CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-433

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

Date	
NDA #	21-433
Applicant	GlaxoWellcome
Name of Drug	Flovent HFA Inhalation Aerosol
Indication	
Document Reviewed	❑ Study FLTA3022: \\cdsesub1\N21433\N_000\2002-02-26A\clinstat\maintenancetreatmentofasthma\flta3022\flta3022.pdf ❑ Data set analyzed: PRED3022 (SD7) ❑ Study FAP30007: \\cdsesub1\N21433\N_000\2002-02-26A\clinstat\maintenancetreatmentofasthma\FAP30007\FAP30007.pdf ❑ Data analyzed: FAP30007Analysis (SD7) ❑ Study FAP30008: \\cdsesub1\N21433\N_000\2002-02-26A\clinstat\maintenancetreatmentofasthma\FAP30008\FAP30008.pdf ❑ Data analyzed: FAP30008Analysis (SD7)
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Key Words	NDA, Clinical Studies

Summary

The statistical evaluation of Studies FLTA3022, FAP30007, and FAP30008 concludes:

- The mean daily uses of prednisone during 16 weeks proved to be significantly less among patients treated with Fluticasone propionate (FP) 440mcg HFA, 880mcg HFA, 440mcg CFC, or 880mcg CFC than those under placebo (Study FLTA3022).
- The differences in the change of percent predicted FEV_1 from baseline, between the FP treatments (88, 220, and 440mcg HFA) and placebo proved to be statistically significant, favoring FP treatments (Studies FAP30007 and FAP30008).

Overall, evidence of the effectiveness of FP HFA at doses ranging from 88 to 440mcg proved to be adequate and statistically significant.

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Introduction

Flovent (FP: fluticasone propionate) HFA inhalation aerosol, 88mcg, 220mcg and 440mcg BID, delivered via HFA, is indicated for —
← . To support the efficacy and safety claim, GlaxoWellcome (name at the time of clinical trial) submitted Studies: FLTA3022, FAP30007, and FAP30008 as pivotal studies.

Tables 1-3, below, summarize the characteristics of Studies FLTA3022, FAP30007, and FAP30008, from a statistical aspect.

Table 1. Characteristics of Study FLTA3022

Study	General Feature	Specific Characteristics
Objectives	The objectives of the study are quoted directly from the NDA as follows. The objective of this study was to "compare the dose related efficacy and safety of fluticasone propionate 440mcg BID and FP 880mcg BID utilizing the 220mcg formulation administered by pressurized metered-dose inhaler propelled by CFC propellants 11/12 or HFA propellant GR106642X for 16 weeks in adolescent and adult oral corticosteroid dependent asthmatics (Sec. 2)."	
Protocol FLTA3022	A 16-week treatment period follows a 2-week screening period	Visit 1 (Screening period ends): Patients takes anti-asthma medication, including corticosteroid (Sec. 3.1.1) Visit 2 (Randomization): Each patient is randomized to one of five treatment groups for 16 weeks. The patient takes treatment medication twice daily and 12 hours apart at 8 AM and 8 PM Weekly Visits until the 16th week.
	Study time line	Study dates: 9/4/1997-5/4/1999 Report date: 9/21/2001
	Randomized	
	Double-blind	
	Parallel-group	▪ FP440mcg HFA ▪ FP880mcg HFA ▪ FP440mcg CFC ▪ FP880mcg CFC ▪ Placebo
	Multi-center	37 centers
	Efficacy variables	The primary efficacy variable is mean daily prednisone use. The patient records the dose of daily prednisone on the diary card, which is reviewed at clinic visits in order to ensure accurate recordings (Sec. 4.1.1).
	Safety variables	▪ Adverse events are assessed at each clinic visit from Visit 2 onward. ▪ Other safety measures.

Table 2. Characteristics of Study FAP30007

Study	General Feature	Specific Characteristics
Objectives	The objectives of the study are quoted directly from the NDA as follows. "The objective of this study was to assess the efficacy and safety of FP 88mcg, 220mcg and 440mcg BID versus placebo in HFA propellant when administered via MDI for 12 weeks to adolescent and adult subjects with asthma who were previously maintained on ICS therapy (Sec. 2.1)."	
Protocol FAP30007	A 12-week treatment period follows a 2-week screening period	Screening Period: During the 2-week screening period, patients continued their existing inhaled corticosteroid, but were switched to VENTOLIN Inhalation Aerosol as needed for asthma-symptom relief. (Sec. 3.1.1) Week 0 (Randomization): Each patient is randomized to one of four treatment groups for 12 weeks. The patient takes two inhalations of the assigned treatment medication twice daily. Weekly Visits for 12 week.
	Study time line	Study dates: 10/26/2000-7/31/2001 Report date: 11/26/2001
	Randomized	Yes
	Double-blind	Yes
	Parallel-group	▪ FP88mcg HFA ▪ FP220mcg HFA ▪ FP440mcg HFA ▪ Placebo
	Multi-center	79 centers
	Efficacy variables	The primary efficacy variable was defined as "mean change from Baseline to Endpoint in morning (AM) pre-dose percent-predicted FEV_1 (Sec. 2.2.1.1)." "For change from baseline measures of efficacy, data were summarized by week and at Endpoint using a last observation carried forward (LOCF) methodology (Sec. 2.2.1)."
	Safety variables	▪ Adverse events ▪ Lab tests and others (Sec. 2.2.3)

Table 3. Characteristics of Study FAP30008

Study	General Feature	Specific Characteristics
Objectives	The objectives of the study are quoted directly from the NDA as follows. "The objective of this study was to assess the efficacy and safety of FP 88mcg, 220mcg and 440mcg BID versus placebo in HFA propellant when administered via MDI for 12 weeks to adolescent and adult subjects with asthma who were previously maintained on bronchodilator therapy (Sec. 2.1)."	
Protocol FAP30008	A 12-week treatment period follows a 2-week screening period	Screening Period: During the 2-week screening period, patients continued their existing inhaled corticosteroid, but were switched to VENTOLIN Inhalation Aerosol as needed for asthma-symptom relief. (Sec. 3.1.1) Week 0 (Randomization): Each patient is randomized to one of four treatment groups for 12 weeks. The patient takes two inhalations of the assigned treatment medication twice daily. Weekly Visits for 12 week.
	Study time line	Study dates: 10/27/2000-8/24/2001 Report date: 11/30/2001
	Randomized	Yes
	Double-blind	Yes
	Parallel-group	▪ FP88mcg HFA ▪ FP220mcg HFA ▪ FP440mcg HFA ▪ Placebo
	Multi-center	78 centers
	Efficacy variables	The primary efficacy variable was defined as "mean change from Baseline to Endpoint in morning (AM) pre-dose percent-predicted FEV_1 (Sec. 2.2.1.1)." "For change from baseline measures of efficacy, data were summarized by week and at Endpoint using a last observation carried forward (LOCF) methodology (Sec. 2.2.1)."
	Safety variables	▪ Adverse events ▪ Lab tests and others (Sec. 2.2.3)

Sponsor's Analyses of Efficacy

Study FLTA3022

Sponsor's Statistical Method

The following description of the sponsor's statistical method is based on contents in the study report (See Sec. 5.4.4 of the study report for details). To compare the treatment effects, a sequential approach was used. A serious of hypothesis tests was arranged as follows:

1. Compare FP880mcg HFA and FP880mcg CFC with placebo separately. If neither comparison demonstrated statistical significance, then no further tests were to be performed.
2. If the above test results were statistically significant, then comparisons of FP HFA and FP CFC with placebo would be made at 440mcg level.
3. To justify the combination of doses across propellants and the combination of propellants across doses, a test of parallelism in dose across propellants was performed. This test was to confirm whether the differences in effects between the doses were similar for both propellants.

The statistical methods for the efficacy analysis can also be found in Sec. 5.3.5, *Efficacy*, under section, *Protocol and Protocol Amendments* (flta3022.pdf). For the convenience of the reader, the key portion of the sponsor's statistical methods is included under Appendix, Sponsor's Statistical Method.

