dizziness	5 (1.0)	5 (1.0)	1 (0.3)
Tremor	1 (0.2)	5 (1.0)	1 (0.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	25 (4.8)	22 (4.4)	12 (3.8)
Back pain	9 (1.7)	5 (1.0)	3 (1.0)
Arthralgia	6 (1.2)	6 (1.2)	2 (0.6)
Muscle cramp	2 (0.4)	5 (1.0)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	18 (3.5)	16 (3.2)	10 (3.2)
Chest pain	4 (0.8)	5 (1.0)	1 (0.3)
Influenza like illness	0	0	3 (1.0)
INVESTIGATIONS	10 (1.9)	15 (3.0)	6 (1.9)
Electrocardiogram change	5 (1.0)	4 (0.8)	4 (1.3)
PSYCHIATRIC DISORDERS	7 (1.4)	9 (1.8)	3 (1.0)
Nervousness	5 (1.0)	3 (0.6)	0

Individual subjects are counted once in each preferred term and once in each System Organ Class
 [Source: DL-059 DB section-1-15-report-body.pdf, Table 12.2.2.1]

Analysis of adverse events in subjects who received only 1 type of treatment

Only 55 subjects received one type of treatment only during the entire double-blind period. Because this sample is so small, and randomization of subjects is lost, results from these subjects are only useful to generate hypotheses for further examination of safety data. No remarkable safety signal was apparent from review of this small selection of subjects (not shown).

Dey analyzed adverse events reported within the first 30 days of initiation of treatment and prior to any switching of treatments that may have occurred, by treatment received. Table 29 shows the numbers of subjects from this population with events, where the incidence of the events was ≥1% more than that in the placebo group.

Table 29. Trial DL-059 double-blind period: Subjects with adverse events occurring before treatment changes and within 30 days of the first dose, if at a $\geq 1\%$ incidence greater than placebo in FFIS treatment arm (safety population)

SYSTEM ORGAN CLASS Preferred term	FFIS 20 μg N=277	FA 12 μg N=268	Placebo N=149
INFECTIONS AND INFESTATIONS	28 (10)	31 (11.6)	12 (8.1)
Bronchitis acute	6 (2.2)	2 (0.7)	0
Nasopharyngitis	5 (1.8)	11 (4.1)	1 (0.7)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	15 (5.4)	14 (5.2)	6 (4.0)
Back pain	6 (2.2)	3 (1.1)	0
Arthralgia	5 (1.8)	2 (0.7)	1 (0.7)

Subjects are counted once within a system organ class and once within a preferred term for each treatment.
 [Source: Trial DL-059 double-blind period section-1-15-report-body.pdf, Table 14.3.1.3]

These results are very limited in scope, and don't point to any safety concern.

Vital signs

Dey summarized vital signs in terms of the criteria in Table 30 (these were specified in the statistical analytical plan).

Table 30. Trial DL-059 double-blind period: Criterion changes in vital signs defined by Dey

Systolic Blood Pressure – High	Value > 179 mm Hg and increase from baseline* of at least 30 mm Hg
Systolic Blood Pressure - Low	Value < 90 mm Hg and decrease from baseline* of at least 30 mm Hg
Diastolic Blood Pressure -High	Value > 104 mm Hg and increase from baseline* of at least 25 mm Hg
Diastolic Blood Pressure -Low	Value < 50 mm Hg and decrease from baseline* of at least 25 mm Hg
Heart Rate – High	Value > 100 bpm and increase from baseline* of at least 20 bpm
Heart Rate – Low	Value < 60 bpm and decrease from baseline* of at least 20 bpm

*baseline is week 12 of the double-blind period

[Source: DL-059 section-1-15-report-body.pdf, Table 9.7.2.8.1]

There was no notable change from baseline in any treatment group (by actual treatment received) in the numbers of subjects with these criterion changes in vital signs. No more than 3 subjects in either active treatment group (with over 200 subjects at each visit) had a criterion change in systolic or diastolic blood pressure. A greater proportion of subjects (8, 3.2%) treated with FFIS at week 12 had a high heart rate, compared to 3 (1.4%) in FA and 1 (0.9%) in placebo; however, patterns at other time points (4 and 8 weeks) did not show consistent pattern of greater heart rate with FFIS.

