CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-077

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

JAN 2 4 2000

NDA Number: 21-077
Applicant: Glaxo Wellcome, Inc.
Name of Drug: Advair Diskus (fluticasone and salmeterol combination product)
Statistical Reviewer: Barbara Elashoff, M.S. (HFD-715)
Chemistry Reviewer: Dale Koble, Ph.D. (HFD-570)
Documents Reviewed: 9/29/99 Volumes 8.1-8.5; electronic data

Background

Glaxo-Wellcome has submitted 18 months of stability data for Advair Diskus. Advair Diskus is a combination product with fluticasone propionate and salmeterol xinaphoate drug products. The fluticasone drug product was studied at doses of 100, 250 and 500 mcg, whereas, salmeterol was studied only at the dose of 50 mcg. Therefore, the combination product will be abbreviated to 50/100, 50/250, or 50/500 to refer to the three different dose combinations. The sponsor has proposed an —month expiration period for the 50/100 and 50/250 doses and a 24 month period for the 50/500 dose. The reviewing chemist has requested Division of Biometrics to perform a statistical review and evaluation of the sponsor's stability data for Fine Particle Mass and Sum of Stages 3 and 4. The specifications for each of the drug products and dose combinations are listed below.

Table 1: Specifications

Dose	Parameter	Specifications	
		Salmeterol	Fluticasone
50/100	Fine Particle Mass	—	—
	Sum of Stages 3 and 4	—	—
50/250	Fine Particle Mass	—	—
	Sum of Stages 3 and 4	—	—
50/500	Fine Particle Mass	—	—
	Sum of Stages 3 and 4	—	—

In addition, the reviewing chemist needed the following questions answered:

1. Does the log-transformation of time provide the best fit to the Fine Particle Mass data, as the sponsor argues?

2. Does the sponsor's new method of testing ten different devices for each determination of ———— (for commercial use) provide similar results to the old method of testing one device per determination (for pre-approval use)? That is, are the sponsor's conclusions from the statistical comparisons of 40C/75% RH stability of the primary and commercial batches valid?

Design of Study
A brief summary of the design of the study the sponsor submitted is necessary to understand the chemist's questions.

At each timepoint, for each batch, several "determinations [redacted] were made. At Time = 0 months ("release"), 8 determinations were made per batch. At all subsequent timepoints (3, 5, 6, 9, 12 and 18 months), 4 determinations were made per batch. A determination was obtained from actuating one device ten times, thus releasing drug from ten blisters (from inside the device). The total amount of drug was deposited into an [redacted] which had 8 levels, or "stages". Measurements of particle mass were obtained at each stage. The sum of stages 1-5 was termed "Fine Particle Mass" and is one of the two variables analyzed for this review. The sum of Stages 3 and 4 is the second variable. In summary, there were 8 values at release and 4 values thereafter for each batch. Each value was obtained using a different device.

Proposed Method
The sponsor proposed to change the method for the post-approval testing. The new method would use one actuation from each of 10 different devices to obtain one "determination". The same 10 devices would be used to obtain the subsequent determinations at a single timepoint (using different blisters). A different set of 10 devices would be used at each timepoint.

Results of Analyses
The statistical procedures in the FDA Guidelines (February 1987) were applied to the stability data provided by the sponsor. The estimated expiration dates were calculated from the specifications limit and the two-sided 95% confidence interval of the regression lines. The sponsor used one-sided (lower) 95% confidence limits. According to the chemist, the values are expected to decrease over time (and not increase). However, the chemist expressed concern that the initial values (at release) be within the upper and lower specifications. Due to this concern, two-sided 95% confidence intervals were used to estimate the expiration dating period. The estimated expiration dating periods for the three doses are listed in Tables 2 and 3. All analyses performed for this review were based on untransformed data.

Table 2: Summary Table of Expiration Dates*
All individual values used in the analyses

		Salmeterol		Fluticasone	
Dose	Parameter	Lower Bound Only (1-sided 95% CI)	Both Bounds (2-sided 95% CI)	Lower Bound Only (1-sided 95% CI)	Both Bounds (2-sided 95% CI)
50/100	Fine Particle Mass	[redacted]			
	Sum of Stages 3 and 4				
50/250	Fine Particle Mass				
	Sum of Stages 3 and 4				
50/500	Fine Particle Mass				
	Sum of Stages 3 and 4				

*If the slopes of different batches were statistically significantly different (at the 0.25 level), separate expiration periods were estimated for each batch.

Table 3: Summary Table of Expiration Dates*
Means of each batch (not individual values) used in the analyses

		Salmeterol		Fluticasone	
Dose	Parameter	Lower Bound Only (1-sided 95% CI)	Both Bounds (2-sided 95% CI)	Lower Bound Only (1-sided 95% CI)	Both Bounds (2-sided 95% CI)
50/100	Fine Particle Mass	20	18	19	18
	Sum of Stages 3 and 4	16	15	18	17
50/250	Fine Particle Mass	20	19	22, 15, 16	20, 14, 15
	Sum of Stages 3 and 4	24	23	18	17
50/500	Fine Particle Mass	42, 32, 30	39, 29, 27	36, 22, 28	33, 19, 25
	Sum of Stages 3 and 4	44, 35, 37	0, 31, 33	34, 21, 31	30, 19, 28

*If the slopes of different batches were statistically significantly different (at the 0.25 level), separate expiration periods were estimated for each batch.

In summary, the shortest expiration date, using a 2-sided 95% confidence interval and including all the individual values in the analyses, was 13 months for the 50/100 dose, 16 months for the 50/250 dose and 26 months for the 50/500 dose. Using just the means in the analyses, the shortest expiration date was 15 months for the 50/100 dose, 14 months for the 50/250 dose and 0 months for the 50/500 dose.

The mean Sum of Stages 3 and 4 for the Salmeterol drug product in the 50/500 dose of Batch SP97/182 was equal to the upper specification limit — , at release, see Table 4 below. The confidence interval at release (time=0) was above the specification limit, therefore the estimated expiration date was equal to zero months for this batch.

Table 4: Batch SP97/214 Mean Results Equal to Upper Specification Limit at Release (Time=0 months)

50/500 Dose Sum of Stages 3 and 4			
Determination	*Temp/RH*	*Result*	
1	25/60	8.5	
2	25/60	8.1	
3	25/60	7.4	
4	25/60	8.1	mean=
5	25/60	7.2	
6	25/60	8.6	
7	25/60	8.5	
8	25/60	7.2	

Additionally, the means of Batch SP97/214 were above the specification limits for Sum of Stages 3 and 4 for both Salmeterol and Fluticasone drug products in the 50/500 dose (see Table 5 below). However, even with these high means, the estimated expiration dates were longer than some of the other batches: 33 months for Salmeterol and 28 months for Fluticasone.

Table 5: Batch SP97/214 Mean Results Above the Specifications

50/500 Dose Sum of Stages 3 and 4				
Drug Product	*Temp/RH*	*Time*	*Result*	
Salmeterol	25/60	9 months	8.8	mean=8.7
	25/60	9 months	9.7	
	25/60	9 months	7.8	
	25/60	9 months	8.3	
Fluticasone	25/60	9 months	90.7	mean=90.0
	25/60	9 months	97.9	
	25/60	9 months	82.6	
	25/60	9 months	88.8	

Statistical Comments

The following comments are provided to answer the chemist's specific questions.

Question #1: Does the log-transformation of time provide the best fit to the Fine Particle Mass data, as the sponsor argues?

Reviewer Comment: The sponsor did not provide any justification that the log-transformation of time provided the best fit. The sponsor should provide the criteria used to determine this. Examples may include (but are not limited to), r-squared values and scatterplots of residuals. Further, the sponsor should explain the rationale for transforming time (the x-variable) and not the y-variable. In their response, they should provide prior precedent for such a transformation.

Question #2: Does the sponsor's new method of testing ten different devices for each determination of ———— (for commercial use) provide similar results to the old method of testing one device per determination (for pre-approval use)? That is, are

the sponsor's conclusions from the statistical comparisons of 40C/75% RH stability of the primary and commercial batches valid?
Reviewer Comment: The sponsor performed analyses to determine that the commercial method is similar to the primary method (used for pre-approval studies). The sponsor's description of the model used was as follows:

> *"The model was fitted using GLM in SAS Version 6.12 using all individual datapoint. The following terms were included: time, product, study(product), time x product (effect of interest), time x study (product) and occasion x study (product) (random effect) where occasion is a class variable equating to time." (Volume 8.1, page 6).*

The sponsor provided a table of p-values from this model. The null hypotheses were that the values were the same. P-values from these models are not enough to determine "similarity" or "equivalence" between methods. If the sponsor wants to statistically compare the two methods, the sponsor needs to demonstrate that 95% confidence intervals exclude a pre-specified relevant difference between the two results.

Conclusions
The estimated expiration dating periods for the 50/500 dose are based on data extrapolation beyond the range of storage time actually observed, which is valid under the assumption that the pattern of deterioration does not change significantly over the extrapolation period.

The proposed — month expiration date for the 50/100 and 50/250 doses are not supported by the 18-month data the sponsor submitted. Using the analysis with all the individual values, the data support a 13-month date for the 50/100 dose and a 16-month date for the 50/250 dose. The proposed 24-month expiration date for the 50/500 dose is supported by the 18-month data the sponsor submitted. These dates are based on the specification limits of fine particle mass and the sum of stages 3 and 4.

/S/

/S/

Barbara Elashoff

1/24/2000

Concur: Dr. Lin
cc:
Orig. NDA 21-077
HFD-570 / Division File
HFD-570 / PJani, DKoble, GPoochikian, Y-YChiu, SJohnson
HFD-715 / Division File, SWilson, KLin

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STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date: JAN 2 0 2000

NDA#:	21-077
Applicant:	Glaxo Wellcome Inc.
Name of Drug:	Advair (salmeterol xinafoate / fluticasone propionate)
Indication:	Asthma (maintenance treatment of asthma [redacted] in patients 12 years of age and older)
Documents Reviewed:	3/24/99 Volumes 1.1; 57-176, electronic data; 9/23/99 Volume 1.1; fax 10/19/99
Statistical Reviewer:	Barbara Elashoff, M.S.
Medical Input:	Susan Johnson, PhD

Summary

- The sponsor submitted five adult studies and one pediatric study to support the efficacy and safety of the combination product, Advair, for the maintenance treatment of asthma [redacted] in patients 12 years of age and older. This review explores the quality and reliability of the efficacy results of Studies 3002 and 3003.