Reviewer's Comments on Statistical Method

- **On Study Objectives** – The sponsor failed to state its study objectives in a straightforward manner. It is not clear to this reviewer whether the sponsor wanted to test a number of predefined hypotheses or merely intended to explore the dose-response relationship.
- **On Statistical Method** – The description of the statistical methods used in the efficacy analysis lacks details. Statistical-test method was not described in the protocol. Only the primary efficacy measure was stated. This could open doors for arbitrary interpretations of the data.
- **On Approach of sequential tests (in the study report)** – Not only does the description of the statistical approach lack clarity, but also contains faulty logic: for example, no reason was given for why the HFA doses needed to be combined and why the two propellants needed to be combined (in order to justify the test for parallelism). Furthermore, the sponsor indicated that for the sequential tests described above, if **both** comparisons (of FP880mcg HFA and FP880mcg CFC) with placebo failed to show a significant difference, no more tests should be conducted. The condition for the second step to be taken was that the p-values from **both** tests showed significant results. What if either FP880mcg HFA or FP880mcg CFC was shown superior to the placebo? The statistical plan did not address the case where only one of the tests was found statistically significant.
- **On Estimate of missing data** – LOCF is used to estimate missing a value, which also was not addressed in the protocol. The appropriateness of such approach is in question when nearly or more than 50% of patients were withdrawn during the study. The data show this is the case.

Sponsor's Conclusions on Efficacy

The sponsor noted that the analysis of efficacy was based on a reduced ITT patient population which excluded three patients who were randomized but withdrew before post randomization assessments (Sec. 5.5 and 7). The primary efficacy variable was the mean daily oral prednisone use.

The following snapshot from Sec. 7, *Efficacy Results* shows the mean prednisone use by treatment. Pairwise comparisons were made between the FP treatment groups and placebo. The statistical significance was also indicated.

Table 4. Efficacy results (Study FLTA3022, Sec. 7)

Summary of Mean Daily Oral Prednisone Use, mg Reduced ITT Population					
	Placebo HFA BID (N=32)	FP 440mcg HFA BID (N=32)	FP 880mcg HFA BID (N=32)	FP 440mcg CFC BID (N=36)	FP 880mcg CFC BID (N=33)
Baseline	14.2	12.5	12.7	13.0	14.3
Weeks 1-16	14.9	5.8[a]	6.2[a]	4.9[a]	5.4[a]
Source Data: Tables 18 and 21 a Different from placebo p<0.001					

The sponsor concluded, "Each fluticasone propionate treatment group had a statistically significantly lower mean daily oral prednisone dose compared with the placebo group ($p<0.001$) (Sec. 7.1)." "The primary efficacy measure, mean oral prednisone dose during Weeks 1-16, was reduced significantly in both FP HFA treatment groups relative to placebo (Sec. 11)."

Reviewer's Comments on Efficacy

It appears that patients received higher doses delivered by the same propellant had a higher mean daily prednisone use than did those in the lower-dose groups. But the positive dose-response relationship is not demonstrated in this study. Numerically, the mean prednisone use in the FP HFA groups was slightly higher that in the FP CFC groups.

Study FAP30007

Sponsor's Conclusions on Efficacy

"The primary efficacy measure for this study was mean change from Baseline in AM pre-dose percent-predicted FEV1 at Endpoint (Week 12 with LOCF) (Sec. 7.1 Primary Efficacy Measure)." The following table, from Sec. 7, *Efficacy Results*, gives a summary of the efficacy outcome.

Table 5. Efficacy results (Study FAP30007, Sec. 7)

Mean Change from Baseline in AM Pre-Dose Percent Predicted FEV_1 at Week 12 (LOCF)
(ITT Population – Study FAP30007)

	PLA HFA (N=104)	FP 88 HFA (N=103)	FP 220 HFA (N=106)	FP 440 HFA (N=102)
Baseline (n)	104	103	106	101
Mean (%)	65.6	65.3	65.5	66.2
Week 12 (n)	102	100	105	98
Mean (%)	58.0	68.1	69.7	72.2
Mean Change	-7.7	2.9	4.2	5.9
LS Mean Change[b] (SE)	-8.3 (1.2)	2.2[a] (1.2)	3.2[a] (1.1)	4.6[a] (1.2)
95% CI[c]	---	(7.7, 13.3)	(8.8, 14.4)	(10.1, 15.8)
95% Dunnett CI[d]	---	(7.1, 13.8)	(8.2, 14.9)	(9.6, 16.4)

Source Data: Table 7.2, Table 7.3, Table 7.4
LOCF = last observation carried forward, LS = least square, SE = standard error
Post-baseline n's are the sample sizes used for LS mean change calculation
a p<0.001 vs. placebo (Hochberg multiplicity adjustment)
b ANCOVA, adjusted for baseline percent predicted FEV_1, region, age, gender, whether or not site had subject participating in PK assessments, and baseline dose level of ICS therapy (low/medium or high)
c 95% confidence interval for the difference between the FP groups and placebo
d 95% confidence interval for the difference between the FP groups and placebo, adjusted for multiple comparisons using Dunnett's method

The sponsor concluded, "For subjects who received ICS therapy at Baseline, treatment with all three dosages of FP HFA (88mcg, 220mcg, and 440mcg) BID resulted in inferentially significant improvements in AM pre-dose percent-predicted FEV 1 compared with placebo (Sec. 7.5. Efficacy Conclusions)." As the final conclusion on efficacy, the sponsor stated, "Treatment with all three dosages of FP HFA (88mcg, 220mcg, and 440mcg) BID resulted in inferentially significant improvements in AM pre-dose percent-predicted FEV_1 compared with placebo **in subjects previously treated with daily inhaled corticosteroid** (Sec. 12, Conclusions)."

Study FAP30008

Sponsor's Conclusions on Efficacy

"The primary efficacy measure for this study was mean change from Baseline in AM pre-dose percent predicted FEV1 at Endpoint (Week 12 with LOCF) (Sec. 7.1. Primary Efficacy Measure)." The following table, from Sec. 7, *Efficacy Results*, gives a summary of the efficacy outcome.

Table 6. Efficacy results (Study FAP30008, Sec. 7)

Mean Change from Baseline in AM Pre-Dose Percent Predicted FEV_1 at Week 12 (LOCF)
(ITT Population – Study FAP30008)

	PLA HFA (N=99)	FP 88 HFA (N=100)	FP 220 HFA (N=98)	FP 440 HFA (N=100)
Baseline (n)	99	99	98	100
Mean (%)	67.0	67.0	67.3	67.1
Week 12 (n)	96	95	95	99
Mean (%)	71.1	76.3	76.8	78.1
Mean Change	4.0	9.5	9.4	11.1
LS Mean Change[a] (SE)	3.4 (1.1)	9.0[a] (1.1)	9.8[a] (1.1)	11.2[a] (1.0)
95% CI[c]	---	(2.7, 8.6)	(3.4, 9.3)	(4.9, 10.7)
95% Dunnett CI[d]	---	(2.2, 9.2)	(2.8, 9.9)	(4.3, 11.3)

Source Data: Table 7.2, Table 7.3, Table 7.4
LOCF = last observation carried forward. LS = least square. SE = standard error
Post-baseline n's are the sample sizes used for LS mean change calculation.
a p<0.001 vs. placebo (Hochberg multiplicity adjustment)
b ANCOVA, adjusted for baseline percent predicted FEV1, region, age, and gender
c 95% confidence interval for the difference between FP groups and placebo
d 95% confidence interval for the difference between FP groups and placebo, adjusted for multiple comparisons using Dunnett's method

The sponsor concluded, "For subjects who received short-acting bronchodilator therapy alone at Baseline, treatment with all three dosages of FP HFA (88mcg, 220mcg, and 440mcg) BID resulted in inferentially significantly greater improvements in AM pre-dose percent-predicted FEV1 compared with placebo (Sec. 7.5. Efficacy Conclusions)." As the final conclusion on efficacy, the sponsor stated, "Treatment with all three dosages of FP HFA (88mcg, 220mcg, and 440mcg) BID resulted in inferentially significantly greater improvements in AM pre-dose percent-predicted FEV_1 compared with placebo **in subjects previously maintained on short-acting bronchodilator therapy alone** (Sec. 11, Conclusions)."