Laboratory analyses

Dey summarized hematology and chemistry, and urinalysis parameters (specific gravity and pH) according to the treatment received at the last visit at which they were determined. These results, like the adverse event data, are of limited utility. Review of summary statistics and shift data shows no pattern of concern for either active treatment in hematology, serum chemistry, and urinalysis parameters. Of particular interest for β -agonists is hyperglycemic and hypokalemic effects. The proportions of subjects who shifted from normal at baseline to high glucose at week 12 or early termination in the FFIS, FA, and placebo groups were 24 (8.6%), 24 (10%), and 13 (9.3%); the corresponding figures for shifts from normal to low potassium were 1 (0.4%), 3 (1.2%), and 2 (1.4%).

Results in open-label period

Investigational treatments

The investigational agents were:

- Dey Formoterol Fumarate Inhalation Solution: Formulation Code/Batch Number: C066A2, C067A2, C068A2
- Comparator Products: Foradil® Aerolizer® (manufactured by Novartis), Formulation Code/Batch Number: 047H2467, S4A020E, S4A023E, S4A014E, S4A024E

Randomization of subjects

Sites were notified of the randomization sequence error in the double-blind period of trial DL-059 on December 3, 2004. Subjects in the double-blind period were given the option to enter the open-label period immediately or to withdraw entirely. Subjects on FFIS or placebo in the double-blind period were treated with FFIS; one half of the subjects on FA in the double-blind period were subsequently treated in the open-label period with FFIS and one half with FA (see "Disposition" below).

Comment

If subjects treated with FFIS at baseline of the double-blind period of DL-059 had remained on FFIS, a nontreatment baseline would be available (for subjects continuing on FFIS) for examination of long-term changes in outcomes such as vital signs or hematology data, for example. However, the great majority of subjects switched treatments. The baseline for the open-label period was defined as week 12 of the double-blind period, a time at which most subjects had been on different treatments. This rendered changes over time problematic to interpret.

Demographics and baseline characteristics

The characteristics of the population enrolled in the open-label period are shown in Table 31. Subjects were generally considerably older than the lower limit of eligibility and there was a slight preponderance of men. About half the subjects currently smoked, and the great majority of subjects were Caucasians. On average, the subjects were overweight as determined by the body-mass index².

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Table 31. Trial DL-059 open-label period: Subject demographics (safety population)

		FFIS 20 µg N=463	FA 12 µg N=106
Age (yr)	Mean (sd)	64.4 (9.71)	63.9 (10.14)
	Median	65	64
	Min, Max	40, 89	40, 85
Age Distribution (yr) (n,%)	<65	227 (49.0%)	54 (50.9%)
	≥65	236 (51.0%)	52 (49.1%)
Gender [n, (%)]	Male	244 (52.7%)	55 (51.9%)
	Female	219 (47.3%)	51 (48.1%)
Race (n [%])	Caucasian	407 (87.9%)	91 (85.8%)
	Hispanic	9 (1.9%)	2 (1.9%)
	Black	42 (9.1%)	11 (10.4%)
	Asian	5 (1.1%)	1 (0.9%)
	Other*	0 (0%)	1 (0.9%)
Currently smokes‡ (n [%])	Yes	226 (48.8%)	62 (58.5%)
	No	235 (50.8%)	43 (40.6%)
	Unknown	2 (0.4%)	1 (0.9%)
Body mass index (kg/m ²)	Mean (sd)	28.15 (6.3)	28.46 (6.4)
	Median	27.1	27.85
	Min, Max	13.8, 56.4	16.1, 50.8

*Dey states: "noted as White" on the case report form
 [Source: DL-059 open-label section-1-15-report-body.pdf, table 11.2.1]

Spirometry was not performed at the outset of the open-label period. Upon request, Dey submitted a summary of spirometrically-determined lung function for subjects who entered into the open-label period, at the last visit it was performed in the double-blind period. For 458 subjects assigned to FFIS and 106 subjects assigned to FA, FEV₁ was very similar to that shown in Table 24 (a mean of 1.34 for FFIS and 1.35 for FA). These figures suggest that there was no remarkable change in FEV₁ during the course of the double-blind portion of the trial.

Disposition of subjects

Table 32 shows the disposition of subjects in the open-label period.