- Study 3002 was a 12-week placebo-controlled study (n=356) evaluating the efficacy and safety of the 50/100 dose of Advair (50 mcg of salmeterol, 100 mcg of fluticasone) in patients ages 12-70. Study 3003 was a 12-week (n=349) placebo-controlled study evaluating the efficacy and safety of the 50/250 dose of Advair (50 mcg of salmeterol, — mcg of fluticasone) in patients ages 12-69. The patient population in Study 3003 had more severe asthma.

- In both studies, three efficacy outcomes were designated as co-primary endpoints. The first, "percent of patients remaining in the study" was used to evaluate the efficacy of the Fluticasone component in Advair. The second and third endpoints, AM pre-dose FEV1 change after one week and FEV1 AUC change after 1 week, were used to evaluate the efficacy of the Salmeterol component in Advair. Statistical significance was achieved for all three co-primary endpoint comparisons, in both studies.

- The sponsor is seeking a claim for two groups of patients: those maintained on inhaled corticosteroids, and those maintained on Salmeterol. Only one of the six studies submitted (Study 3002) randomized patients previously maintained on Salmeterol. In this study, approximately 24 patients per treatment group fulfilled this criteria. Descriptive statistics from this small subset did not provide sufficient data of the efficacy of Advair in patients previously maintained on Salmeterol alone.

- The treatment effects of the FEV1 AUC values should be evaluated with caution because 20% of patients in Study 3002 and 29% in Study 3003 did not provide a full day of 12-hour serial FEV1 measurements at the baseline and Week 1 visits. The percentages of patients whose FEV1 curves in-clinic could not be estimated varied across treatment groups. These differences across treatment groups detract from the overall quality of the study and thus from the reliability of the study results.

1 Introduction

The drug product discussed in this review is a combination of two drug substances that are currently approved for use in patients with asthma. Fluticasone is approved for oral inhalation (Rotadisk formulation) at doses of 50 to 1000 mcg BID and there is also an approved intranasal formulation (Flonase). Salmeterol at a dose of 50 mcg BID is a long-acting beta-agonist and is currently available in the approved Serevent Diskus formulation. The sponsor submitted five adult studies and one pediatric study to demonstrate the safety and efficacy of the combination product, Advair Diskus. Two of the studies (3002 and 3003) compare the combination product to each of the individual components. Three of the studies (3017, 3018, and 3020) were designed to demonstrate equivalence of Advair to the two components used concurrently. The sixth study (3019) includes the combination arm, a Fluticasone arm, and a concurrent use arm. Thus, Study 3019 was designed to compare the combination product to one of the individual components and concurrent use of both components. Only the two studies that compare Advair to each of the individual components (Studies 3002 and 3003) will be reviewed in this document.

Studies 3002 and 3003 were conducted concurrently and used similar designs. Significant differences between the two studies included: patient population; baseline therapy; and dose groups. Studies 3002 and 3003 had 40 and 42 investigators, respectively. Twelve investigators participated in both studies.

Table 1: Study Backgrounds

Study Number	Dates	Countries	Purpose SF = Advair F = Fluticasone S = Salmeterol	Patient Population (Entrance Criteria) IC = Inhaled Corticosteroid	Treatment Arms (all BID)
3002	8/96-7/97	[illegible]	[illegible]	[illegible]	SF 50/100 S 50 F 100 Placebo
3003	8/96-7/97	[illegible]	[illegible]	[illegible]	SF 50/250 S 50 F 250 Placebo
3019	5/96-11/97	France Germany Netherlands	Designed to demonstrate superiority of SF over F alone and equivalence with concurrent use	Used specific IC for 3 months continuously (at doses > in Study 3003); symptomatic on this treatment (no FEV requirements)	SF 50/500 F 500 S 50 + F 500
3017	7/96-5/97	Portugal S Africa Spain UK	Designed to demonstrate equivalence of SF with concurrent use	Used specific IC for 3 months continuously (at doses in between Study 3002 + Study 3003); symptomatic on this trt (no FEV requirements)	SF 50/100 S 50 + F 100
3018	7/96-7-97	Canada Denmark Finland Norway Sweden	Designed to demonstrate equivalence of SF with concurrent use	Used specific IC for 3 months continuously (at doses in between Study 3003 + Study 3019); symptomatic on this trt	SF 50/250 S 50 + F250
3020	11/96-9/97	Est,Fin Lit,Net Nor,Por S Africa,Spa Sweden	Designed to demonstrate equivalence of SF with concurrent use in pediatric patients	Used specific IC for 3 months continuously (at doses in between Study 3002 + Study 3003); symptomatic on this trt	SF 50/100 S 50 + F 100

* Thomas Edwards was under investigation at the time of this review. The sponsor provided analyses both including and excluding his data.

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1.1 Study Design

Studies 3002 and 3003 were multicenter randomized, double-blind, placebo-controlled parallel group studies. The study population of Study 3002 included two different groups of patients: those who had "sub-optimal" control of asthma while treated with inhaled corticosteroids continuously for at least 3 months, and those who had sub-optimal control of asthma while treated with salmeterol.[1] *(However, randomization was not stratified based on these two different population groups.)* The study population of Study 3003 was patients who had sub-optimal control of asthma while treated with inhaled corticosteroids daily for at least 4 weeks prior to the

[1] "Sub-optimal" control does not have a standardized definition, as per the American Thoracic Society. The sponsor worded the study population in Study 3002 as follows: "Patients included in the study were adolescents and adults with a diagnosis of asthma using the American Thoracic Society (ATS) definition who had sub-optimal control of asthma while treated with either inhaled corticosteroids or salmeterol. Inclusion criteria for reversibility after VENTOLIN were designed to select patients who had the potential to benefit from twice daily use of a combination of inhaled corticosteroid and a long-acting Beta2-agonist." The wording in Study 3003 was identical except excluded the words "or salmeterol".

first visit. The doses of inhaled corticosteroids that the patients in Study 3003 were taking were higher than those in Study 3002 (see Table 2, below).

Table 2: Inhaled Corticosteroid Doses Used Prior to Visit 1 and throughout run-in period

Drug Name	Study 3002 doses (mcg/day)	Study 3003 doses (mcg/day)
Beclomethasone Dipropionate	252-420	462-672
Triamcinolone acetonide	600-1000	1100-1600
Flunisolide	1000	1250-2000
Fluticasone propionate	176	440

Study 3002 had a placebo-controlled run-in period of 2 weeks duration. The patients used their current therapy (inhaled corticosteroid or salmeterol) and Ventolin for prn use in addition to the placebo Diskus inhaler BID. The run-in period served as a baseline assessment for the safety and efficacy variables. Study 3003 had a 2-week baseline run-in period as well, however, the patients did not receive placebo. They used their own inhaled corticosteroid plus Ventolin for prn use.

Table 3: Summary of Patient Population and Baseline Therapy

Study	Patient Population (Entrance Criteria)	Baseline Therapy
3002	Group 1: used specific IC for 3 months continuously; Group 2: used salmeterol for 1 week w/o IC; All: 40-85% pred FEV_1; ≥ 15% reversibility	Placebo BID via DISKUS, + continued previous IC therapy or salmeterol + Ventolin as rescue
3003	Used specific IC for 3 months continuously (at doses > in 3002); 40-85% pred FEV_1; ≥ 15% reversibility	No placebo; Continued previous IC therapy + Ventolin as rescue

After the run-in phase, if the patients met the inclusion criteria, they were randomized to one of the following treatment groups:

- Salmeterol/fluticasone propionate combination product BID via one Diskus inhaler
- Salmeterol BID via Diskus inhaler
- Fluticasone propionate BID via Diskus inhaler
- Placebo BID via Diskus inhaler

The dose of Salmeterol was 50 mcg in both studies, whereas the dose of Fluticasone was 100 mcg in Study 3002 and 250 mcg in Study 3003. The combination product salmeterol/fluticasone propionate will be abbreviated to SF 50/100 and SF 50/250 in this review to refer to the combination product groups in Studies 3002 and 3003, respectively. The other treatment groups will be referred to as S 50, F 100 and F 250.

In summary, the treatment arms were:

Study 3002:	SF 50/100	Study 3003:	SF 50/250
	S 50		S 50
	F 100		F 250
	Placebo		Placebo

The double-blind treatment period was 12 weeks, with visits every week (± 2 days) for the first 6 weeks, then every 2 weeks.

Table 4 Visit Schedule

Visit	1	2	3	4	5	6	7	8	9	10
Day	-14	1	7	14	21	28	42	56	70	84
Time to next visit	2 wks	1 wk	1 wk	1 wk	1 wk	2 wks	2 wks	2 wks	2 wks	2 wks

Pulmonary function was measured at every visit. Patients with a history of asthma who had

- an FEV1 40-85% of the predicted value at Visit 1; and
- demonstrated ≥15% reversibility in FEV1 within 30 minutes following 2 puffs of Ventolin at screening (Visit 1)

were eligible for enrollment into the baseline phase of the study. Patients who completed the run-in period were eligible to be randomized to double-blind study drug if they met the following criteria:

1. Demonstrated reproducible lung function at Clinic Visit 2 as defined by:
   - a best baseline clinic Visit 2 FEV1 within ±15% of the best pre-Ventolin Visit 1 FEV1; and
   - a best baseline FEV1 at Visit 2 of 40-85% of the predicted value;

2. In the 7 days immediately preceding Visit 2, demonstrated relative asthma stability per diary card defined as:
   - if patients previously used inhaled corticosteroids (in Study 3003, this criteria applied to all patients), no more than 3 days with 12 puffs/day of Ventolin use; in Study 3002, if patients previously used salmeterol, no more than 3 days with 6 puffs/day of Ventolin use; and
   - no more than 3 nights with awakenings due to asthma requiring treatment with Ventolin;

3. Demonstrated adequate compliance defined as completion of diary card, ability to withhold anti-asthma medications, and at least 70% compliance with the study drug regimen during the run-in period.