Reviewer's Evaluation of Efficacy for Study FLTA3022

Patients' Distribution

The numbers and percentages of patients by treatment and sex are populated in Table 7. The patients appeared to be evenly distributed between the sexes.

Table 7. Patients by treatment and sex (Study FLTA3022)

	Treatment										Total	
	PlaceboHFA		FP440HFA		FP880HFA		FP440CFC		FP880CFC			
	No	%	No	%	No	%	No	%	No	%	No	%
Sex												
F	19	59.38	19	59.38	18	56.25	18	50.00	14	42.42	88	53.33
M	13	40.63	13	40.63	14	43.75	18	50.00	19	57.58	77	46.67
Total	32	100.00	32	100.00	32	100.00	36	100.00	33	100.00	165	100.00

Source: Data set: AnalysisPred3022.sd7, visit: 0, patients: ITT (SAS Code 4.)

Table 8 shows the numbers and percentages of patients by treatment and status of completion. Patients received placebo had a 65.6% of dropout rate compared with 33% among other groups. The dropout rate among FP880HFA patients is 40.6%, the highest dropout rate among treated groups. The overall rate of dropout across treatments was 32.7%. The effect of such a high rate of dropout should not be ignored while interpreting the data.

Table 8. Patients by treatment and status of completion (Study FLTA3022)

	Treatment										Total	
	PlaceboHFA		FP440HFA		FP880HFA		FP440CFC		FP880CFC			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Complete												
No	21	65.63	6	18.75	13	40.63	6	16.67	8	24.24	54	32.73
Yes	11	34.38	26	81.25	19	59.38	30	83.33	25	75.76	111	67.27
Total	32	100.00	32	100.00	32	100.00	36	100.00	33	100.00	165	100.00

Source: Data set: AnalysisPred3022.sd7, visit: 0, patients: ITT (SAS Code 5.)

Table 9 shows that the main reason for early withdrawal was the lack of efficacy. Eighteen (18) patients in placebo group dropped out, about six-fold that in any other treatment group.

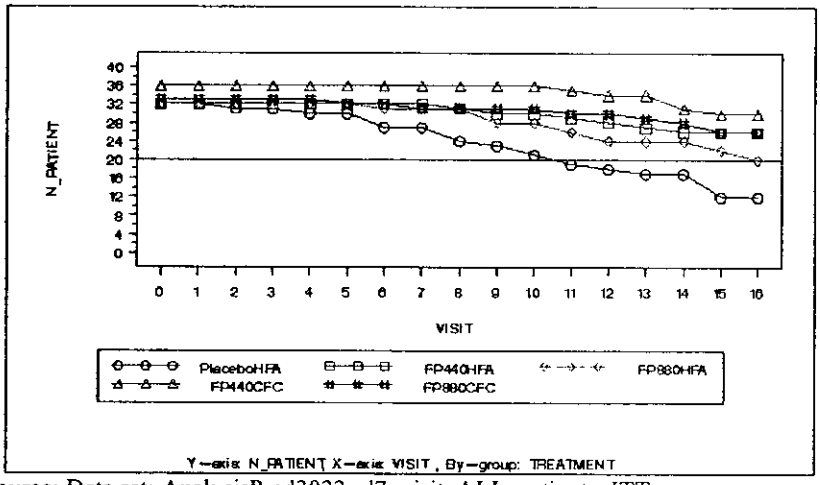
Table 9. Reasons for dropout (Study FLTA3022)

	Reason for dropout			Total
	Adverse event	Lack of efficacy	Other	
	No.	No.	No.	No.
Treatment				
PlaceboHFA		18	3	21
FP440HFA		2	4	6
FP880HFA	3	4	6	13
FP440CFC	1	3	2	6
FP880CFC	1	2	5	8
Total	5	29	20	54

Source: Data set: AnalysisPred3022.sd7, visit: 0, patients: ITT, COMPANAL=0

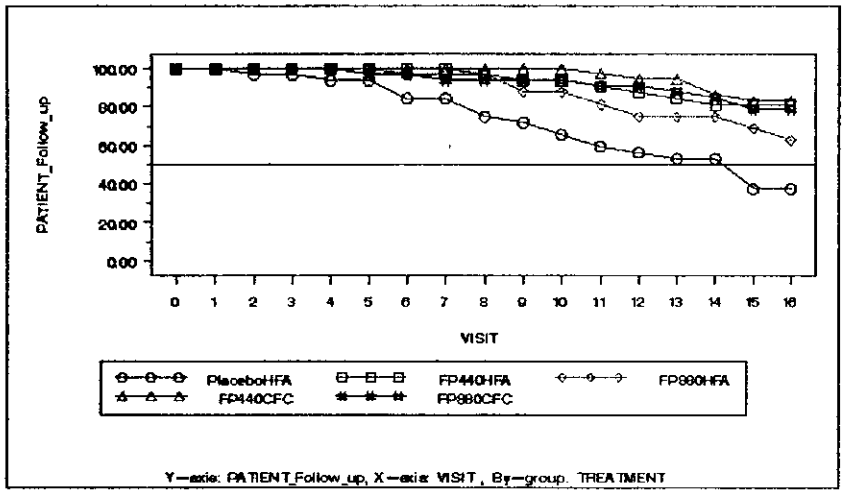
Figure 1, below, shows the number of patients staying in study by week, while Figure 2, the percentages of patients staying in study by week. The placebo patients had a higher rate of dropout than did those in other groups. At the end of the study, only 11 patients (34.4%) in the placebo group remained, while those in other groups maintained a 59.4% or more follow-up rate (See Table 8, above). Note that the use of prednisone, as the primary efficacy measure, might be influenced by the high rate of withdrawal, particularly in the placebo group; therefore it needs to be factored in the evaluation of efficacy. Perhaps the method of LOCF and any other methods of missing-data imputation, which are likely to introduce biases, should not be considered.

Figure 1. Number of patients in study by week (Study FLTA3022)



Source: Data set: AnalysisPred3022.sd7, visit: ALL, patients: ITT

Figure 2. Percent of follow-ups by week (study FLTA3022)



Source: Data set: AnalysisPred3022.sd7, visit: ALL, patients: ITT

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Reviewer's Statistical Analysis

The following Table 10 and Table 11 show simple (unadjusted) means of daily prednisone use by treatment and status of completion. Table 10 indicates that, at baseline, the mean daily prednisone uses were similar across treatment groups.

Table 10. Mean daily prednisone use at baseline (Week 0) (Study FLTA3022)

	#Patients	Prednisone use
		Mean
Treatment		
PlaceboHFA	32	14.219
FP440HFA	32	12.500
FP880HFA	32	12.734
FP440CFC	36	12.986
FP880CFC	33	14.318

Source: Data set: AnalysisPred3022.sd7, visit: Week 0, patients: ITT

The mean daily prednisone uses averaged over Weeks 1 to 16 are shown in Table 11. The mean daily prednisone uses in the placebo was about twice that in any FP groups.

