CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-254

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical

NDA#:	21-254
APPLICANT:	Glaxo Wellcome Inc.
NAME OF DRUG:	Advair HFA (fluticasone propionate/ salmeterol) Inhalalation Aerosol 44 mcg/21 mcg, 110 mcg/21 mcg, 220 mcg/21mcg
INDICATION:	Treatment of Asthma in adults and adolescents
DOCUMENTS REVIEWED:	Volumes 1.1, 8.1-8.37 and datasets dated December 20, 2000 and March 15, 2001.

This review pertains to the evaluation of four Phase 3 studies in patients with asthma.

The medical officer for this submission is L. McClain, M.D. (HFD-570), with whom this review was discussed.

I. Background

This reviewer discovered that the original datasets provided did not contain important derived variables. The sponsor was requested to provide these datasets. The sponsor's submission of March 15, 2001 provided the requested datasets.

Advair Diskus was approved August 24, 2000.

In this review Advair HFA will also be referred to as "SFC" (Salmeterol Fluticasone Combination). Salmeterol will also be referred to as "SALM". Fluticasone propionate will also be referred to as "FP".

II. Study SAS30003

A. Study Description and Method of Analysis

This was a randomized, double-blind, placebo-controlled, parallel-group study comparing Advair HFA (88mcg/42mcg) with the individual components (via the CFC MDI) and placebo HFA in asthma patients previously treated with inhaled corticosteroids, inhaled short-acting beta$_2$-agonists or salmeterol. [redacted] ..] During a two-week run-in period, patients continued receiving their previous asthma therapy (inhaled corticosteroids or beta$_2$-agonists). Patients on short-acting beta$_2$-agonists were switched to Ventolin CFC. All patients received, in addition, single-blind placebo HFA.

Subjects who completed the single-blind run-in period were eligible to be randomly assigned to double-blind treatment, if they demonstrated relative asthma stability per the

following diary card criteria:
1. During the 7 days prior to Visit 2 the subject must not have experienced more than 3 days with:
- Group 1 (Inhaled Corticosteroids): >12 puffs/day of Ventolin use.
- Group 2 (PRN short-acting $beta_2$-agonists): >12 puffs/day of Ventolin use.
- Group 2 (Salmeterol): >6 puffs/day of Ventolin use.

2. During the 7 days prior to Visit 2 -no more than 3 nights with awakenings due to asthma requiring treatment with Ventolin.
3. Group 2 (PRN short-acting $beta_2$-agonists): During the 7 days prior to Visit 2 the subject must have a total symptom score of ≥7 based on a scale of 0-5:
0 = No symptoms during the day
1 = Symptoms for one short period during the day
2 = Symptoms for two or more short periods during the day
3 = Symptoms for most of the day which did not affect my normal daily activities
4 = Symptoms for most of the day which did affect my normal daily activities
5 = Symptoms so severe that I could not go to work or perform normal daily activities.

In addition, subjects were required to:
1. Demonstrate a best FEV_1 of 40%-85% of the predicted value during Visit 2 (based on ECCS "Standardization of Lung Function Tests" standards for ≥18 years, or Polgar standards for ages 12-17 years and race adjusted for African-Americans.
2. Demonstrate reproducible lung function at Visit 2 defined as a best baseline Visit 2 FEV_1, at the 30 minute pre-dose or the 0 timepoint PFT, within ±15% of the best pre-Ventolin Visit 1 FEV_1.
3. Demonstrate adequate compliance defined as completion of diary card and ability to withhold anti-asthma medications. Subjects must have been at least 70% compliant with the study drug regimen at this visit to continue in the study. If a subject was not 100% compliant with completion of diary card and/or study drug regimen, the site personnel re-educated the subject on diary card completion and study drug regimen. The re-education of a subject was documented in the subject's source document.

PEFR and FEV_1 Stability Limits were calculated at Visit 2 for all subjects who met the above criteria.
- **PEFR Stability Limit:** This was calculated using the mean morning PEFR from the 7 days preceding Visit 2, using the morning PEFR from the day of Visit 2 as Day 7. A 20% decrease in this mean was calculated and used for the duration of the study.
- **FEV_1 Stability Limit:** This was calculated by taking a 20% decrease in the best FEV_1 obtained at the 0 timepoint PFT for Visit 2. This value was used for the remainder of the study.