Study medication was administered BID. Pulmonary function tests were performed at each clinic visit. Twelve-hour serial pulmonary function tests were performed at Visits 2, 3 and 10.

1.2 Primary & Secondary Efficacy Variables

The main objective of Studies 3002 and 3003 was to compare the combination product to each of its individual components. Other objectives included comparing the product and the individual components to placebo, and comparing the individual components to each other.

The sponsor stated in the protocols of both studies that the combination product (SF) was not expected to "separate itself" from each of the components using a single efficacy measure. Therefore, the primary efficacy variables which were used to compare SF to each of the components were different, see Table 4 below.

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Table 5 Primary Efficacy Variables and Analysis

Comparison	Evaluates the Efficacy of:	Primary Efficacy Variable	Analysis
3002: SF 50/100 vs. S 50 3003: SF 50/250 vs. S 50	Fluticasone Component in Advair	Percent of patients remaining in the study	Log-rank test that censors patients who discontinued due to reasons other than lack of efficacy
3002: SF 50/100 vs. F 100 3003: SF 50/250 vs. F 250	Salmeterol Component in Advair	AM FEV1 at Endpoint	ANOVA on Change from best Visit 2 pre-dose FEV1 to Last Valid pre-dose FEV1 with factors: treatment, center cluster†, (& in Study 3003, stratum for prior IC use)
	Salmeterol Component in Advair	Area Under the Serial FEV1 curve (AUC) at Week 1 relative to baseline	ANOVA on Change from Visit 2 pre-dose FEV1* to Visit 3 (after 1 week of double-blind treatment) with factors: treatment, center cluster†, (& in Study 3002, stratum for prior IC use)

* There were two pre-dose FEV1 measurements, one 30 minutes prior to dosing and one immediately prior. The average of these two values was used as the baseline FEV1.

† The protocol stated that the factor would be "investigators". The study report states that the centers would be grouped by location if the sample size was < 20 at the site.

The Fluticasone component of Advair was evaluated by comparing Advair to *Salmeterol*, whereas the Salmeterol component was evaluated by comparing Advair to *Fluticasone*.

Efficacy Evaluation of Fluticasone Component in Advair

For the Salmeterol 50 comparisons (i.e., the comparisons that evaluated the efficacy of the Fluticasone component of the combination product), the primary endpoint was **Percent of Patients Remaining in Study**. The protocol analysis was a log-rank test that censored patients who discontinued due to reasons other than lack of efficacy. Therefore, a more meaningful wording of the primary efficacy variable would be: the percent of patients discontinuing due to lack of efficacy. Before beginning the scheduled clinical assessments for Visits 3-10, the latest diary card information and PFT results were assessed to determine subject stability. To continue in the study, each subject had to have satisfied all of the following diary card and PFT criteria at each visit:

- ≤ 2 days within the 7 days immediately preceding the visit in which ≥12 puffs/day of Ventolin are used.
- ≤ 2 nights with awakenings due to asthma requiring treatment with Ventolin during the 7 days preceding the visit.
- ≤ 3 days during the 7 days immediately preceding the visit in which the subject is below the PEFR stability limit calculated at Visit 2 (see below).
- An FEV1 at each visit ≥ FEV1 Stability Limit calculated at Visit 2

PEFR Stability Limit: 20% decrease in the mean morning PEFR recorded on the diary cards from the 7 days preceding Clinic Visit 2, including the morning PEFR on the day of Clinic Visit 2.

FEV1 Stability Limit: 20% decrease in the best FEV1 obtained at the Clinic Visit 2, 30 minute pre-dose pulmonary function test.

If a patient did not meet these continuation criteria, s/he was discontinued and the reason was considered to be "lack of efficacy". Patients were also discontinued due to lack of efficacy if they experienced a clinical asthma exacerbation requiring emergency intervention, hospitalization, or treatment with asthma medications in addition to those allowed by the protocol.

Efficacy Evaluation of Salmeterol Component in Advair

For the Fluticasone 100 and 250 comparisons with the combination product, the two co-primary efficacy variables were **AM pre-dose FEV1** at endpoint (last visit) and **FEV1 AUC during 12-**

hour serial pulmonary function tests obtained following 1 week of treatment. At every visit, each measurement of FEV1 was done in triplicate, and the best effort, defined as the highest of the triplicate values, was captured electronically.

Additionally, on Treatment Day 1, and after 1 and 12 weeks of treatment, twelve hour serial pulmonary function tests were performed at these timepoints: 30 minutes (±5 minutes) prior to dosing with study drug, immediately prior to study drug dosing, and at 30 minutes (±5 minutes), 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 10 hours and 12 hours (±15 minutes for hourly determinations) post dosing. At each of the time points triplicate determinations were done.

At each clinic visit, the highest of three measurements of **AM pre-dose FEV1** values was captured electronically. Patients withheld short-acting inhaled Beta2-agonist therapy for at least 6 hours before each clinic visit. Patients were reminded not to take their study medication on the morning of their clinic visits. The method used to analyze this variable was an ANOVA with change from baseline FEV1 to last valid pre-dose FEV1 (endpoint) as the dependent variable and treatment, and "cluster" as factors. (In Study 3002, an indicator variable for prior inhaled corticosteroid use was also included as a factor.) "Cluster" was a variable that denoted a location for a particular center. Centers were grouped according to location if their sample size was < 20. If their sample size was ≥ 20, they were considered to be a "cluster" in and of themselves and not combined with other centers.

The method used to analyze **FEV1 AUC** after one week of treatment (Visit 3) was an Analysis of Variance (ANOVA) with change from baseline FEV1 as the dependent variable, and treatment, and "cluster" as factors. (In Study 3002, an indicator variable for prior inhaled corticosteroid use was also included as a factor.) "Baseline FEV1" was the average of the two pre-dose measurements (30 minutes prior to dosing and immediately prior to dosing) *at Visit 2*, the baseline visit. It is assumed that the reason the sponsor used the pre-dose measurements from Visit 2 to calculate the AUC at Visit 3 was because the pre-dose FEV1 measurements at Visit 3 were expected to be much higher for some patients. The higher the pre-dose measurements, the lower the AUC values. In order not to penalize the treatment groups with higher mean pre-dose measurements at Visit 3, the sponsor chose to use the pre-dose measurements at Visit 2 for the baseline value in the calculation of the change from baseline AUC scores. The decision to use the Visit 2 pre-dose values to calculate the AUC at Visit 3 was described in the protocol.

Even though only one comparison was the "primary" comparison for each of these three primary variables, it appears as though the sponsor put all four treatment groups into the model and used contrasts and pairwise comparisons for the test of the "primary" comparison for the AM FEV1 and FEV1 AUC analyses. This reviewer analyzed the data in more limited models and found that the conclusions were the same.

Secondary Efficacy Variables

The sponsor also recorded and analyzed the following efficacy measures, comparing each arm to the others:

- Percent of Predicted Normal FEV1
- Morning and Evening PEFR
- Asthma Quality of Life Questionnaire (AQLQ)
- Sleep Related Quality of Life Using the Sleep Scale
- Asthma Symptom Scores
- Nights With Awakenings Due to Asthma
- Rescue Ventolin Usage

The results of these secondary efficacy variables will not be presented in this review (see the reviewing medical officer's review).

2 Results

2.1 Investigative Sites

A total of 42 centers participated in Study 3002 and 40 in 3003 (see Table 5 below). Twelve centers participated in both studies. Of the 42 centers that participated in Study 3002, 36 randomized any patients; and 39 out of the 40 centers in Study 3003 randomized patients. The centers that did not randomize patients participated in both studies and randomized patients into the other study. The center that enrolled the most patients was Dr. Chervinsky, with 31 patients in Study 3002 and 21 in Study 3003. The most remarkable thing about this center was that with 52 patients total, virtually all patients screened were eligible for randomization (94% and 95% in Studies 3002 and 3003 respectively) and of the patients who were randomized, 100% completed the entire study, had no protocol violations, and were included in the efficacy population. Dr. Chervinsky was audited for both studies. No major violations were found.

One of the centers, Dr. Thomas Edwards, was under investigation for [redacted] during the time of this review. Unless otherwise indicated, his data have been excluded from all analyses presented in this review.

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ble 6: Investigators Sorted in Order of Total Number of Patients Randomized into Both Studies

stigator	Study 3002 Number Screened	Number Rand-omized	Percent Rand-omized	# Incor-rectly Rand-omized	Number in Efficacy Population	Study 3003 Number Screened	Number Rand-omized	Percent Rand-omized	# Incor-rectly Rand-omized	Number in Efficacy Population	Total # Rand-omized	Percent of Total in Efficacy Population(s)
rvinsky P	33	31	94		31	22	21	95		21	52	100
nstein S	27	27	100		24	19	12	63		11	39	90
ards T	30	21	70		21	16	12	75	1	11	33	97
or J	21	14	67	3	11	21	17	81		17	31	90
e J	18	18	100		18	9	9	100		8	27	96
dom H	8	5	63		5	24	19	79		19	24	100
rman D	19	12	63	4	7	18	11	61	1	9	23	70
noff A	10	8	80		8	19	14	74		14	22	100
en R	28	21	75		21						21	100
biro G	11	7	64		7	17	14	82		13	21	95
s G	32	19	59	1	18						19	95
as J						22	19	86		19	19	100
T	18	17	94		16						17	94
orce C	21	17	81		17						17	100
nell D	19	16	84		16						16	100
ak A	3	2	67		2	17	14	82	1	11	16	81
tealegre F	15	10	67	2	7	6	5	83	1	3	15	67
er J						18	14	78		14	14	100
ry W						18	14	78	1	12	14	86
rence M						25	13	52		13	13	100
delson L						14	12	86		12	12	100
< Z	4		0			15	12	80		11	12	92
: D	15	11	73		11						11	100
er H	20	11	55		11						11	100
iru M	16	11	69	1	10						11	91
an R	19	11	58		11						11	100
dewalker M						15	11	73		9	11	82
e M	2		0			17	11	65		11	11	100
n K						16	10	63		9	10	90
erg E	9	5	56		5	6	5	83		5	10	100
rmed J	13	10	77	1	9						10	90
kow W						11	10	91		10	10	100
nael G	11	10	91		10						10	100
er J						14	9	64		8	9	89
e R						9	9	100		7	9	78
rman M						9	6	67		6	6	100
T						7	6	86		6	6	100
anroth M	11	6	55	1	5						6	83
nt S	10	5	50		5						5	100
vart G	11	5	45		5						5	100
nas D						5	5	100		5	5	100
on T						8	5	63		5	5	100
demi J	9	4	44		4						4	100
n J						6	4	67		4	4	100
sman J						8	4	50		4	4	100
lson M						6	4	67		0	4	0
ido G	6	4	67		4						4	100
son J	4	4	100	1	3						4	75
ard W	4	4	100		4						4	100
l W						7	4	57		4	4	100
ch G						6	3	50		3	3	100
vam D	10	3	30		3						3	100
be R						5	3	60		3	3	100
ll N	3		0			9	3	33		3	3	100
stein A	3	3	100		2						3	67