Table 11. Mean daily prednisone use averaged over weeks 1-16 (Study FLTA3022)

	#Patients	Prednisone use
		Mean
Treatment		
PlaceboHFA	32	12.711
FP440HFA	32	5.380
FP880HFA	32	6.242
FP440CFC	36	4.584
FP880CFC	33	5.597

Source: Data set: AnalysisPred3022.sd7, visit: Weeks 1–16, patients: ITT

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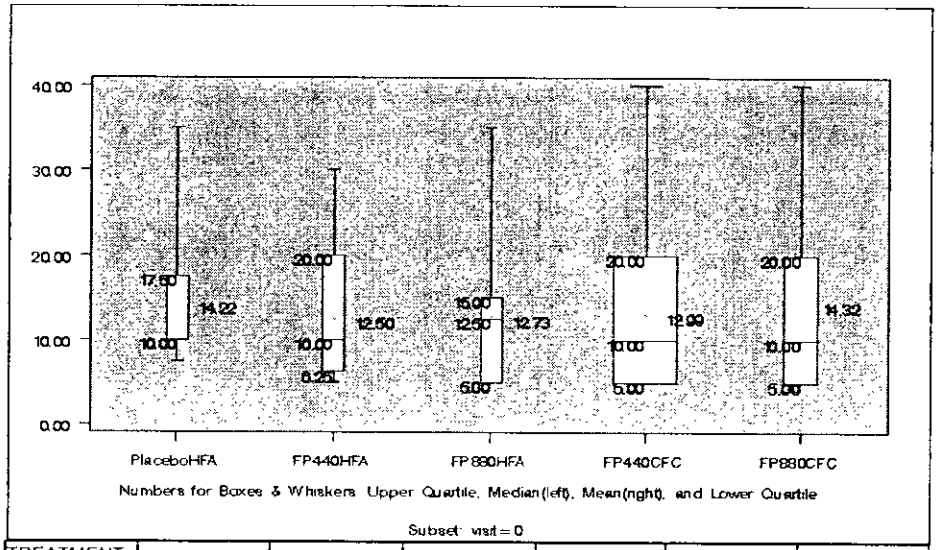
Visual displays of Table 10 and Table 11 are shown in Figure 3 and Figure 4, below. At baseline, the differences in mean prednisone uses among the treatment groups did not appear to be much different.

Figure 3. Mean daily prednisone use at baseline (Week 0) (Study FLTA3022)

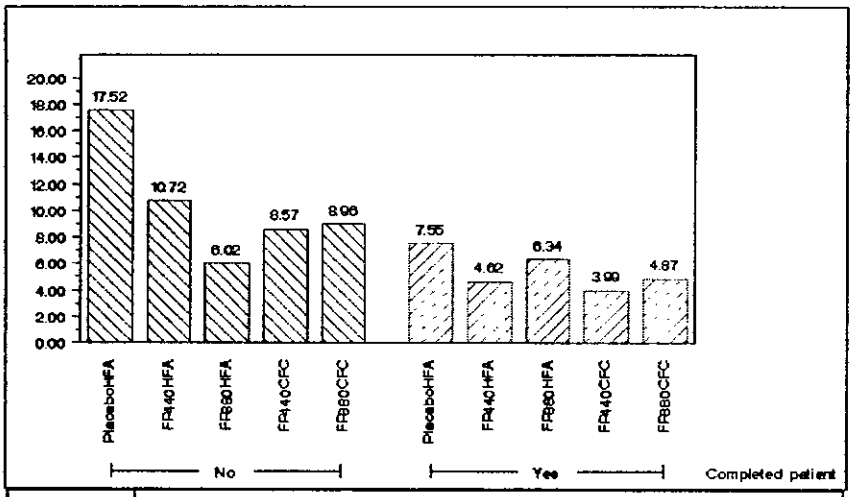


TREATMENT, Unformatted	Treatment	Mean	Std.	Upper Quartile	Median	Lower Quartile
0	PlaceboHFA	14.219	7.308	17.500	10.000	10.000
1	FP440HFA	12.500	7.014	20.000	10.000	6.250
2	FP880HFA	12.734	7.333	15.000	12.500	5.000
3	FP440CFC	12.986	8.779	20.000	10.000	5.000
4	FP880CFC	14.318	10.556	20.000	10.000	5.000

Source: Data set: AnalysisPred3022.sd7, visit: Week 0, patients: ITT

Figure 4 showed that, over weeks 1-16, the gap between the actively treated and the placebo-treated was wider among those who withdrew prematurely than those stayed for the entire trial. Note the fact that the majority of early withdrawal was due to the lack of efficacy, as shown in Table 9, above. This might, to some extent, explain why patients of early withdrawal, in general, relied (used) more prednisone than did the completers. Please note that, the mean prednisone use between FP880HFA and placebo were similar: 6.34 and 7.55 among the completers

Figure 4. Mean daily prednisone use averaged over weeks 1-16 (Study FLTA3022)

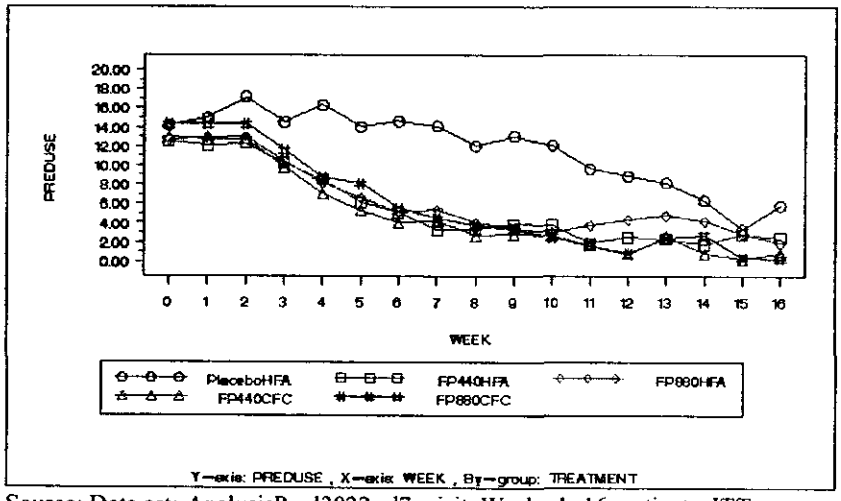


	Completed patient					
	No			Yes		
	#Patients	Prednisone use Mean	N*	#Patients	Prednisone use Mean	N*
Treatment						
PlaceboHFA	21	17.516	195	11	7.550	176
FP440HFA	6	10.722	61	26	4.622	416
FP880HFA	13	6.023	145	19	6.344	304
FP440CFC	6	8.574	74	30	3.986	480
FP880CFC	8	8.961	89	25	4.873	400

*: "N" represents the number of observations based on which the mean is calculated.
Source: Data set: AnalysisPred3022.sd7, visit: Weeks from 1 to 16, patients: All

Although the primary efficacy variable was defined as the mean daily use of prednisone over 16 weeks, it is useful to visualize how weekly averages changed. Figure 5, below, indicates a generally downward trend of prednisone use across treatment groups. Because of the high percentages of dropouts, Figure 6 and Figure 7 display by-week mean daily prednisone uses for completers and dropouts, respectively.

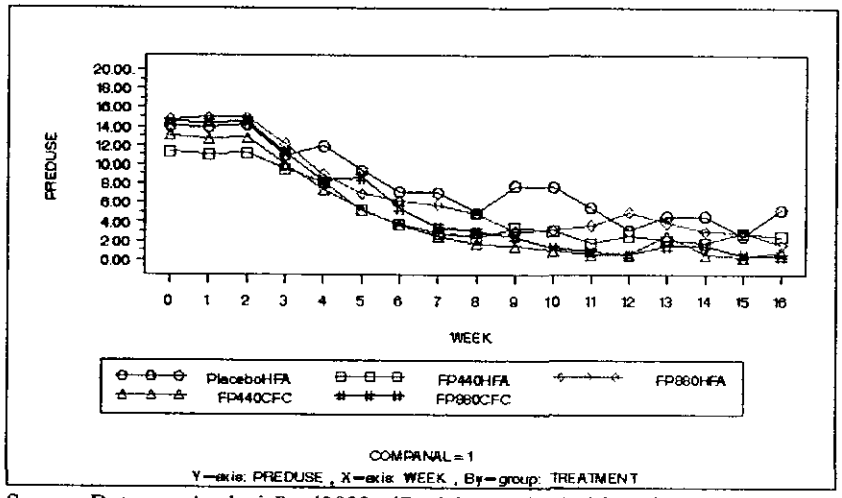
Figure 5. Mean daily prednisone use by week (Study FLTA3022)



Source: Data set: AnalysisPred3022.sd7, visit: Weeks 1–16, patients: ITT

For the completers, the pattern of the mean daily prednisone uses was similar across all treatment groups. The reduction of prednisone use among the placebo patients appears to be similar among drug-treated patients.