Patients within a center who completed the run-in period and met all entrance criteria were stratified according to previous asthma medication and the randomly assigned to one of the following treatment groups:
1. Advair HFA (88mcg /42mcg) BID (2 inhalations 44mcg/21mcg BID)
2. Salmeterol CFC MDI 42mcg BID (2 inhalations 21 mcg BID)

3. Fluticasone propionate CFC 88mcg BID (2 inhalations 44mcg BID)
4. Placebo HFA (2 inhalations BID)

All patients were dispensed Ventolin and instructed to continue to use as needed and to withhold it for 6 hours prior to returning for scheduled clinic visits. On treatment clinic visits were held on Day 1, Weeks 1-4, and Weeks 6,8,10 and 12.

At Day 1 (Visit 2) and Week 12 (Visit 10), serial PFTS were done 30 minutes prior to dosing, immediately predose (time 0), 30 minutes, and 1,2,3,4,6,8,10 and 12 hours post-dose. At Visit 3-9, one set of PFTs were performed pre-dose.

During Visits 3-10, pre-defined continuation criteria were used to withdraw subjects with worsening asthma. Before beginning the scheduled clinical assessments for Visits 3-10, the latest diary card and PFT results were assessed to determine a subject's eligibility to continue. Subjects were discontinued from the study due to worsening asthma if one of the following criteria were met during the 7 days immediately preceding the visit: more than 3 days in which the PEFR fell below the PEFR Stability Limit calculated at Visit 2; more than 2 days in which ≥12 puffs/day of Ventolin were used (6 puffs/day for subjects on baseline salmeterol); or more than 2 nights with awakenings due to asthma requiring treatment with Ventolin.

Subjects discontinued for lack of efficacy or a clinical asthma exacerbation were considered complete and evaluable subjects. The patient could, also, discontinue the study on his/her own volition. The patient was then brought back for a discontinuation visit.

Endpoint was defined as the last available on-treatment FEV_1 measurement recorded for each subject, with the following restrictions:

- Endpoint only came from a scheduled visit or from a Discontinuation Visit;
- Endpoint did not come from a visit more than 1 day after discontinuation of study drug;
- If a Discontinuation Visit occurred more than 2 days after the last dose of study drug, then endpoint was assigned the FEV_1 value from the last scheduled visit, and not from the Discontinuation Visit.

Data recorded on the morning of all visits was recorded on the diary card and was to be included in the clinic evaluation. Subjects were also required to have:
1. Demonstrated an $FEV_1 \geq$ the FEV_1 Stability Limit calculated at Visit 2.

If the continuation criteria were met at each visit, the appropriate visit procedures were performed. Subjects who did not meet these continuation criteria were to be discontinued from the study for lack of efficacy, an indicator of worsening asthma. Subjects were also discontinued for 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.

Primary Efficacy Measures

• AUC(bl) on Treatment Day 1 and at Treatment Week 12 were used to assess the difference between the combination product and fluticasone propionate. The multiplicity issues associated with testing this primary efficacy measure at two time points was handled using the intersection-union method of Neuhauser, et al (The evaluation of multiple clinical endpoints, with application to asthma. Drug Information Journal; 1999; 33; pp. 471-7) as follows:
To reject the null hypothesis of no treatment difference between the combination product and fluticasone propionate, at least one of these two p-values must be significant at the 0.025 level, OR both p-values must be significant at the 0.05 level.

• The changes from baseline at endpoint in morning predose FEV_1 and in the probability of remaining in the study were used to assess the difference between the combination product and salmeterol. The multiplicity issues associated with testing two primary efficacy measures to address one primary question was handled using the intersection-union method of Neuhauser et al as follows:
To reject the null hypothesis of no treatment difference between the combination product and salmeterol, at least one of these two p-values must be significant at the 0.025 level, OR both p-values must be significant at the 0.05 level.