Flutica-sone
84
45 (54%)
75 (89%)
40±16
40
18-67
0
23 (27%)
61 (73%)

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2.4 *Subject Accountability*

A total of 356 patients were randomized into Study 3002 and 331 patients in Study 3003. In both studies, all randomized patients received at least one dose of treatment. The table below shows the sponsor's calculations of the total number of patients who withdrew and those who were withdrawn due to lack of efficacy. The placebo group had a very large percentage of dropouts in both studies (66% and 72% in Studies 3002 and 3003, respectively). The Salmeterol group followed with 45% and 51% in Studies 3002 and 3003. Fluticasone had 26% and 27%, and finally the combination product had an 18% and 17% dropout rate in the two studies, 3002 and 3003, respectively. The large number of placebo and Salmeterol dropouts make comparisons involving these two arms difficult.

Table 9: Sponsor's Table (including Thomas Edwards)

	Study 3002			Study 3003		
	Total N Random-ized	Total Number (%) With-drawn	# (%) With-drawn Due to Lack of Efficacy	Total N Random-ized	Total Number (%) With-drawn	# (%) With-drawn Due to Lack of Efficacy
Placebo	82	54 (66%)	41 (50%)	93	67 (72%)	58 (62%)
Combination (SF)	92	17 (18%)	3 (3%)	84	14 (17%)	4 (5%)
Salmeterol	92	41 (45%)	32 (35%)	38	45 (51%)	33 (38%)
Fluticasone	90	23 (26%)	10 (9%)	84	23 (27%)	19 (23%)

This reviewer could not replicate the sponsor's results using a cutoff number for days on study. However, the results of a tabulation of the number of patients who had fewer than 84 days on study, and the number who had fewer than 80 days on study were similar to those of the sponsor's. The numbers are presented in the appendix Table 1. The results presented below exclude Thomas Edwards' data. The primary comparison for this endpoint was between Combination and Salmeterol. The Combination product had lower percentages of dropouts than the Salmeterol group in both studies, no matter how dropout was defined. The results were similar in both strata of patients (those who used salmeterol prior and those who used inhaled corticosteroids prior). In both studies, the treatment groups were ordered as follows, from least percent of dropouts to most: Combination, Fluticasone, Salmeterol and Placebo. Among the subset of patients with prior salmeterol use in Study 3002, the Fluticasone group appeared to have similar rates of dropout as the combination product.

Table 10: Number and Percent of Patients Who Were On Study For <84 and <80 Days Excluding Thomas Edwards' Data

	Study 3002			Study 3003		
	Total N Random-ized	# (%) <84 Days On Study	# (%) <80 Days On Study	Total N Random-ized	# (%) <84 Days On Study	# (%) <80 Days On Study
Placebo	77	53 (69%)	49 (64%)	90	65 (72%)	61 (68%)
Combination (SF)	87	26 (30%)	14 (16%)	81	20 (25%)	10 (12%)
Salmeterol	86	41 (48%)	33 (38%)	85	45 (53%)	40 (47%)
Fluticasone	85	30 (35%)	21 (25%)	81	28 (35%)	21 (26%)

* Percentages are almost identical including Thomas Edwards' data; from Placebo to Fluticasone in the same order as in the table, defined as <84 days Study 3002: 70, 29, 49, and 34 percent; Study 3003: 73, 25, 53, and 35 percent. The full table is provided in the appendix Table 1.

The sponsor's presentation of the results of the protocol analysis are provided below. For Study 3002, the sponsor demonstrated statistically significant differences when comparing Advair to both placebo and Salmeterol. In Study 3003, Advair was statistically significantly different from placebo, Salmeterol and Fluticasone.

Table 13: Study 3002 Sponsor's Results Probability of Remaining in Study (Volume 55, page 66)
Includes Dr. T. Edwards

	Placebo	SFC 50/100	Salmeterol 50 mcg	FP 100 mcg
Probability of Remaining in the Study; n patients withdrawn due to lack of efficacy				
Efficacy Population[a]	40	3[b,c]	32[b]	8[b]
Intent-to-Treat Population[a]	41	3[b,c]	32[b]	9[b]

[a] overall treatment effect ($p<0.001$)
[b] differs from placebo ($p\leq0.007$)
[c] differs from salmeterol 50 mcg ($p<0.001$)

Table 14: Study 3003 Sponsor's Results Probability of Remaining in Study (Volume 64, page 58)
Includes Dr. T. Edwards

	Placebo	SFC 50/250	Salmeterol 50 mcg	FP 250 mcg
Probability of Remaining in the Study; n patients withdrawn due to lack of efficacy				
Efficacy Population[a]	56	4[b,c]	28[b]	19[b]
Intent-to-Treat Population[a]	58	4[b,c]	33[b]	19[b]

[a] overall treatment effect ($p<0.001$)
[b] differs from placebo ($p<0.001$)
[c] differs from salmeterol 50 mcg and fluticasone propionate 250 mcg ($p\leq0.001$)

Table 15: Reviewer's Results Probability of Remaining in Study
Excludes Dr. T. Edwards
Intent-to-Treat
No censoring
P-values obtained from a Log-Rank Test

		Placebo	Advair	Salmeterol	Fluticasone
Study 3002	Median Time to Dropout	21	NA	NA	NA
	p-value comparison to Placebo		0.0001	0.0011	0.0001
	p-value comparison to Advair			0.0042	0.3328
Study 3003	Median Time to Dropout	29	NA	83	NA
	p-value comparison to Placebo		0.0001	0.0013	0.0001
	p-value comparison to Advair			0.0001	0.1119

NA: not applicable: less than 50% of the patients in this treatment group dropped out, therefore, the time at which 50% of the patients dropped out cannot be calculated.

The reviewer's results are similar to the sponsor's, with the exception of one comparison (Fluticasone vs. Advair in Study 3003). Fluticasone was not statistically significantly different from Advair in either Study 3002 or 3003, using the reviewer's analyses.

Kaplan-Meier curves (without censoring patients who dropped out due to reasons other than lack of effect) are provided below for both studies (and in Study 3002, for both subsets). The placebo patients who had previously used Inhaled Corticosteroids dropped out earlier and more often than patients who had previously used Salmeterol. Among the patients who had previously used Salmeterol, the dropout pattern did not appear to differ between Fluticasone and Advair.

Figure 1: Study 3002: Probability of Patients Remaining in Study by Treatment Group
(Includes Dr. T. Edwards: Total N=356)

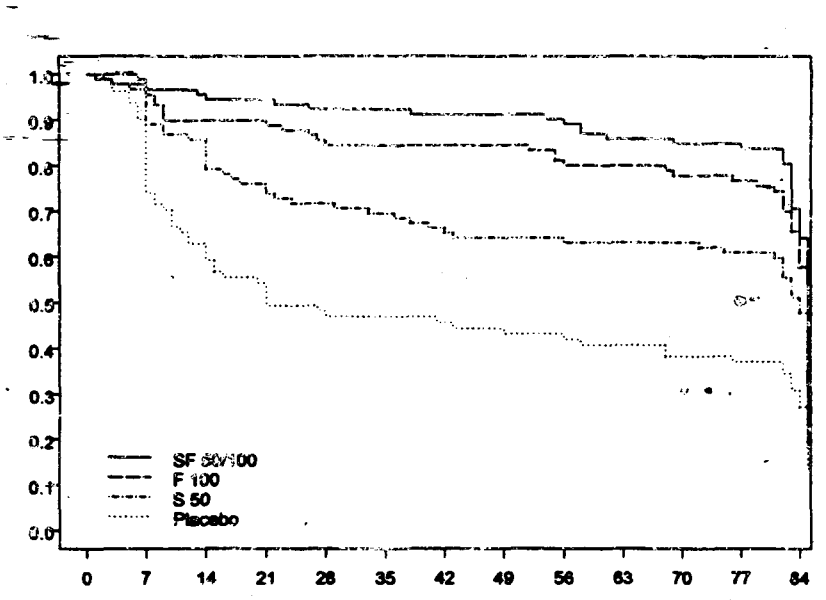
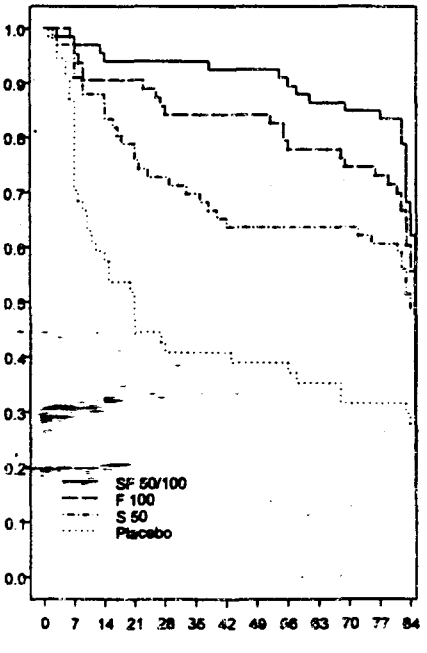


Figure 2: Study 3002: Probability of Patients Remaining in Study by Treatment Group and by Prior Use Status
(Includes Dr. T. Edwards)