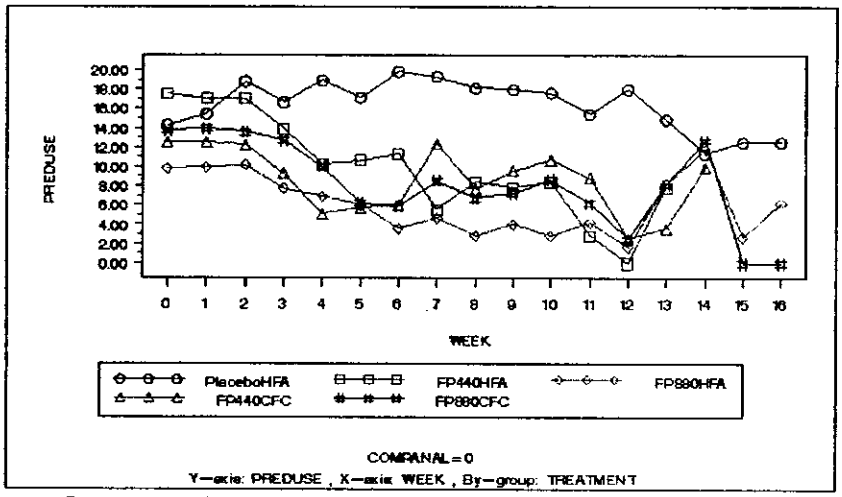
Figure 6. Mean daily prednisone use by week for completers (Study FLTA3022)



Source: Data set: AnalysisPred3022.sd7, visit: Weeks 1–16, patients: ITT, COMPANAL=1

The mean daily prednisone uses demonstrated greater variations among the dropouts than the completers (Figure 7, below).

Figure 7. Mean prednisone use by week for dropouts (Study FLTA3022)



Source: Data set: AnalysisPred3022.sd7, visit: Weeks 1–16, patients: ITT, COMPANAL=0

The reviewer's statistical analysis was done applying ANCOVA, including the terms of TREATMENT, CENTER, PATIENT'S COMPLETION STATUS, and PRE-TREATMENT MEAN DAILY PREDNISONE USE as the baseline. Table 12 shows that the mean daily uses of prednisone were significantly less among the treated groups than that among the placebo group.

Table 12. Comparisons of 16-week mean daily prednisone uses between treated groups and the placebo group (Study FLTA3022)

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
FP880HFA vs placebo	1	3669.151265	3669.151265	78.97	<.0001
FP880CFC vs placebo	1	4459.052253	4459.052253	95.97	<.0001
FP440HFA vs placebo	1	3592.243234	3592.243234	77.31	<.0001
FP440CFC vs placebo	1	5401.180026	5401.180026	116.25	<.0001

Source: Data set: AnalysisPred3022.sd7, visit: Weeks 1–16, patients: ITT
SAS Code: SAS Code 1. ANCOVA for Study FLTA3022

The following subset analysis indicates that, among the completers, the difference in mean prednisone use between FP880HFA and placebo was not statistically significant (Table 13).

Table 13. Comparisons of 16-week mean daily prednisone uses between treated groups and the placebo group among the completers (Study FLTA3022)

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
FP880HFA vs placebo	1	87.708187	87.708187	2.22	0.1367
FP880CFC vs placebo	1	671.996383	671.996383	16.98	<.0001
FP440HFA vs placebo	1	510.029562	510.029562	12.89	0.0003
FP440CFC vs placebo	1	1003.658794	1003.658794	25.37	<.0001

Source: Data set: AnalysisPred3022.sd7, visit: Weeks 1–16, patients: ITT and COMPANAL=1
SAS Code: SAS Code 1. ANCOVA for Study FLTA3022

Reviewer's Conclusion for Study FLTA3022

- The percentages of dropouts were high: 65.6% in placebo group and ranging 16.7-40.6% in FP treatment groups. The major reason for dropout was lack of efficacy (in treated groups).
- The 16-week mean daily uses of prednisone were significantly less among the FP treatment groups than among the placebo patients.
- Among the completers, the difference in mean prednisone use between FP880mcg HFA and placebo did not appear to be much different, though numerically FP880mcg HFA had a slightly lower LS-mean than did placebo.

Reviewer's Evaluation of Efficacy for Study FAP30007

Patients' Distribution

The number and percentage of patients by treatment and sex are listed in Table 7. The number and percentage of patients are slightly higher in the females than in the males (223 and 59% vs. 154 and 41%). But the distribution of patients between the two sex groups appeared to be fairly balanced.

Table 14. Patients by treatment and sex (Study FAP30007)

	Treatment								Total	
	PlaceboHFA		FP88HFA		FP220HFA		FP440HFA			
	N	%	N	%	N	%	N	%	N	%
Sex										
F	50	57.47	50	53.76	60	57.69	63	67.74	223	59 15
M	37	42.53	43	46 24	44	42 31	30	32.26	154	40.85
Total	87	100.00	93	100 00	104	100.00	93	100.00	377	100.00

Source: Data set: Pfi30007.sd7, visit: 20, patients: ITT

Table 15 shows the numbers and percentages of patients by treatment and status of completion. A total of 54% of patients received placebo dropped out, compared with a combined 46% dropout rate among treated groups. The overall percentage of dropout across treatments was 23.6%. The effect of such a high rate of dropouts among placebo treated patients was considered during the efficacy evaluation.

Table 15. Patients by treatment and status of completion (Study FAP30007)

	Treatment								Total	
	PlaceboHFA		FP88HFA		FP220HFA		FP440HFA			
	N	%	N	%	N	%	N	%	N	%
Completed patient										
No	47	54.02	8	8 60	20	19.23	14	15 05	89	23 61
Yes	40	45.98	85	91.40	84	80.77	79	84.95	288	76.39
Total	87	100.00	93	100.00	104	100 00	93	100.00	377	100.00

Source: Data set: Pfi30007.sd7, visit: 20, patients: ITT

Table 9 indicates that the number-one cause for dropout was lack of efficacy. A total of 37 patients in the placebo group dropped out due to lack of efficacy, representing a much higher number of dropouts than that in any other treatment group and for any other reason.

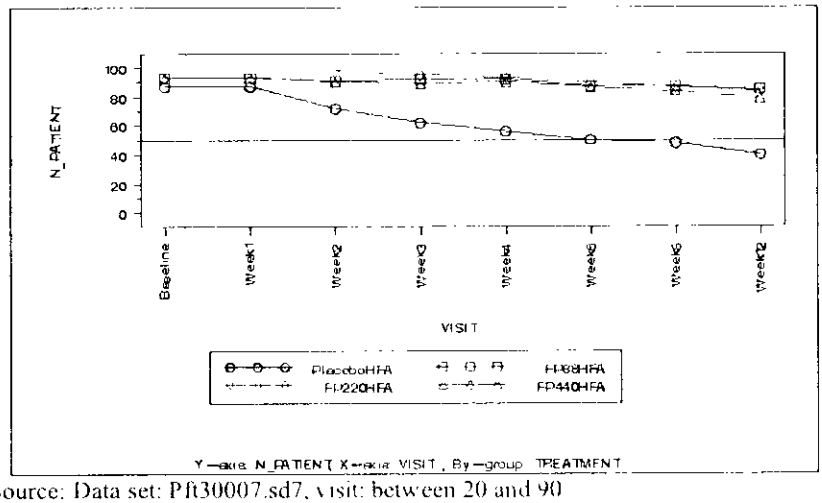
Table 16. Reasons for dropout (Study FAP30007)

	Treatment				Total
	PlaceboHFA	FP88HFA	FP220HFA	FP440HFA	
	N	N	N	N	N
Reason for dropout					
Adverse event	4		3	3	10
Consent withdrawn	1	1	1	1	4
Lack of efficacy	37	6	11	5	59
Noncompliance				1	1
Other	3	1	2	2	8
Protocol violation	2		3	2	7
Total	47	8	20	14	89