Baseline for analyses of serial FEV_1 data on Treatment Day 1 and at Treatment Week 12 were defined as the average of the –30 minute predose and 0 hour predose FEV_1 values measured on Treatment Day 1. This baseline was also used for the analyses of morning predose FEV_1 using ANOVA (analysis of variance). If one of these two predose FEV_1 measurements was missing, then the non-missing value was used as the baseline value. Predose for analysis of serial FEV_1 data at Treatment Week 12 was defined as the average of the –30 minute predose and 0 hour FEV_1 measures from Treatment Week12. This average pre-dose value (Time 0) was used in the calculation of FEV_1 AUC(bl). LOCF values were used in the calculation of FEV_1 AUC(bl), if the patient did not complete the serial PFTs.

The study was conducted at 36 U.S. centers in order to complete at least 320 evaluable subjects with 80 subjects per treatment arm. Sample size calculations were performed at a significance level of 0.05 and were based on two-sided t-tests. The primary treatment comparisons were the combination product versus each active comparator alone.

Investigator clusters are groups of investigators such that, within a cluster, the Investigators are from geographically similar regions. This combining of investigative sites was done in order to minimize the possibility of bias when many small centers contributed to the subject population. It was performed prior to unblinding of study treatments. Treatment-by-cluster interaction was tested in a supplemental analysis.

Data from previous studies of the salmeterol/fluticasone propionate combination product suggested that a reasonable assumption for the standard deviation of AUC(bl) after 1 day of treatment is 4.1 Liter Hours (equivalent to 0.34L over a 12-hour period). The sample size of 80 subjects per treatment arm would provide more than 90% power to detect a

treatment difference, in AUC(bl) on Treatment Day 1, of 3.6L-hours (equivalent to 0.3L over 12 hours) for any pairwise treatment comparison. In addition, 80 subjects per treatment group would provide more than 90% power to detect a difference in AUC(bl), after 12 weeks treatment, of 3.5L-hours (equivalent to 0.29L over 12 hours), assuming a standard deviation of 5.3L-hours (equivalent to 0.44L over 12 hours). Also, the targeted sample size of 80 subjects per treatment arm would provide more than 85% power to detect a difference of 0.25L in mean change from baseline at endpoint in morning predose FEV_1, assuming a standard deviation of 0.5L. Power calculations described above are not adjusted for multiple comparisons.

Efficacy variables were tested using an ANOVA model that included terms for treatment, investigator cluster, and stratum.

B. Results

There were 360 patients [87 in the placebo group, 92 in the SFC 88/42 combination product group, 92 in the SALM 42 dose group, and 89 in the FP 88 dose group] randomized at 36 investigative sites. There were 7 Investigator clusters. Of these 360 patients, 279 (78%) completed the double blind treatment period [56 (64%) in the placebo group, 85 (92%) SFC 88/42 in the combination dose group, 63 (68%) in the SALM 42 dose group, and 75 (84%) in the FP88 dose group].

The treatment groups were comparable at baseline in demographic and asthma severity. There were 134 patients in the corticosteroid strata and 226 (84 Salmeterol and 142 short-acting $beta_2$–agonists) in the other strata.

There was no evidence of treatment-by-cluster or treatment-by-stratum interaction for any of the primary efficacy parameters.

Endpoints demonstrating need for Fluticasone in the combination product

The table below gives the percentages of patients who were withdrawn for lack of efficacy (worsening asthma). Significantly higher percentages withdrew for worsening asthma in the placebo and SALM 42 groups than in the SFC 88/42 combination product group. The withdrawals were mainly for nighttime awakenings and reaching FEV_1 stability limit for the placebo group and for clinical exacerbation in the SALM 42 group.

Probability of Remaining in the Study

	Placebo (N=87)	**SFC 88/42 (N=92)**	**SALM 42 (N=92)**	**FP 88 (N=89)**
Number (%) withdrawn due to Worsening asthma	24[b] (28%)	2 (2%)[a]	23 (25%)	7 (8%)

[a] differs from placebo and salmeterol ($p<0.001$)

[b] an additional placebo patient, #3224, withdrew after the 12 week treatment period.