Total N =250

Prior Use: Inhaled Corticosteroids



Total N=106

Prior Use: Salmeterol

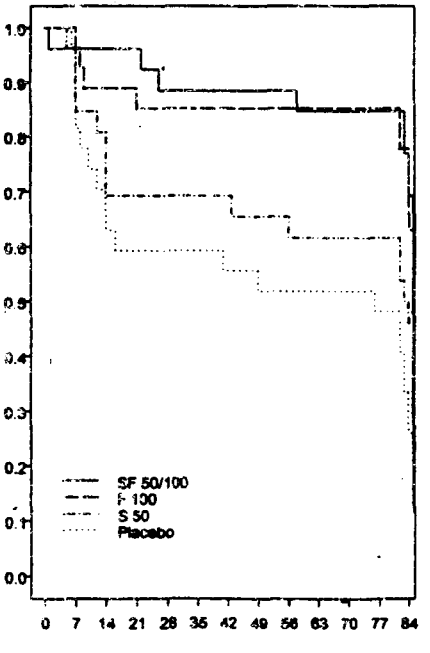
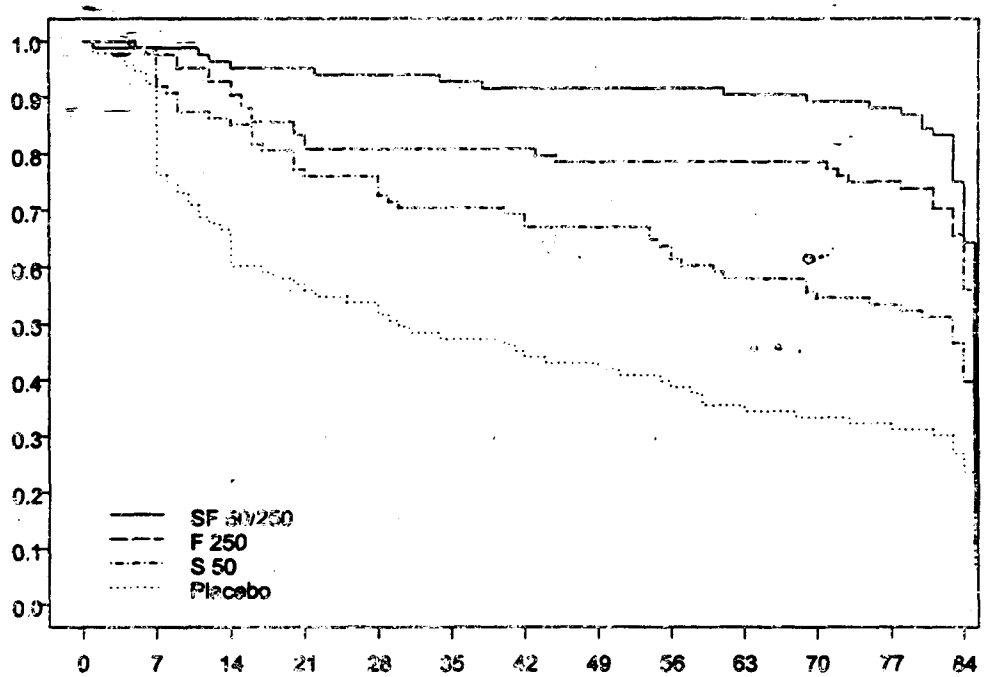


Figure 3: Study 3003: Probability of Patients Remaining in Study by Treatment Group
(Includes Dr. T. Edwards: Total N=349)



2.6 AM FEV1 (Pre-Dose)

As mentioned above, the Salmeterol component of the combination product was evaluated by comparing the Combination product with Fluticasone using two co-primary endpoints: AM FEV1 at endpoint and AUC values at Visit 3. The pre-dose AM FEV1 values at the patient's last visit were compared with the Visit 2 (baseline) pre-dose AM FEV1 values. Recall that there were 2 pre-dose values (30 minutes prior to dosing and just prior to dosing).

The mean values of AM FEV1 were plotted at each time point in Figures 4-6, below. No data were carried forward to compute these means. The mean estimates for the Placebo and Salmeterol groups towards the middle and end of the study should be viewed with caution due to the large dropout rates.

Figure 6 depicts a difference between "Prior Use Status" subgroups in the magnitude of response. The patients who used Salmeterol prior to the study, rather than inhaled corticosteroids, demonstrated a greater response to the study treatment, regardless of treatment group. However, the *difference between Advair and Fluticasone* treatment arms was smaller amongst the patients who used Salmeterol prior to the study than those who used inhaled corticosteroids. There was a total of 52 patients with prior Salmeterol use randomized to the Fluticasone and Advair arms. Due to the small numbers of patients, and the small mean differences seen over time in AM FEV1 between Fluticasone and Advair, the efficacy of the Salmeterol component of the combination product has not been clearly established based on this endpoint in the population of patients who used Salmeterol prior to the study.

Figure 4: Study 3002: Change from Baseline in Morning Predose FEV1 by Treatment Group (Includes Dr. T. Edwards)

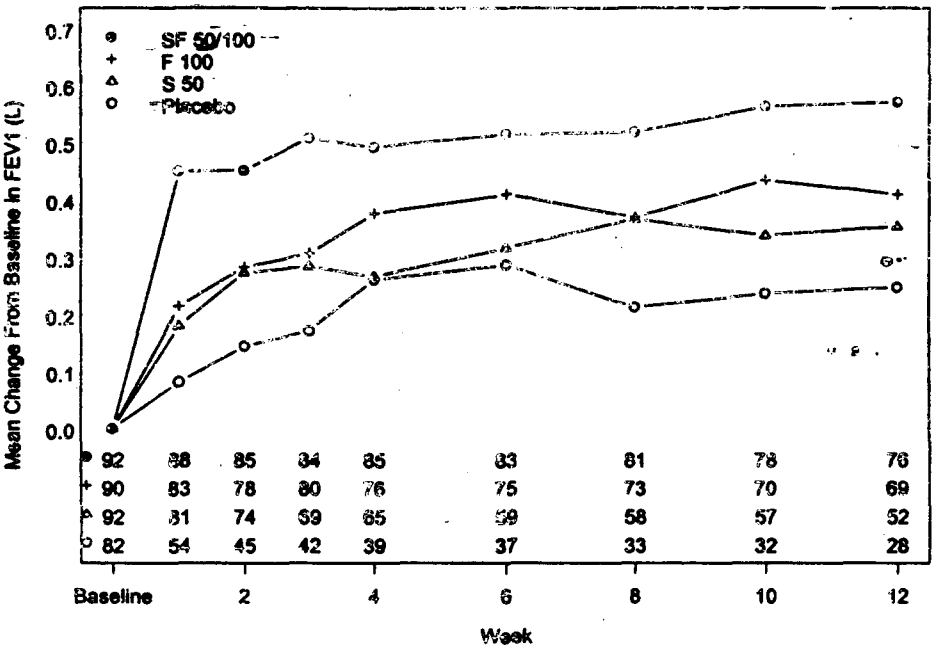


Figure 5: Study 3002: Change from Baseline in Morning Predose FEV1 by Treatment Group and Prior Use Status (Includes Dr. T. Edwards)

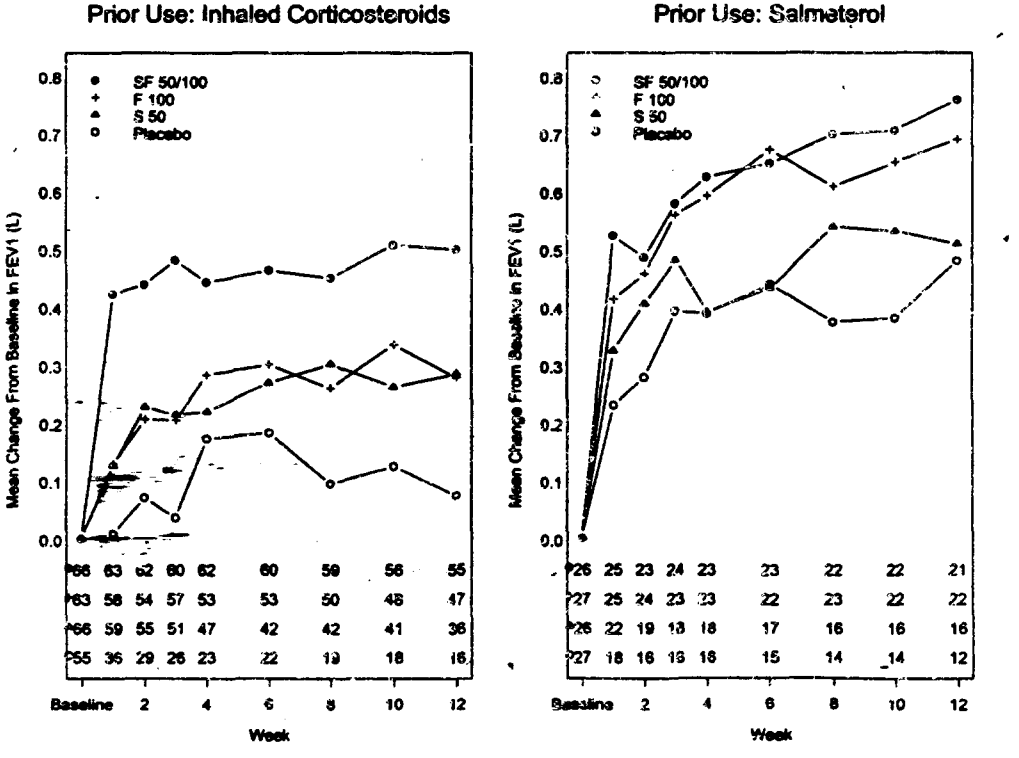
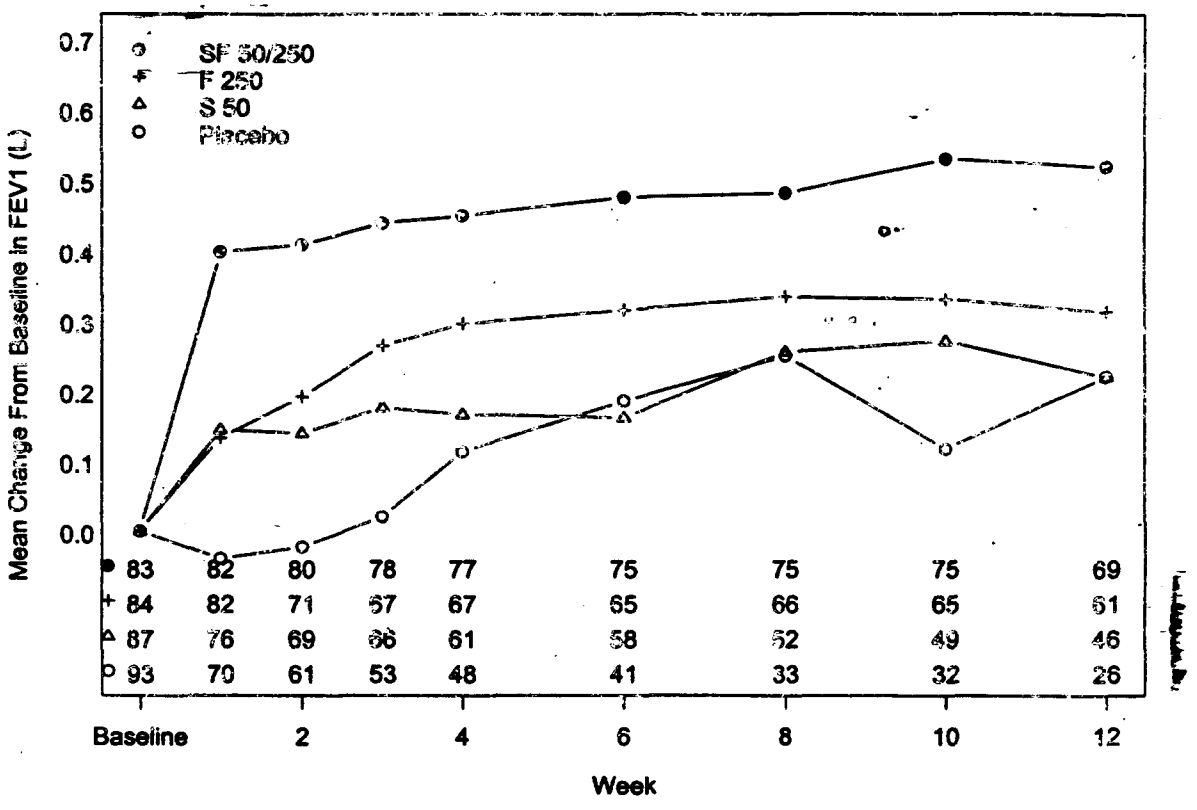