Source: Data set: Pft30007.sd7, visit: 20, patients: ITT and COMPANAL= 0

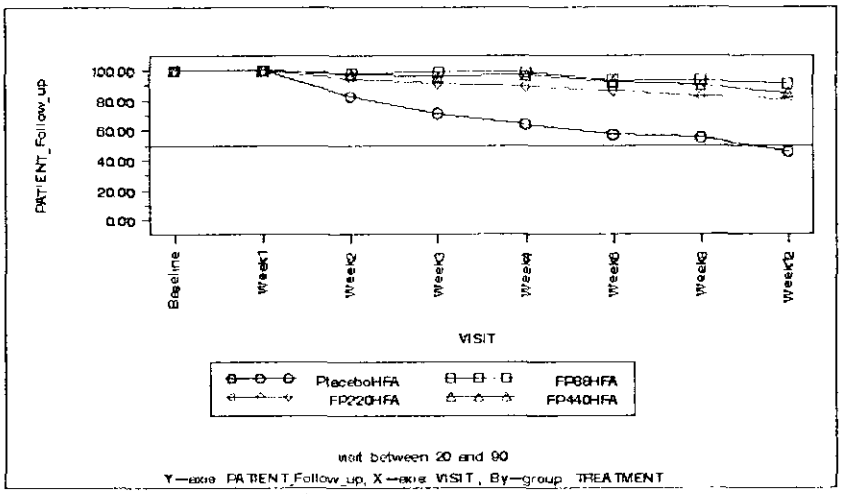
Figure 8, below, shows the number of patients staying in study by week, while Figure 9, the percentage of patients staying in study by week. The placebo patients started to withdraw significantly at Week 2 and onwards. The trend of dropout was slower among the treatment groups. Note that, at Week 12, the rate of follow-up for the placebo group was 45.98% (Figure 9).

Figure 8. Number of patients in study by week (Study FAP30007)



Source: Data set: Pft30007.sd7, visit: between 20 and 90

Figure 9. Percent of follow-ups by week (study FAP30007)



Source: Pft30007analysis, visit between 20 and 90

Reviewer's Statistical Analysis

Table 17, Table 18, and Table 19 show the number of patients and the unadjusted (raw) means of percent predicted FEV_1 at baseline, Week 12, and at endpoint (Week 12 and LOCF for missing at Week 12).

Table 17. Mean percent predicted FEV_1 at baseline (Study FAP30007)

	#Patients	FEV1 Pct Predicted at baseline
		Mean
Treatment		
PlaceboHFA	87	65.744
FP88HFA	93	65.004
FP220HFA	104	65.504
FP440HFA	93	66.414

Source: Data set: Pft30007.sd7, visit: 20, patients: ITT

Table 18. Mean percent predicted FEV_1 at Week 12 (Study FAP30007)

	#Patients	FEV1: pct predicted
		Mean
Treatment		
PlaceboHFA	40	66.535
FP88HFA	85	70.212
FP220HFA	84	73.101
FP440HFA	79	74.487

Source: Data set: Pft30007.sd7, visit: 90, patients: ITT

Table 19. Mean percent predicted FEV_1 at endpoint (Week 12 LOCF) (Study FAP30007)

	#Patients	FEV1: pct predicted
		Mean
Treatment		
PlaceboHFA	87	63.549
FP88HFA	93	69.097
FP220HFA	104	70.633
FP440HFA	93	73.009

Source: Data set: Pft30007.sd7, visit: Endpoint, patients: ITT

The following two tables, Table 20, and Table 21 show the number of patients and the unadjusted (raw) means of changes in percent predicted FEV_1 from baseline, measured at Week 12, and at endpoint (Week 12 and LOCF for missing at Week 12), respectively.

Table 20. Mean change in percent predicted FEV_1 from baseline at Week 12 (Study FAP30007)

	#Patients	FEV1: Chg in Pct Predicted from baseline
		Mean
Treatment		
PlaceboHFA	40	-0.082
FP88HFA	85	4.751
FP220HFA	84	6.374
FP440HFA	79	7.705

Source: Data set: Pft30007.sd7, visit: 90, patients: ITT

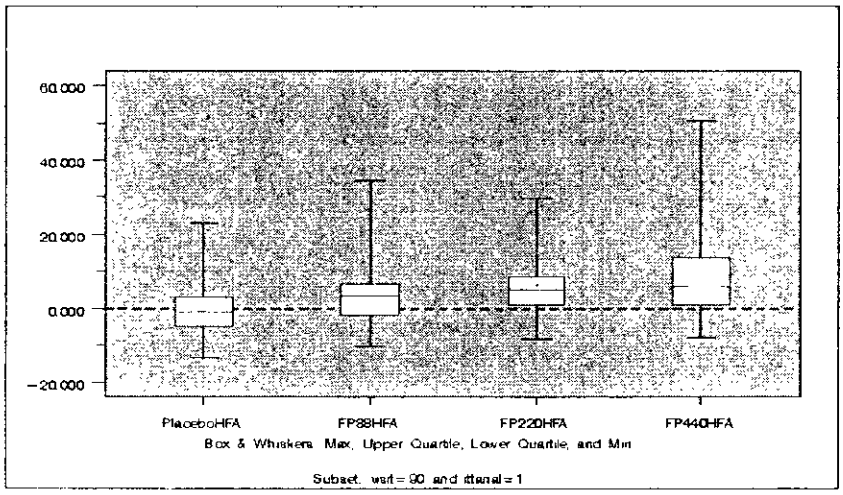
Table 21. Mean change in percent predicted FEV_1 from baseline at endpoint: Week 12 LOCF (Study FAP30007)

	#Patients	FEV1: Chg in Pct Predicted from baseline
		Mean
Treatment		
PlaceboHFA	87	-2.194
FP88HFA	93	4.092
FP220HFA	104	5.129
FP440HFA	93	6.595

Source: Data set: Pft30007.sd7, visit: endpoint, patients: ITT

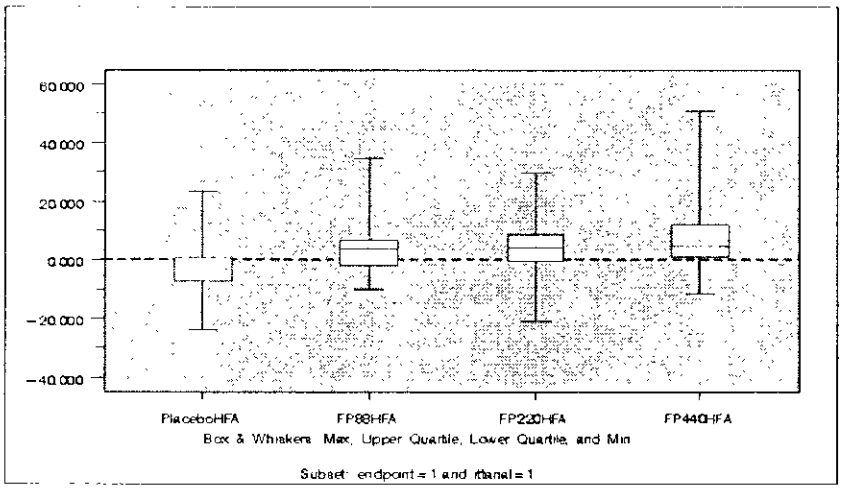
Figure 10 and Figure 11, below, depict the means shown in Table 20 and Table 21 above. Note that the change in percent predicted FEV_1 from baseline increases with dose.

Figure 10. Change in percent predicted FEV_1 from baseline at Week 12 (Study FAP30007)



Source: Data set: Pft30007analysis.sd7, visit: 90, patients: ITT

Figure 11. Change in percent predicted FEV_1 from baseline at endpoint: Week 12 LOCF (Study FAP30007)



Source: Data set: Pft30007analysis.sd7, visit: endpoint, patients: ITT

Analysis of covariance (ANCOVA) was performed on the change in percent predicted FEV_1 from baseline, at Week 12 and at endpoint (Week 12 LOCF). Because of the high percentage of dropouts, particularly in the control group, the results with and without LOCF were compared to confirm the consistency. The ANCOVA model includes terms of treatment, center, status of completion, and baseline percent predicted FEV_1 as the covariate.