The table below shows the mean changes from baseline at endpoint in morning pre-dose FEV_1. The Endpoint results below do not contain the values of patients 3276 (SFC 88/42), 3003 (SALM 42), and 3111(FP 88), who only had Day 1 FEV_1 assessments. The SFC 88/42 combination product was significantly more effective than placebo and its components.

Mean Change from Baseline at Endpoint in Morning Pre-Dose FEV_1 (L)

Period	Placebo (N=87)		SFC 88/42 (N=92)		SALM 42 (N=92)		FP 88 (N=89)	
	Mean (L)	Mean Change	Mean (L)	Mean Change	Mean (L)	Mean Change	Mean (L)	Mean Change
Baseline	2.27		2.29		2.33		2.20	
Endpoint	2.40	0.14	2.86	0.58[a]	2.58	0.25	2.55	0.36

[a] differs from placebo, salmeterol and fluticasone propionate ($p \leq 0.004$)

Endpoints demonstrating need for Salmeterol in the combination product

The table below shows the Mean FEV_1 AUC(bl) on Day 1 and Week 12. The combination product was significantly more effective than placebo and fluticasone propionate at Day 1 and Week 12. It was also significantly more effective than Salmeterol at Week 12.

Mean Serial FEV_1 AUC(bl) (L-hours) after 1 Dose and 12 Weeks of Treatment

	Placebo (n=87)	SFC 88/42 (n=92)	SALM 42 (n=92)	FP 88 (N=89)
Treatment Day 1 (n)	87	92	92	89
Treatment Day 1 mean AUC(bl) (L-hours)	2.0	6.7[a]	6.1	2.7
Treatment Week 12 (n)	56	85	63	75
Treatment Week 12 mean AUC(bl) (L-hours)	2.6	9.0[b]	6.5	5.6

[a] differs from placebo and fluticasone propionate ($p<0.001$)

[b] differs from placebo, salmeterol, and fluticasone propionate ($p \leq 0.006$)

C. Reviewer's Comments

This reviewer duplicated the results of the primary efficacy analyses from the datafiles provided.

Advair HFA (88/42) was significantly more effective than its components using the multiple endpoint rules of Neuhauser, et al. In particular, it was significantly better than Salmeterol for both probability of remaining in the study and mean change in morning pre-dose FEV_1 at endpoint at less than the 0.05 level and was significantly better than fluticasone propionate for both AUC(bl) at Day 1 and Week 12 at less than 0.05. It was also significantly better than placebo for all four endpoints. The use of multiple endpoint rules is more justifiable when comparing a combination against its components than they

would be in comparisons against placebo. Against placebo, a primary endpoint would usually be dictated. Advair HFA (88/42) showed more efficacy than demanded by the multiple endpoint rules (more effective than salmeterol in AUC(bl) at Week 12 and more effective than fluticasone propionate in mean change from baseline in endpoint morning pre-dose FEV_1).

III. Study SAS30004

A. Study Description and Method of Analysis

This study was similar to study SAS30003 with the exceptions that all patients were being treated with corticosteroids at baseline and the combination product was SFC 220/42 rather than SFC 88/42. The fluticasone propionate product was FP 220. Since all patients were on corticosteroids, there was no group stratification. Therefore, the Group 2 requirements, described above, do not apply. Stratum was not a factor in the ANOVA.

B. Results

There were 365 patients [89 in the placebo group, 94 in the SFC 220/42 combination product group, 91 in the SALM 42 dose group, and 91 in the FP 220 dose group] randomized at 45 U.S. investigative sites. There were 7 investigator clusters. Of these, 243 (67%) completed the double blind treatment period [34 (38%) in the placebo group, 81 (86%) in the SFC 220/42 combination group, 57 (63%) in the SALM 42 dose group, and 71 (78%) in the FP 220 dose group].

The treatment groups were comparable at baseline in the demographic factors and asthma severity.

There was no evidence of treatment-by-cluster interaction for any of the primary efficacy parameters.

Endpoints demonstrating need for Fluticasone in the combination product

The table below gives the percentages of patients who were withdrawn for lack of efficacy (worsening asthma). Significantly higher percentages withdrew for worsening asthma in the placebo and SALM 42 groups than in the SFC 220/42 combination product group.