Table 32. Trial DL-059 open-label period: Disposition by treatment received (safety population)

	FFIS 20 µg (n=463)	FA 12 µg (n=106)
Patients entering extension	463	106
Patients completed	281 (60.7)	68 (64.2)
Patients discontinued	182 (39.3)	38 (35.8)
Adverse event	27 (5.8)	7 (6.6)
Termination of study by Dey	4 (0.9)	0
Protocol violation	6 (1.3)	1 (0.9)
Lost to follow-up	24 (5.2)	6 (5.7)
Withdrawal of consent	77 (16.6)	10 (9.4)
Other	44 (9.5)	14 (13.2)
Time to treatment discontinuation*		
n	182	38
Mean (sd)	185 (104)	207 (98)
Median	202.5	225.0
Min, max	1, 380	1, 351

* among those who discontinued, not the entire treatment group
 [Source: section-1-15-report-body.pdf, table 10.1.1]

Similar and large proportions of subjects discontinued from either treatment arm during this year-long trial. Among those who discontinued, the time to discontinuation was earlier in the FFIS group than in the FA group (however, see Exposure below for mean duration of treatment in each treatment arm taken as a whole, which was similar). Discontinuations for adverse events occurred at a 6-7% rate. The major reason for discontinuation was “withdrawal of consent,” which occurred notably more frequently in the FFIS group than in the FA group. As a group the subjects in the FFIS group discontinued 3 weeks earlier than subjects in the FA group. Twenty-one of the 58 total subjects who discontinued due to “other” reasons discontinued due to Hurricane Katrina, from a single site, in August 2005.

Comment

The imbalance between treatment groups in the proportions of subjects who discontinued due to the withdrawal of consent leaves open the possibility that FFIS is less well-tolerated than FA. However, it is noteworthy that where the reason for discontinuation is stated as an adverse event, the proportions of subjects are similar between the treatment groups.

Protocol violations

Protocol violations mostly consisted of visits outside the time window (± 3 days at the Week 12 visit, ± 7 days at the other visits) specified by the protocol. The total number of these violations that occurred outside 7 days was small. These violations would not be expected to have a notable effect on the collection of safety information from the trial.

Exposure

Table 33 shows that the duration of exposure was similar between the two treatment groups and that the daily dose was close to (and a little below) the projected dose in each treatment group.

Table 33. Trial DL-059 open-label period: Exposure (safety population)

	Statistics:	FFIS 20 mcg (n=463)	FA 12 mcg (n=106)*
Duration of Exposure (days)	n	448	104
	Mean (sd)	313.6 (103.67)	320.7 (97.41)
	Median	359.0	357.0
	Min, max	7, 453	4, 450
Duration distribution (days) (n; %)	<180	61 (13.6)	12 (11.5)
	180-<365	232 (51.8)	54 (51.9)
	≥365	155 (34.6)	38 (36.5)
Mean daily Dose (mcg/days)	n	447	104
	Mean (sd)	38.2 (19.68)	22.1 (3.49)
	Median	39.3	23.6
	Min, max	4, 437*	4, 25

[Source: section-1-15-report-body.pdf, table 12.1.1]

Concomitant medication use

Use of medications for COPD was balanced between the treatment arms (Table 34). Use of other medications did not suggest a safety concern (not shown).

Table 34. Trial DL-059 open-label period: Use of medications for COPD (subjects with use at >5% in either treatment arm)*

	FFIS 20 µg N=463	FA 12 µg N=106
All use	339 (73.2)	73 (68.9)
Salbutamol	258 (55.7)	58 (54.7)
Fluticasone propionate	80 (17.3)	20 (18.9)
Combivent	37 (8.0)	8 (7.5)
Ipratropium bromide	32 (6.9)	11 (10.4)
Budesonide	22 (4.8)	5 (4.7)
Fluticasone	21 (4.5)	4 (3.8)
Tiotropium bromide	21 (4.5)	5 (4.7)
Montelukast sodium	19 (4.1)	7 (6.6)

* Use at least once by a subject in the treatment arm

[Source: Trial DL-059 open-label period section-1-15-report-body.pdf, Table 14.1.3]

Adverse events

Deaths

Six subjects treated with FFIS and 2 treated with FA died, as summarized below:

FFIS

- 69 year-old man died of cardiac arrest on day 18. Medical conditions included hypertension, dyslipidemia, myocardial infarction.
- 78 year-old man died of exacerbation of COPD on day 272. He had had a treatment interruption for a prior COPD exacerbation. Medical conditions included thoracic scoliosis and a prior thoracotomy.
- 62 year-old man died of myocardial infarction on day 379, 15 days after completing the trial. Medical conditions included two myocardial infarctions and hypertension.
- 50 year-old man died of "coronary artery disease" on day 191, 3 days after stopping treatment. He had no prior related medical history.