Figure 6: Study 3003: Change from Baseline in Morning Predose FEV1 by Treatment Group (Includes Dr. T. Edwards)



Descriptive statistics and results from analyses are provided in Tables 16-17, below, excluding Dr. T. Edwards' data. The results were similar without his data. Patient #1513 was randomized to the Salmeterol group in Study 3003. The sponsor did not provide any FEV1 data for this patient. Therefore, the number of patients in the Salmeterol group in Study 3003 is 84, rather than 85.

Descriptive statistics are provided below for Visit 2, endpoint and change from baseline for each treatment group. Study 3002 is divided into two groups, those who used Inhaled Corticosteroids (IC) prior to randomization, and those who used Salmeterol. The baseline values for both subgroups look similar, with the "IC Use Prior" group having slightly higher values. However, the change from baseline values are different across the subgroups. The most striking difference occurs in the two placebo groups. The "IC Use Prior" placebo group experienced a slight mean decrease in AM PEV1 (-0.06 L) whereas the "Salmeterol Use Prior" placebo group experienced an increase of 0.24 L. The difference in dropout rates may have confounded this result (IC Use Prior Placebo: 68%, Salmeterol Use Prior Placebo: 54%). The other treatment groups were similar across subgroups with the treatment arms in the "IC Use Prior" subgroup having slightly smaller mean changes from baseline than those in the "Salmeterol Use Prior" subgroup. The results of Study 3003 resemble those of the "IC Use Prior" subgroup from Study 3002 for all three variables (Visit 2, Endpoint and Change).

Table 16: Study 3002 AM FEV1 at Endpoint (last valid FEV1 value) by Treatment & Strata
Excludes T. Edwards

		Visit 2 (Average of 30 min prior and just prior to dosing)				Endpoint (Average of 30 min prior and just prior to dosing)				Change			
	n	Mean	Std Dev	Min	Max	Mean	Std Dev	Min	Max	Mean	Std Dev	Min	Max
IC Use Prior													
Placebo	53	2.12	0.58			2.06	0.63			-0.06	0.40		
SF 50/100	63	2.26	0.58			2.70	0.74			0.44	0.43		
S 50	63	2.14	0.64			2.27	0.77			0.14	0.43		
F100	61	2.15	0.58			2.35	0.71			0.20	0.36		
Salmeterol Use Prior													
Placebo	24	2.22	0.49			2.46	0.76			0.24	0.52		
SF 50/100	24	1.95	0.61			2.60	0.80			0.65	0.54		
S 50	23	2.12	0.57			2.44	0.83			0.32	0.52		
F 100	24	2.02	0.72			2.62	0.89			0.60	0.53		

Table 17: Study 3003 AM FEV1 at Endpoint (last valid FEV1 value) by Treatment
Excludes T. Edwards

		Visit 2 (Average of 30 min prior and just prior to dosing)				Endpoint (Average of 30 min prior and just prior to dosing)				Change			
	n	Mean	Std Dev	Min	Max	Mean	Std De	Min	Max	Mean	Std Dev	Min	Max
Placebo	90	2.19	0.63			2.16	0.74			-0.03	0.40		
SF 50/100	81	2.23	0.66			2.71	0.81			0.48	0.44		
S 50	84	2.20	0.57			2.30	0.60			0.10	0.38		
F100	81	2.12	0.52			2.36	0.63			0.24	0.41		

The primary comparison for the AM FEV1 efficacy endpoint was Advair versus Fluticasone. The model used to test the difference in mean change from baseline was an ANOVA with treatment and center cluster. In Study 3002, a binary variable indicating the prior use strata was included in the model. The results demonstrated a statistically significant difference between Advair and Fluticasone in both studies. Comparisons with either the Placebo group or the Salmeterol group are unreliable due to the high dropout rates in both arms.

Treatment interactions with center, center cluster, and prior use strata (Study 3002 only) were tested at the conservative level of alpha=0.25 and not found to be statistically significant. Even though the treatment-by-prior use strata interaction term in Study 3002 was not statistically significant, the unadjusted means were indicative of little difference between the combination product and fluticasone in the Salmeterol Prior Use group, see Table 16, above, (SF 50/100: 0.65 L; F 100: 0.60 L). Adjusting for center cluster differences does not account for the small differences between the treatments (an ANOVA performed on Salmeterol Prior Use patients only, yielded LS Means SF 50/100: 0.64 L; F 100: 0.59 L). The results presented in this review exclude Dr. T. Edwards data. The results were similar to those with his data.

Table 18: Results of AM FEV1 Analyses
Excludes T. Edwards

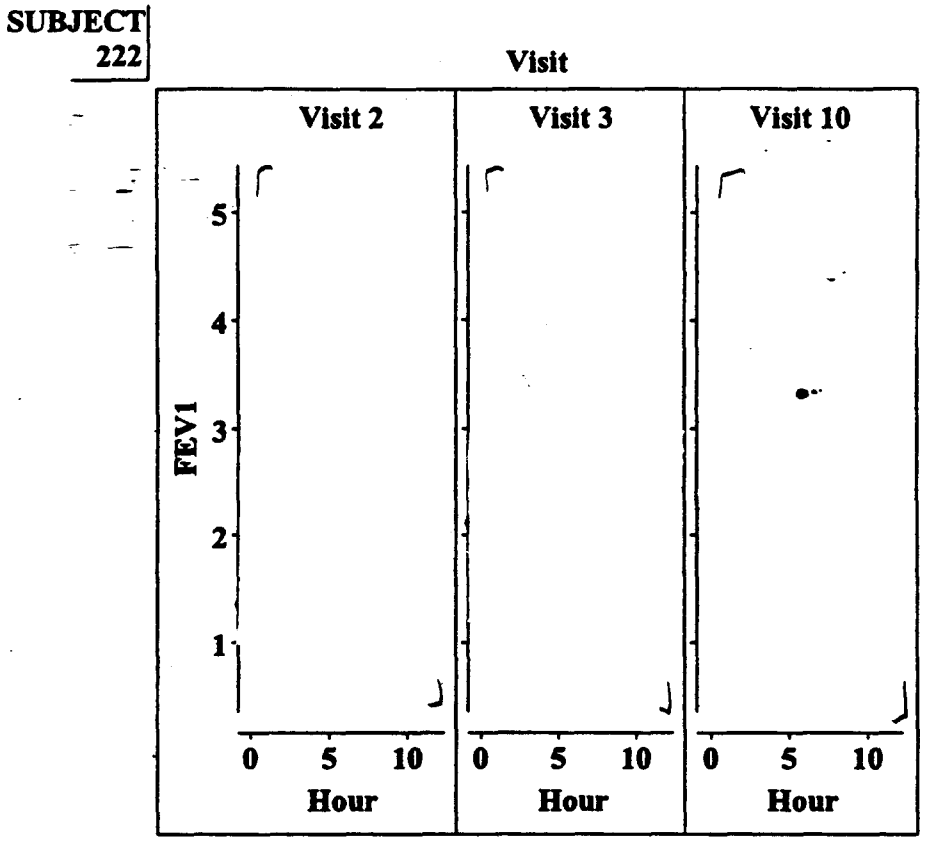
Study 3002 ANOVA: treatment, cluster, prior use strata	n	LS Mean Change	Study 3003 ANOVA: treatment, cluster	n	LS Mean Change
Placebo	77	0.055	Placebo	90	-0.039
SF 50/100	87	0.533	SF 50/250	81	0.476
S 50	86	0.220	S 50	84	0.087
F100	85	0.348	F250	81	0.232
	Diff	**p-value**		**Diff**	**p-value**
SF 50/100 vs. F 100	0.185	0.0048	SF 50/250 vs. F 250	0.244	0.0002
SF 50/100 vs. Placebo	0.478	0.0001	SF 50/250 vs. Placebo	0.515	0.0001
SF 50/100 vs. S 50	0.313	0.0001	SF 50/250 vs. S 50	0.389	0.0001
F 100 vs. Placebo	0.293	0.0001	F 250 vs. Placebo	0.271	0.0001
S 50 vs. Placebo	0.165	0.0143	S 50 vs. Placebo	0.126	0.0463
F 100 vs. S 50	0.128	0.0510	F 250 vs. S 50	0.319	0.0256

2.7 Visit 3 AUC Relative to Visit 2 Pre-dose FEV1

The second co-primary endpoint for the Salmeterol evaluation (Combination product versus Fluticasone) was the change in the AUC value at Visit 3 as compared to Visit 2. More specifically, the area under the curve at Visit 3 was calculated using the Visit 2 pre-dose FEV1 as baseline. In general, patients had higher FEV1 values at Visit 3 prior to dosing than at Visit 2 prior to dosing (see appendix Tables 4-7). The increase was most pronounced among the patients randomized to Advair. Since these patients had greater lung function prior to dosing at Visit 3, the FEV1 response to receiving the drug was small. The AUC values at Visit 3 were small. In order not to penalize the treatment arm with higher mean FEV1 values prior to dosing at Visit 3, and to make use of the FEV1 curve at Visit 3, the baseline value at Visit 2 was used for the "floor value" at Visit 3 to calculate an "alternative AUC" at Visit 3. As specified in the protocol, the "change in AUC" variable was then calculated by subtracting the AUC value at Visit 2 from the "alternative AUC" value at Visit 3.