Table 22 Shows the LS-means and 95% confidence intervals for the mean percent predict FEV_1 changes from baseline.

Table 22. 95% confidence intervals for the mean percent predict FEV_1 changes from baseline (Study FAP30007)

TREATMENT	FEVPCTPREDCHG LSMEAN	95% Confidence Limits	
PlaceboHFA	-1.811428	-3.910486	0.287630
FP88HFA	2.065881	-0.144824	4.276585
FP220HFA	3.162914	1.171041	5.154787
FP440HFA	5.275293	3.081617	7.468969

Source: Data set: Pft30007.sd7, visit: endpoint, patients: ITT

Table 23 shows the test result of the following null hypothesis: There is no difference between the FP treatment groups and the placebo in percent predicted FEV_1 changes from baseline. Multiple comparisons were adjusted using the Dunnett's method to control the overall type-1 error under the 0.05 level. Note that the means here are LS-means. The differences in percent predicted FEV_1 changes from baseline between the FP treatments and the placebo are shown to be statistically significant.

Table 23. ANCOVA of Change in percent predicted FEV_1 from baseline at endpoint: Comparisons with placebo (Week 12 LOCF) (Study FAP30007)

TREATMENT	FEVPCTPREDCHG LSMEAN	H0:LSMean=Control
		Pr > |t|
PlaceboHFA	-1.81142829	
FP88HFA	2.06588057	0.0240
FP220HFA	3.16291400	0.0018
FP440HFA	5.27529290	<.0001

Source: Data set: Pft30007.sd7, visit: endpoint, patients: ITT

The comparisons between FP treatments and placebo, above, can also be expressed in terms of confidence intervals. In Table 24, "j" represent the placebo, and "i=2," FP88HFA, "i=3," FP220HFA; "i=4," FP440HFA.

Table 24. 95% confidence intervals of the differences in percent predicted FEV_1 from baseline between FP treatments and placebo (Study FAP30007)

Least Squares Means for Effect TREATMENT				
i	j	Difference Between Means	Simultaneous 95% Confidence Limits for LSMean(i)-LSMean(j)	
2	1	3.877309	0.414569	7.340049
3	1	4.974342	1.599074	8.349611
4	1	7.086721	3.580620	10.592822

Source: Data set: Pft30007.sd7, visit: endpoint, patients: ITT

The differences in percent predicted FEV_1 changes from baseline between the FP treatments and the placebo are shown to be statistically significant.

For additional information, Table 25 lists selected tables from the ANCOVA. The program used to compute the tables is: Analysis3000730008.SAS.

Table 25. ANCOVA model (Study FAP30007)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	83	12790.58919	154.10348	2.25	<.0001
Error	293	20111.52322	68.64001		
Corrected Total	376	32902.11241			

R-Square	Coeff Var	Root MSE	FEVPCTPREDCHG Mean
0.388747	233.7188	8.284927	3.544828

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TREATMENT	3	1596.106298	532.035433	7.75	<.0001
CENTER	78	6743.180073	86.451027	1.26	0.0899
COMPANAL	1	1812.238456	1812.238456	26.40	<.0001
FEVPCTPREDBASE	1	5.903992	5.903992	0.09	0.7695

Source: Data set: Pft30007.sd7, visit: endpoint, patients: ITT

Comments on Sponsor's Data

The sponsor applied the LOCF approach to fill in the missing observations. For some patients' data, this method was not done as described : The last observations before missing data were not used to carry forward. Instead, numbers other than last observations were used. In Study FAP30007, the number of patients whose data were treated this way is shown in Table 26. A complete list of these patients can be found in the Appendix.

Table 26. Patients with incorrect estimates for missing observations while LOCF was applied (Study FAP30007)

Treatment	Number of Patients
PlaceboHFA	50
FP88HFA	15
FP220HFA	12
FP440HFA	14
All	91

Source: Pftsumm / Computer program: SAS Code 3

Reviewer's Conclusion for Study FAP30007

The statistical results are summarized as follows:

- The differences in percent predicted FEV_1 changes from baseline between the FP treatments and the placebo prove to be statistically significant.
- The same analysis was repeated using Week-12 data alone (without LOCF). It reached the same statistical conclusions.

Reviewer's Evaluation of Efficacy for Study FAP30008

Patients' Distribution

The numbers and percentages of patients by treatment and sex are listed in Table 27. The number and percentage of patients are slightly higher in the females than in the males (201 and 53% vs. 177 and 47%). But the distribution of patients between the two sex groups appeared to be fairly balanced.

Table 27. Patients by treatment and sex (Study FAP30008)

	Treatment								Total	
	PlaceboHFA		FP88HFA		FP220HFA		FP440HFA			
	N	%	N	%	N	%	N	%	N	%
Sex										
F	49	52.69	59	62.11	38	41.76	55	55.56	201	53.17
M	44	47.31	36	37.89	53	58.24	44	44.44	177	46.83
Total	93	100.00	95	100.00	91	100.00	99	100.00	378	100.00

Source: Data set: Pft30008.sd7, visit: 20, patients: ITT

Table 28 shows the numbers and percentages of patients by treatment and status of completion. A total of 26% of patients received placebo dropped out, compared with a combined 15% dropout rate among treated groups. The overall percentage of dropout across treatments was 17.5%.

Table 28. Patients by treatment and status of completion (Study FAP30008)

	Treatment								Total	
	PlaceboHFA		FP88HFA		FP220HFA		FP440HFA			
	N	%	N	%	N	%	N	%	N	%
Completed patient										
No	24	25.81	21	22.11	11	12.09	10	10.10	66	17.46
Yes	69	74.19	74	77.89	80	87.91	89	89.90	312	82.54
Total	93	100.00	95	100.00	91	100.00	99	100.00	378	100.00

Source: Data set: Pft30008.sd7, visit: 20, patients: ITT

Table 9 indicates that the number-one cause for dropout was the lack of efficacy. A total of 12 patients in the placebo group and 9 in FP88HFA group dropped out due to lack of efficacy, representing a much higher number of dropouts due to lack of efficacy than those in FP220HFA and FP440HFA groups.

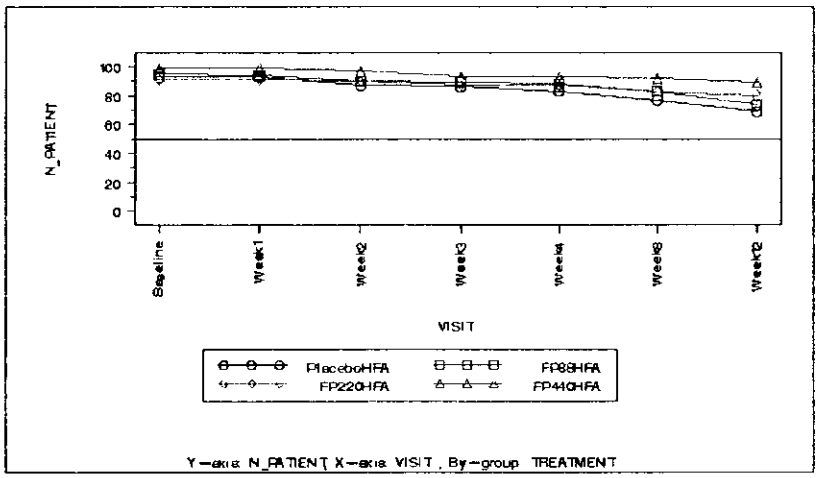
Table 29. Reasons for dropout (Study FAP30008)

	Treatment				Total
	PlaceboHFA	FP88HFA	FP220HFA	FP440HFA	
	N	N	N	N	N
Reason for dropout					
Adverse event			1	4	5
Consent withdrawn	5	5	4	2	16
Lack of efficacy	12	9	3	2	26
Lost to follow up	1	2		1	4
Noncompliance	1	2			3
Other	2	2	3		7
Protocol violation	3	1		1	5
Total	24	21	11	10	66