- 65 year-old man died of congestive heart failure on day 345, 12 days after treatment was discontinued for the event. He had had a recent gastrointestinal bleeding event. Medical conditions included an abdominal aortic aneurysm on day 18 for which he had received a treatment interruption, hyperlipidemia, history of cardiac bypass surgery, ischemic cardiomyopathy, and deep venous thrombosis.
- 82 year-old man died of non-small cell lung cancer on day 403; he had completed the trial after a year of treatment

FA

- 69 year-old woman died of multi-organ failure that started on day 59. No relevant past medical history is reported.
- 66 year-old woman who died of an intracerebral hemorrhage on day 347. Medical conditions included obesity, cholecystitis, and pancreatitis.

Comment

Bearing in mind that the enrollment in FFIS was approximately 4-fold that of FA, the greater number of FFIS cases does not itself suggest a safety concern. Three of the 4 cases of death due to cardiovascular disease in the FFIS group had a relevant medical history.

Serious adverse events

Table 35 shows serious adverse events, sorted by system organ class and preferred term, with respect to treatment.

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**Table 35. Trial DL-059 open-label period: subjects with serious adverse events
(n (%), safety population)**

SYSTEM ORGAN CLASS Preferred term	FFIS 20 µg N=463	FA 12 µg N=106
INFECTIONS AND INFESTATIONS	19 (4.1)	3 (2.8)
Pneumonia	8 (1.7)	1 (0.9)
Bronchitis acute	4 (0.9)	1 (0.9)
Diverticulitis	2 (0.4)	0
Beta haemolytic streptococcal infection	1 (0.2)	0
Bronchitis	1 (0.2)	0
Cellulitis	1 (0.2)	0
Gastroenteritis viral	1 (0.2)	0
Groin abscess	1 (0.2)	0
Lobar pneumonia	1 (0.2)	1 (0.9)
Staphylococcal infection	1 (0.2)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	18 (3.9)	9 (8.5)
Chronic obstructive airways disease exacerbated	12 (2.6)	7 (6.6)
Pneumothorax	2 (0.4)	0
Dyspnoea	1 (0.2)	0
Pleuritic pain	1 (0.2)	0
Pulmonary mass	1 (0.2)	0
Respiratory failure	1 (0.2)	0
Pleural effusion	0	1 (0.9)
Respiratory disorder	0	1 (0.9)
CARDIAC DISORDERS	15 (3.2)	2 (1.9)
Myocardial infarction	5 (1.1)	0
Cardiac failure congestive	3 (0.6)	0
Coronary artery disease	3 (0.6)	2 (1.9)
Acute myocardial infarction	1 (0.2)	0
Angina unstable	1 (0.2)	0
Cardiac arrest	1 (0.2)	0
Supraventricular tachycardia	1 (0.2)	0
HEPATOBIILIARY DISORDERS	4 (0.9)	1 (0.9)
Cholelithiasis	2 (0.4)	0
Bile duct obstruction	1 (0.2)	1 (0.9)
Cholecystitis	1 (0.2)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (0.9)	2 (1.9)
Ankle fracture	1 (0.2)	0
Femoral neck fracture	1 (0.2)	0
Multiple fractures	1 (0.2)	0
Rib fracture	1 (0.2)	0
Spinal fracture	1 (0.2)	0
Anastomotic ulcer haemorrhage	0	1 (0.9)
Gun shot wound	0	1 (0.9)
NERVOUS SYSTEM DISORDERS	4 (0.9)	1 (0.9)
Syncope	2 (0.4)	0
Cerebral infarction	1 (0.2)	0
Syncope vasovagal	1 (0.2)	0
Transient ischaemic attack	1 (0.2)	0
Cerebral haemorrhage	0	1 (0.9)
VASCULAR DISORDERS	4 (0.9)	1 (0.9)
Iliac artery thrombosis	1 (0.2)	0
Intermittent claudication	1 (0.2)	0