Several patients did not stay in the clinic the entire day at Visit 2 or 3, or had missing values in the middle of the day, with observed measurements on either side of the missing timepoint ("bounded missing"). The percentages of patients with missing data at either visit were greatest among the placebo patients and least among the combination product patients, in both studies. This phenomenon is indicative of poor study conduct and diminishes the reliability of the results. The sponsor chose to use Last Observation Carried Forward (LOCF) to impute data for patients who did not remain in the clinic for the entire day of serial FEV1 measurements. The FEV1 curves were quite unpredictable for some patients and this reviewer does not consider LOCF a viable option for imputation. For example, the serial FEV1 values for Patient #222 are plotted in Figure 7 below. If this patient had discontinued in the early part of the day, the AUC value would be largely overestimated. There is no reason to believe that values would stay constant over time in this situation. In fact, the values are expected to drop. The results of serial measurements in patients who remained in the clinic the entire day depicted instances of values increasing to an apex and then dropping, and instances of fluctuating values over the course of the day. It is difficult to predict the direction of bias the LOCF method may have introduced.

Figure 7: Serial FEV1 Measurements for Patient #222



Since it is difficult to predict the FEV1 curve for a given patient, the reviewing medical officer requested that the following procedures be used for the analyses performed for this review:

- for patients with missing data after Time=X at Visit 3, use the baseline curve (Visit 2) in place of the Visit 3 curve, and
- for patents with "bounded" missing data, interpolate the missing values using the values on either side of the missing data.

Two separate analyses were performed for this review. The first analysis uses all patients with full AUC data at Visit 3 (Subset #1). The second analysis uses all patients with full AUC data at Visit 3 or Visit 2 (Subset #2).

The table below provides the numbers of patients who had full AUC data at both Visits 2 and 3; patients with full data at Visit 2, but not at Visit 3; patients with full data at Visit 3, but not at Visit 2; and patients with missing data at both visits. The treatment group with the greatest percentage of patients with missing data at one or both visits was the placebo group, whereas Advair had the least percentage. If a patient left the clinic due to lack of effect, excluding these patients will yield a subgroup of patients that has greater FEV1 values, and/or AUC values. The fact that the missing data is related to treatment group makes the results of the analyses (both the sponsor's and the reviewer's) less reliable.

Table 20: Reviewer's Results of AUC Analyses Using Subset #1 (described in text)
Excludes T. Edwards

Study 3002 ANOVA: treatment, cluster, prior use strata	n	LS Mean Change
Placebo	64	3.092
SF 50/100	86	7.688
S 50	85	5.266
F100	80	3.882

	Diff	p-value
SF 50/100 vs. F 100	3.806	0.0001
SF 50/100 vs. Placebo	4.596	0.0001
SF 50/100 vs. S 50	2.422	0.0001
F 100 vs. Placebo	0.790	0.3279
S 50 vs. Placebo	2.174	0.0067
F 100 vs. S 50	-1.384	0.0642

Study 3003 ANOVA: treatment, cluster	n	LS Mean Change
Placebo	72	0.877
SF 50/250	78	6.490
S 50	77	3.642
F250	72	2.580

	Diff	p-value
SF 50/250 vs. F 250	3.910	0.0001
SF 50/250 vs. Placebo	5.613	0.0001
SF 50/250 vs. S 50	2.848	0.0001
F 250 vs. Placebo	1.703	0.0119
S 50 vs. Placebo	2.765	0.0001
F 250 vs. S 50	1.062	0.1086

Table 21: Reviewer's Results of AUC Analyses Using Subset #2 (described in text)
Excludes T. Edwards

Study 3002 ANOVA: treatment, cluster, prior use strata	n	LS Mean AUC
Placebo	40	3.661
SF 50/100	83	7.751
S 50	74	5.421
F100	72	4.080

	Diff	p-value
SF 50/100 vs. F 100	3.671	0.0001
SF 50/100 vs. Placebo	4.090	0.0001
SF 50/100 vs. S 50	2.330	0.0034
F 100 vs. Placebo	0.419	0.6704
S 50 vs. Placebo	1.760	0.0742
F 100 vs. S 50	-1.341	0.1033

Study 3003 ANOVA: treatment, cluster	n	LS Mean AUC
Placebo	49	0.739
SF 50/250	77	6.456
S 50	62	3.973
F250	66	2.703

	Diff	p-value
SF 50/250 vs. F 250	3.753	0.0001
SF 50/250 vs. Placebo	5.717	0.0001
SF 50/250 vs. S 50	2.483	0.0007
F 250 vs. Placebo	1.964	0.0156
S 50 vs. Placebo	3.234	0.0001
F 250 vs. S 50	-1.270	0.0897

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3 Conclusions

The sponsor submitted five adult studies and one pediatric study to support the efficacy and safety of the combination product, Advair for the maintenance treatment of asthma — _____ - in patients 12 years of age and older. The sponsor is seeking a claim for two groups of patients: those maintained on inhaled corticosteroids, and those maintained on Salmeterol.

Study 3002 was a 12-week placebo-controlled study (n=356) evaluating the efficacy and safety of the 50/100 dose of Advair in patients ages 12-70. Study 3003 was a 12-week (n=349) placebo-controlled study evaluating the efficacy and safety of the 50/250 dose of in patients ages 12-69.

In both studies, three efficacy outcomes were designated as co-primary endpoints. The first, "percent of patients remaining in the study" was used to evaluate the efficacy of the Fluticasone component in Advair. The second and third endpoints, AM pre-dose FEV1 change after one week and FEV1 AUC change after 1 week, were used to evaluate the efficacy of the Salmeterol component in Advair. Statistical significance was achieved for all three co-primary endpoint comparisons, in both studies. Comparisons of efficacy measurements with placebo and Salmeterol are not reliable due to the large percentages of dropouts in these two groups.

Only one of the six studies submitted (Study 3002) randomized patients previously maintained on Salmeterol alone. Due to the small numbers of patients in this subset (approximately 24 per treatment group) and the small mean differences between Advair and Fluticasone, Study 3002 provided insufficient evidence that the Salmeterol component in Advair was beneficial to patients who were previously on Salmeterol.

The treatment effects of the FEV1 AUC values should be evaluated with caution because 20% of patients in Study 3002 and 29% in Study 3003 did not provide a full day of 12-hour serial FEV1 measurements at the baseline and week 1 visits. The percentages of patients whose FEV1 curves could not be estimated were different across treatment groups. Since the missing serial FEV1 data were related to treatment group, the results of the AUC measurements are less reliable.

/S/

Barbara Elashoff

Concur: Dr. Wilson /S/ 1-20-00

cc:
Orig. NDA 21-077
HFD-570 / Division File
HFD-570 / PJani, SJohnson, RMeyer
HFD-715 / Division File, SWilson, BElashoff

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Appendix Table 1: Number and Percent of Patients Who Were On Study For <84 and <80 Days Including Thomas Edwards' data

	Study 3002			Study 3003		
	Total N Random-ized	# (%) <84 Days On Study	# (%) <80 Days On Study	Total N Random-ized	# (%) <84 Days On Study	# (%) <80 Days On Study
Placebo	82	57 (70%)	52 (63%)	93	68 (73%)	64 (69%)
Combination (SF)	92	27 (29%)	15 (16%)	84	21 (25%)	11 (13%)
Salmeterol	92	45 (49%)	36 (39%)	88	47 (53%)	42 (48%)
Fluticasone	90	31 (34%)	22 (24%)	84	29 (35%)	22 (26%)

Appendix Table 2: Study 3002 by Prior Use Group Number and Percent of Patients Who Were On Study For <84 and <80 Days

Including Thomas Edwards' data

Study 3002	Salmeterol Use Prior n=106			Inhaled Corticosteroid Use Prior n=250		
	Total N Random-ized	# (%) <84 Days On Study	# (%) <80 Days On Study	Total N Random-ized	# (%) <84 Days On Study	# (%) <80 Days On Study
Placebo	27	18 (67%)	14 (52%)	55	39 (71%)	38 (69%)
Combination (SF)	26	6 (23%)	4 (15%)	66	21 (32%)	11 (17%)
Salmeterol	26	13 (50%)	10 (38%)	66	32 (48%)	26 (39%)
Fluticasone	27	6 (22%)	4 (15%)	63	25 (40%)	18 (29%)

Appendix Table 3: Number of Patients with Missing Data for FEV1 curve at Visits 2 and 3
Numbers exclude T Edwards (percentages similar when including T Edwards)
No FEV1 data for Patient #1513 (Salmeterol, Study 3003), therefore, the numbers add up to 84 instead of 85.