Probability of Remaining in the Study

	Placebo (N=89)	**SFC 220/42 (N=94)**	**SALM 42 (N=91)**	**FP 220 (N=91)**
Number (%) withdrawn due to Worsening asthma	48 (54%)	7(7%)[a]	22[b](24%)	10[b](11%)

[a] differs from placebo and salmeterol ($p<0.001$)

[b] an additional SALM 42 patient, #8845, and an additional FP 220 patient, # 4218, withdrew after the 12 week treatment period.

The table below shows the mean changes from baseline at endpoint in morning pre-dose FEV_1. The Endpoint results below do not contain the values of patients 3937 and 9101 (SFC 88/42), 3961 (SALM 42), 4045(FP 88), and 4217 (Placebo), who only had Day 1 FEV_1 assessments. The SFC 220/42 combination product was significantly more effective than placebo and its components.

Mean Change from Baseline at Endpoint in Morning Pre-Dose FEV_1 (L)

Period	Placebo (N=89)		SFC 220/42 (N=94)		SALM 42 (N=91)		FP 220 (N=91)	
	Mean (L)	Mean Change	Mean (L)	Mean Change	Mean (L)	Mean Change	Mean (L)	Mean Change
Baseline	2.17		2.23		2.22		2.18	
Endpoint	2.06	-0.12	2.64	0.41[a]	2.36	0.15	2.36	0.19

[a] differs from placebo, salmeterol and fluticasone propionate ($p<0.001$)

Endpoints demonstrating need for Salmeterol in the combination product

The table below shows the mean FEV_1 AUC(bl) on Day 1 and Week 12. The combination product was significantly more effective than placebo and fluticasone propionate at Day 1 and Week 12. It was also significantly more effective than Salmeterol at Week 12.

Mean Serial FEV_1 AUC(bl) (L-hours) after 1 Dose and 12 Weeks of Treatment

	Placebo (n=89)	SFC 220/42 (n=94)	SALM 42 (n=91)	FP 220 (N=91)
Treatment Day 1 (n)	89	94	91	91
Treatment Day 1 mean AUC(bl) (L-Hours) (L-hours)	0.6	5.4[a]	6.1	2.1
Treatment Week 12 (n)	34	81	57	71
Treatment Week 12 mean AUC(bl) (L-hours)	1.4	7.0[a,b]	5.3	3.6

[a] differs from placebo and fluticasone propionate ($p<0.001$)
[b] differs from salmeterol ($p=0.020$)

C. Reviewer's Comments

This reviewer verified the results of the primary efficacy analyses from the datafiles provided.

Advair HFA (220/42) was significantly more effective than its components using the multiple endpoint rules of Neuhauser, et al. In particular, it was significantly better than Salmeterol for both probability of remaining in the study and mean change in morning pre-dose FEV_1 at endpoint at less than the 0.05 level and was significantly better than fluticasone propionate for both AUC(bl) at Day 1 and Week 12 at less than 0.05. It was also significantly better than placebo for all four endpoints. Advair HFA (88/42) showed

more efficacy than demanded by the multiple endpoint rules (more effective than salmeterol in AUC(bl) at Week 12 and more effective than fluticasone propionate in mean change from baseline in endpoint morning pre-dose FEV_1).

IV. Study SAS30001

A. Study Description and Method of Analysis

This study was similar to study SAS30003 with the exceptions listed below. All patients were being treated with short-acting beta $_2$-agonists at baseline. Since all patients were on short-acting beta$_2$-agonists, there was no group stratification and Group 1 and Group 2 (Salmeterol) requirements, given above, do no apply. Stratum was not a factor in the ANOVA. In addition, there was no placebo group. A patient was not automatically withdrawn from this study if they met the worsening asthma conditions. As such this endpoint was not used to compare Advair with Salmeterol. The primary endpoint for the Advair versus salmeterol comparison was mean change from baseline at endpoint in morning pre-dose FEV_1.

B. Results

There were 283 patients [95 in the SFC 88/42 combination product group, 91 in the SALM 42 dose group, and 97 in the FP 88 dose group] randomized at 26 U.S. investigative sites. There were 7 investigator clusters. Of these, 257 (91%) completed the double blind treatment period [86 (91%) in the SFC 88/42 combination dose group, 82 (90%) in the SALM 42 dose group, and 89 (92%) in the FP 88 dose group].