SYSTEM ORGAN CLASS Preferred term	FFIS 20 µg N=463	FA 12 µg N=106
Peripheral vascular disorder	1 (0.2)	0
Temporal arteritis	1 (0.2)	0
Atherosclerosis	0	1 (0.9)
GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS	3 (0.6)	1 (0.9)
Chest pain	2 (0.4)	0
Multi-organ failure	1 (0.2)	1 (0.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (0.6)	2 (1.9)
Intervertebral disc degeneration	1 (0.2)	0
Intervertebral disc protrusion	1 (0.2)	0
Osteoarthritis	1 (0.2)	1 (0.9)
Localised osteoarthritis	0	1 (0.9)
GASTROINTESTINAL DISORDERS	2 (0.4)	0
Gastric ulcer	1 (0.2)	0
Pancreatitis	1 (0.2)	0
Pancreatitis acute	1 (0.2)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS)	2 (0.4)	0
Lung neoplasm malignant	1 (0.2)	0
Non-small cell lung cancer	1 (0.2)	0
PSYCHIATRIC DISORDERS	2 (0.4)	1 (0.9)
Depression	2 (0.4)	0
Drug dependence	0	1 (0.9)
Renal and urinary disorders	2 (0.4)	0
Renal artery stenosis	1 (0.2)	0
Renal insufficiency	1 (0.2)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.2)	0
Benign prostatic hyperplasia	1 (0.2)	0

[Source: section-1-15-report-body.pdf, table 14.3.1.2.1]

Three serious adverse events were considered related to treatment by the investigator, all in FFIS: 2 reports of COPD exacerbation and 1 report of supraventricular tachycardia.

Serious cardiac disorders not resulting in death also occurred at a slightly increased rate in the FFIS group. The following summaries include only the most remarkable aspects of the past medical history (PMH).

Myocardial infarction

FFIS

- 83 year-old male, on day 336, resolved no sequelae. PMH: coronary artery bypass surgery (Case also listed as "acute myocardial infarction")
- 53 year-old female, on day 161, dose interrupted, resolved no sequelae. No relevant PMH.
- 76 year-old male, on day 131, dose discontinued, resolved no sequelae. No relevant PMH.
- 78 year-old male, on day 265, dose discontinued, resolved no sequelae. PMH: hypertension and atrial fibrillation, hypercholesterolemia.
- 77 year-old male, on day 50, dose discontinued, resolved no sequelae. PMH: myocardial infarction and cerebrovascular accident.

Cardiac failure

FFIS

- 65 year-old male, on day 108, resolved no sequelae. PMH: angina, resolved no sequelae.
- 75 year-old male, on day 126, resolved no sequelae. PMH: hypertension, coronary artery disease

Coronary artery disease

FFIS

- 62 year-old male, on day 87, resolved no sequelae. PMH: MI, angina, coronary artery bypass surgery
- 62 year-old female, on day 347, resolved no sequelae. PMH: congestive heart failure

FA

- 61 year-old male, on day 186, resolved no sequelae. Drug interrupted. PMH: borderline hypertension
- 72 year-old male, on day 121, resolved no sequelae. Drug discontinued. PMH: hypercholesterolemia

Angina, unstable

FFIS

- 73 year-old female, on day 17, resolved no sequelae. Drug interrupted. PMH: congestive heart failure, coronary artery disease

Supraventricular tachycardia

FFIS

- 63 year-old male, on day 219, resolved no sequelae. Drug discontinued. PMH: cardiac arrhythmia and "cardiac arterial patch"

Comment

The small number of subjects in the FA treatment arm increases the uncertainty around the estimate of the relative proportion of cases between the treatment arms; the increase in the percent of cardiac cases may be a chance event, a few more cases in the FA arm equalizing the proportions of cases.

Events leading to discontinuation

There was a small increase in the numbers of subjects with myocardial infarctions and pneumonia (3 in FFIS compared to none in FA for each type of event) leading to discontinuation (Table 36).

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