	Study 3002				Study 3003			
	Placebo	SF 50/100	S 50	F 100	Placebo	SF 50/100	S 50	F 100
Full Data	40	83	74	70	47	73	59	61
Both Visits, missing at V2	0	0	0	2	2	4	3	5
Total	40	83	74	72	49	77	62	66
Both Visits, missing at V3	4	1	3	3	10	1	8	5
Visit 2 only, no missing valu	20	2	8	5	13	0	7	1
Total	24	3	11	8	23	1	15	6
Visit 2 only, missing at V2	10	1	1	2	11	1	5	1
Both visits, missing at both	3	0	0	3	7	2	2	8
Total	13	1	1	5	18	3	7	9
ITT	82	92	92	90	93	84	88	84
ITT excluding T. Edwards	77	87	86	85	90	81	85	81
Full data at Visit 3	40 (52%)	83 (95%)	74 (86%)	72 (85%)	49 (53%)	77 (95%)	62 (73%)	66 (81%)
Full data at Visit 3 or Visit 2	64 (83%)	86 (99%)	85 (99%)	80 (94%)	72 (80%)	78 (96%)	77 (91%)	72 (89%)

Key:
Full Data: patients had full AUC curves at both visits (includes situations of "bounded missing"
Both Visits, missing at V2: patients were present at both visits, but had missing data at Visit 2
Both Visits, missing at V3: patients were present at both visits, but had missing data at Visit 3
Visit 2 only, no missing values: patients were present only at Visit 2, had full AUC curve
Visit 2 only, missing at V2: patients were present only at Visit 2, had missing data at Visit 2
Both visits, missing at both: patients were present at both visits, but had missing data at both

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Appendix Table 4: Study 3002: Descriptive Statistics of Visits 2 and 3

* Visit 3 AUC values presented in this table were calculated using the Visit 3 value prior to dosing. "Change in AUC" was calculated using Visit 2 baseline for Visit 2 and Visit 3 baseline for Visit 3.

		Visit 2 Baseline				Visit 2 AUC				Visit 3 Baseline				Visit 3 AUC				Change in AUC			
Prior Use: Inhaled Corticosteroids	N	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Full Data at Visit 3																					
Placebo	28	2.24	0.47			2.53	3.76			2.32	0.49			1.45	3.29			-1.08	4.33		
SF 50/100	61	2.28	0.57			5.98	5.19			2.70	0.72			2.27	2.61			-3.72	4.51		
S 50	55	2.19	0.65			5.28	3.85			2.31	0.71			3.17	3.18			-2.11	3.28		
F 100	53	2.21	0.56			2.00	2.03			2.36	0.69			1.39	2.11			-0.81	2.49		
Missing values at Visit 3, used Visit 2 Data for Visit 3																					
Placebo	14	1.94	0.63			1.47	3.01			2.20	0.81			0.65	2.02			-2.21	3.42		
SF 50/100	2	1.65	0.82			1.89	1.89														
S 50	8	1.85	0.51			3.54	2.90			1.71	0.75			-0.51	0.49			-0.18	0.72		
F 100	3	1.73	0.24			1.68	3.32														
No full AUC curve at either visit																					
Placebo	10	2.05	0.74			-1.21	0.78			1.90	1.02			-1.10	1.53			0.58	1.25		
SF 50/100																					
S 50																					
F 100	5	1.72	0.74			-0.82	1.41			2.12	0.54			-1.28	0.58			0.19	0.95		
Prior Use: Salmeterol																					
	N	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Full Data at Visit 3																					
Placebo	12	2.32	0.46			4.34	7.11			2.57	0.77			2.35	2.22			-1.99	7.63		
SF 50/100	22	1.96	0.63			5.36	3.53			2.45	0.65			2.16	2.02			-3.20	3.43		
S 50	19	2.13	0.56			6.11	4.09			2.47	0.74			2.25	2.25			-3.86	4.11		
F 100	19	2.04	0.58			3.85	5.25			2.50	0.76			0.34	2.60			-3.51	3.87		
Missing values at Visit 3, used Visit 2 Data for Visit 3																					
Placebo	10	2.07	0.55			3.76	4.05			2.38	0.36			-0.31	0.44			-5.61	5.64		
SF 50/100	1	2.11	-			14.89	-			3.44	-			1.95	-			-12.75	-		
S 50	3	2.35	0.54			4.84	3.87			1.73	-			6.42	-			1.93	-		
F 100	5	1.95	1.22			2.82	3.86			1.39	0.56			0.36	0.67			-2.76	3.71		
No full AUC curve at either visit																					
Placebo	2	2.36	0.11			0.45	0.78			2.97	-			-2.92	-			-2.82	-		
SF 50/100	1	1.66	-			0.71	-			-	-			-	-			-	-		
S 50	1	1.26	-			1.11	-			-	-			-	-			-	-		
F 100	0	-	-			-	-			-	-			-	-			-	-		

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Appendix Table 5: Study 3002 More Descriptive Statistics of Visits 2 and 3

		Visit 2 Baseline	Visit 3 Baseline	Visit 3 AUC Relative to Visit 2 Baseline				Change in AUC using Visit 2 Baseline for both AUCs			
Prior Use: Inhaled Corticosteroids											
	N	Mean	Mean	Mean	Std Dev	Min	Max	Mean	Std Dev	Min	Max
Full Data at Visit 3											
Placebo	28	2.24	2.32	2.52	4.55			-0.01	2.44		
SF 50/100	61	2.28	2.70	7.35	6.06			1.36	3.24		
S 50	55	2.18	2.31	4.80	4.72			-0.48	3.41		
F 100	53	2.21	2.36	3.11	3.64			1.10	2.54		
Missing values at Visit 3, used Visit 2 Data for Visit 3											
Placebo	14	1.94	2.20	1.47	3.01			0.00	0.00		
SF 50/100	2	1.65		1.89	1.69			0.00	0.00		
S 50	8	1.85	1.71	3.54	2.90			0.00	0.00		
F 100	3	1.73		1.68	3.32			0.00	0.00		
No full AUC curve at either visit											
Placebo	10	2.05	1.90								
SF 50/100											
S 50											
F 100	5	1.72	2.12								

Prior Use: Salmeterol											
	N	Mean	Mean	Mean	Std Dev	Min	Max	Mean	Std Dev	Min	Max
Full Data at Visit 3											
Placebo	12	2.32	2.57	5.41	6.58			1.07	2.66		
SF 50/100	22	1.96	2.45	8.10	4.37			2.74	3.18		
S 50	19	2.13	2.47	6.36	4.43			0.25	3.03		
F 100	19	2.04	2.50	5.92	6.37			2.07	2.36		
Missing values at Visit 3, used Visit 2 Data for Visit 3											
Placebo	10	2.07	2.38	3.76	4.05			0.00	0.00		
SF 50/100	1	2.11	3.44	14.69				0.00			
S 50	3	2.35	1.73	4.84	3.87			0.00	0.00		
F 100	5	1.95	1.39	2.82	3.86			0.00	0.00		
No full AUC curve at either visit											
Placebo	2	2.36	2.97								
SF 50/100	1	1.66									
S 50	1	1.26									
F 100	0										

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Appendix Table 6: Study 3003 Descriptive Statistics of Visits 2 and 3

* Visit 3 AUC values presented in this table were calculated using the Visit 3 value prior to dosing. "Change in AUC" was calculated using Visit 2 baseline for Visit 2 and Visit 3 baseline for Visit 3.

	N	Visit 2 Baseline Mean	SD	Min	Max	Visit 2 AUC Mean	SD	Min	Max	Visit 3 Baseline Mean	SD	Min	Max	Visit 3 AUC Mean	SD	Min	Max	Change in AUC Mean	SD	Min	Max
Full Data at Visit 3																					
Placebo	49	2.34	0.63			1.52	3.21			2.35	0.69			0.97	3.25			-0.55	3.22		
SF 50/250	77	2.23	0.67			4.95	3.35			2.62	0.74			1.91	2.32			-3.04	2.93		
S 50	62	2.25	0.58			4.54	3.43			2.44	0.82			1.89	2.81			-2.65	3.89		
F 250	66	2.15	0.55			1.86	2.68			2.33	0.61			0.65	2.27			-1.21	2.65		
Missing values at Visit 3, used Visit 2 Data for Visit 3																					
Placebo	23	2.03	0.60			0.89	3.21			1.99	0.58			-0.27	1.05			-1.17	4.40		
SF 50/250	1	1.84	-			9.26	-			2.75	-			2.77	-			-6.49	-		
S 50	15	2.16	0.55			2.26	1.82			1.93	0.48			1.03	1.30			-2.08	1.28		
F 250	6	2.09	0.32			0.85	0.75			1.97	0.37			0.42	0.73			-0.37	0.75		
No full AUC curve at either visit																					
Placebo	18	1.97	0.57			-0.25	1.30			1.82	0.45			-0.38	0.81			0.15	1.67		
SF 50/250	3	2.26	0.78			2.30	1.92			3.11	1.33			0.52	0.73			-2.64	2.44		
S 50	7	1.90	0.51			1.29	1.39			2.09	0.38			0.40	0.98			-1.44	0.22		
F 250	9	1.95	0.31			-0.68	1.40			1.92	0.34			-0.54	1.10			0.39	1.12		

Appendix Table 7: Study 3003 More Descriptive Statistics of Visits 2 and 3

	N	Visit 2	Visit 3	Visit 3 AUC Relative to Visit 2 Baseline Mean	Std Dev	Min	Max	Change in AUC using Visit 2 Baseline for both AUCs Mean	Std Dev	Min	Max
Full Data at Visit 3											
Placebo	49	2.34	2.35	1.03	4.50			-0.50	3.09		
SF 50/250	77	2.23	2.62	6.59	4.79			1.65	3.12		
S 50	62	2.25	2.44	4.18	3.32			-0.36	3.16		
F 250	66	2.15	2.33	2.90	3.78			1.04	2.38		
Missing values at Visit 3, used Visit 2 Data for Visit 3											
Placebo	23	2.03	1.99	0.89	3.21			0.00	0.00		
SF 50/250	1	1.84	2.75	9.26	-			0.00	-		
S 50	15	2.16	1.93	2.26	1.82			0.00	0.00		
F 250	6	2.09	1.97	0.85	0.75			0.00	0.00		
No full AUC curve at either visit											
Placebo	18	1.97	1.62								
SF 50/250	3	2.26	3.11								
S 50	7	1.90	2.09								
F 250	9	1.95	1.92								