The treatment groups were comparable at baseline in demographic and asthma severity, except for age, with the combination product younger than the component groups.

There was no evidence of treatment-by-cluster interaction for any of the primary efficacy parameters.

Endpoint demonstrating need for Fluticasone in the combination product

The table below shows the mean changes from baseline at endpoint in morning pre-dose FEV_1. The Endpoint results do not include the data from Subject 2521 (SFC 88/42) because this patient had only Day 1 FEV_1 assessments. The SFC 88/42 combination product was significantly more effective than its components.

Mean Change from Baseline at Endpoint in Morning Pre-Dose FEV_1 (L)

Period	SFC 88/42 (N=95)		SALM 42 (N=91)		FP 88 (N=97)	
	Mean (L)	Mean Change	Mean (L)	Mean Change	Mean (L)	Mean Change
Baseline	2.37		2.34		2.31	
Endpoint	3.06	0.69[a,b]	2.81	0.47	2.82	0.51

[a] differs from salmeterol (p=0.004)
[b] differs from fluticasone propionate (p=0.016)

Endpoints demonstrating need for Salmeterol in the combination product

The table below shows the mean FEV_1 AUC(bl) on Day 1 and Week 12. The week 12 analysis does not include subject # 2445 who had only a predose FEV_1 value, which was not carried forward. The combination product was significantly more effective than fluticasone propionate at Day 1 and Week 12. It was also significantly more effective than Salmeterol at Week 12.

Mean Serial FEV_1 AUC(bl) (L-hours) after 1 Dose and 12 Weeks of Treatment

	SFC 88/42 (n=95)	SALM 42 (n=91)	FP 88 (N=97)
Treatment Day 1 (n)	95	91	97
Treatment Day 1 mean AUC(bl) (L-hours)	7.2[a]	7.6	2.9
Treatment Week 12 (n)	86	82	88
Treatment Week 12 mean AUC(bl) (L-hours)	10.6[a,b]	8.2	7.2

[a] differs from fluticasone propionate (p<0.001)
[b] differs from salmeterol (p=0.013)

C. Reviewer's Comments

This reviewer duplicated the results of the primary efficacy analyses from the datafiles provided. If age is included as a covariate because of the difference in age between the treatment groups, the results are still significant for the primary efficacy analyses.

Advair HFA (88/42) was significantly more effective than its fluticasone propionate using the multiple endpoint rules of Neuhauser, et al. In particular, it was significantly better than fluticasone propionate for both AUC(bl) at Day 1 and Week 12 at less than 0.05. It was also significantly better than Salmeterol for mean change in morning pre-dose FEV_1 at endpoint at less than the 0.05 level. Advair HFA (88/42) showed more efficacy than demanded by the multiple endpoint rules (more effective than salmeterol in AUC(bl) at Week 12 and more effective than fluticasone propionate in mean change from baseline in endpoint morning pre-dose FEV_1).

V. Study SFCB3023

A. Study Description and Method of Analysis

This was a randomized, double-blind, double dummy, parallel-group study comparing Advair HFA (440mcg/42mcg), given twice daily, with the combination product given by Diskus (500mcg/50), given twice daily, and FP 440 mcg MDI with CFC formulation, given twice daily in adult and adolescent patients previously treated with corticosteroids (beclomethasone dipropionate, budesonide or flunisolide at a dose of 1500-2000mcg/day or fluticasone propionate at a dose of 750-1000mcg/day for at least four weeks prior to Visit 1).

During the run-in period, patients had to have a mean morning PEFR during the last consecutive days (minimum of 4 days of data) > 50% and < 85% of their PEFR measured 15 minutes after administration of 400mcg of Ventolin at Visit 2 and have recorded a cumulative total symptom score (daytime plus nighttime) of 8 for the last 7 consecutive days (minimum of 4 days data of the run-in- period). To enter the treatment period their FEV_1 had to be > 50% and < 100% of predicted normal at Visit 2.

During the run-in period patients continued using their inhaled corticosteroids and were provided Ventolin as a rescue medication. During the 12 week treatment period patients were supplied one Diskus/Accuhaler inhaler and one pressurized MDI to blind the study.

Subjects were asked to measure their PEFR using a mini-Wright peak flow meter every morning on waking and every evening. Subjects were asked to ensure that all PEFR measurements were made before taking study medication or rescue Ventolin. Three measurements of PEFR were taken on each occasion and only the highest value recorded.

The primary efficacy measure was the change from baseline in mean morning PEFR averaged over Treatment Weeks 1-12. Treatment groups were defined to be equivalent if the 95% confidence intervals for the treatment difference fell within ±15L/min.

Investigators who randomized fewer than 19 patients were grouped in clusters based on geographic proximity of sites. Investigators who randomized 19 or more patients were defined as stand-alone clusters.

The sponsor analyzed change from baseline in mean morning PEFR averaged over Weeks 1-12 with an analysis of covariance with treatments, sex, and investigator cluster as factors; and age and baseline morning PEFR as covariates.

B. Results

A total of 510 patients were randomized into this trial at 61 centers in 13 countries. There were 21 investigator clusters. One patient, who is not included in the intent-to-treat population, never received treatment. There were 176 in the SFC 440/42 MDI group, 161 in the SFC 500/50 Diskus group, and 172 in the FP 440 MDI group. In total, 62 patients were withdrawn 21(12%) from the MDI combination, 19(12%) from the Diskus

combination group and 22 (13%) from the FP 440 group. The most common reason for withdrawal was an adverse event.

The treatment groups were comparable at baseline in demographic and baseline pulmonary function.

There were 6 patients (3 on SFC 440/42 MDI, 2 on SFC 500/50 Diskus, and 1 on FP 440 MDI) who were not included in the primary efficacy analysis. Five of these patients had no post-treatment data and one patient had no run-in data. The primary efficacy analysis included 503 patients (173 on SFC 440/42 MDI, 159 on SFC 500/50 Diskus and 171 on FP 440 MDI).

Treatment-by-cluster interaction was not significant (P=0.8724) in a model including main effects and baseline PEFR.

The table below gives the results of the 95% confidence interval on the difference in mean morning PEFR between the MDI and Diskus Combination products. The two combination products were comparable.

Mean Morning PEFR (L/min)- Statistical Analysis for Weeks 1-12 MDI combination Vs. Diskus combination (Intent-to-treat Population)			
Adjusted Mean Change		Treatment Difference	95% Confidence Limit
MDI Combination	Diskus Combination		
50	48	-2	-11,7

The table below gives the results of the 95% confidence interval on the difference in mean morning PEFR between the MDI combination product and the FP 500 product. The MDI combination product was significantly more effective than the FP 500 product.

Mean Morning PEFR (L/min)- Statistical Analysis for Weeks 1-12 MDI combination Vs. FP 440 group (Intent-to-treat Population)				
Adjusted Mean Change		Treatment Difference	p-Value	95% Confidence Interval
MDI Combination	FP 440			
50	27	-23	<0.001	-32,-14

C. Reviewer's Comments

This reviewer verified the results of the primary efficacy analysis from the datafiles provided.

Advair HFA was significantly more effective than FP 440 and was comparable to the diskus combination product using the sponsor's comparability rule (95% confidence limit completely contained within ± 15L/min).

V. Overall Conclusions

Advair HFA (88/42) was shown to be more effective than its components (given in CFC formulation) and placebo HFA in Study SAS30003 (patients on corticosteroids or $beta_2$-agonists) and Study 30001 (patients using $beta_2$-agonists alone) using multiple endpoint rules. Advair HFA (220/42) was shown to be more effective than its components (given in CFC formulation) and placebo HFA in Study SAS30004 (patients on corticosteroids) using multiple endpoint rules. Study SFCB3023 showed Advair (440/42) was comparable to the Diskus (500/50) formulation and more effective than FP 440 (CFC formulation) for the primary efficacy analysis of change from baseline in mean morning PEFR averaged over Weeks 1-12.

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

Concur: Dr. Wilson

This review contains 13 of text.
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