Source: Data set: Pft30008.sd7, visit: 20, patients: ITT and COMPANAL=0

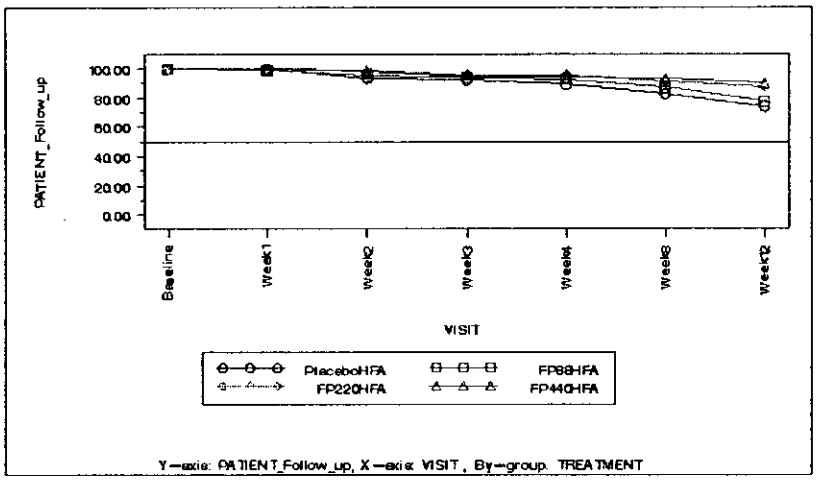
Figure 12, below, shows the number of patients staying in study by week, while Figure 13, the percentage of patients staying in study by week.

Figure 12. Number of patients in study by week (Study FAP30008)



Source: Data set: Pft30008.sd7, visit: between 20 and 90

Figure 13. Percent of follow-ups by week (study FAP30008)



Source: Pft30008analysis, visit between 20 and 90

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Reviewer's Statistical Analysis

Table 30, Table 31, and Table 32 show the number of patients and the unadjusted (raw) means of percent predicted FEV_1 at baseline, Week 12, and at endpoint (Week 12 and LOCF for missing at Week 12).

Table 30. Mean percent predicted FEV_1 at baseline (Study FAP30008)

	#Patients	FEV1: Pct Predicted at baseline
		Mean
Treatment		
PlaceboHFA	93	66.975
FP88HFA	95	66.703
FP220HFA	91	67.248
FP440HFA	99	66.995

Source: Data set: Pft30008.sd7, visit: 20, patients: ITT

Table 31. Mean percent predicted FEV_1 at Week 12 (Study FAP30008)

	#Patients	FEV1: pct predicted
		Mean
Treatment		
PlaceboHFA	69	72.819
FP88HFA	74	79.165
FP220HFA	80	77.648
FP440HFA	89	78.718

Source: Data set: Pft30008.sd7, visit: 90, patients: ITT

Table 32. Mean percent predicted FEV_1 at endpoint (Week 12 LOCF) (Study FAP30008)

	#Patients	FEV1: pct predicted
		Mean
Treatment		
PlaceboHFA	93	71.552
FP88HFA	95	76.397
FP220HFA	91	77.378
FP440HFA	99	78.281

Source: Data set: Pft30008.sd7, visit: Endpoint, patients: ITT

The following two tables, Table 33 and Table 34 show the number of patients and the unadjusted (raw) means of changes in percent predicted FEV_1 from baseline, measured at Week 12, and at endpoint (Week 12 and LOCF for missing at Week 12), respectively.

Table 33. Mean change in percent predicted FEV_1 from baseline at Week 12 (Study FAP30008)

	#Patients	FEV1: Chg in Pct Predicted from baseline
		Mean
Treatment		
PlaceboHFA	69	5.812
FP88HFA	74	11.649
FP220HFA	80	10.916
FP440HFA	89	11.751

Source: Data set: Pft30008.sd7, visit: 90, patients: ITT

Table 34. Mean change in percent predicted FEV_1 from baseline at endpoint: Week 12 LOCF (Study FAP30008)

	#Patients	FEV1: Chg in Pct Predicted from baseline
		Mean
Treatment		
PlaceboHFA	93	4.576
FP88HFA	95	9.694
FP220HFA	91	10.130
FP440HFA	99	11.286

Source: Data set: Pft30008.sd7, visit: endpoint, patients: ITT

Figure 14 and Figure 15, below, depict the means shown in Table 33 and Table 34, above.

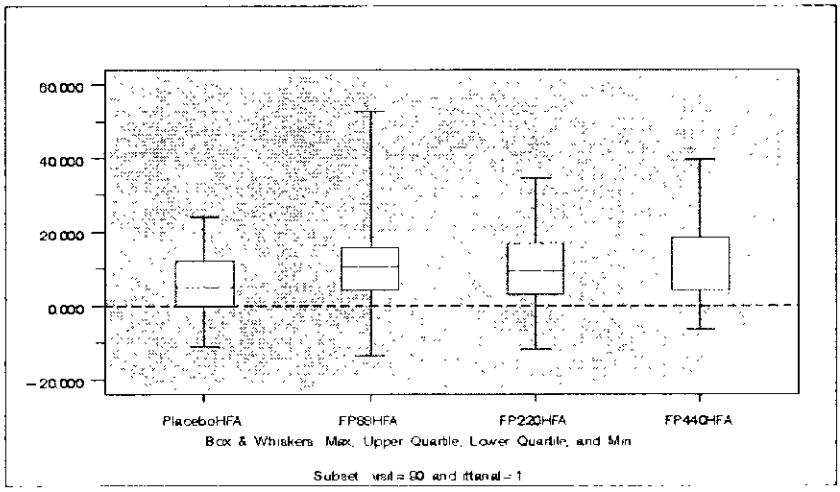
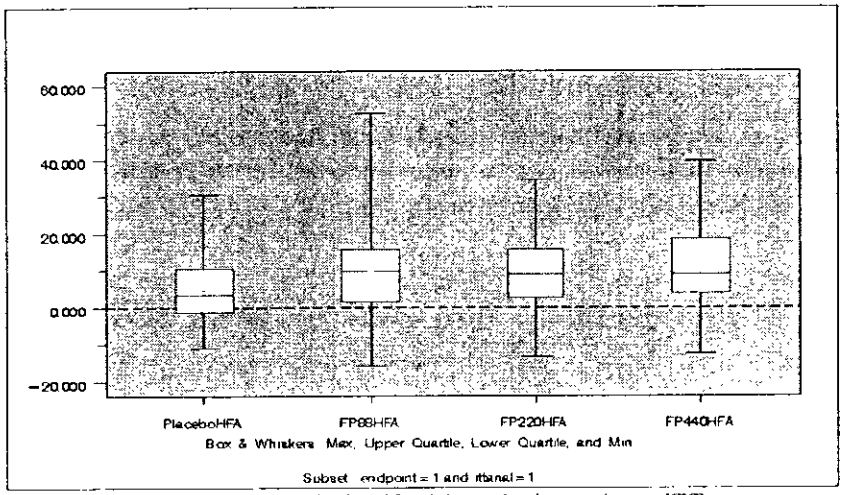


Figure 14. Change in percent predicted FEV_1 from baseline at Week 12 (Study FAP30008)

Source: Data set: Pft30008analysis.sd7, visit: 90, patients. ITT

Figure 15. Change in percent predicted FEV_1 from baseline at endpoint: Week 12 LOCF (Study FAP30008)



Source: Data set: Pft30008analysis.sd7, visit: endpoint, patients: ITT

Analysis of covariance (ANCOVA) was performed on the change in percent predicted FEV_1 from baseline, at Week 12 and at endpoint (Week 12 LOCF). Because of the high percentage of dropouts, particularly in the control group, the results with and without LOCF were compared to confirm the consistency. The ANCOVA model includes terms of treatment, center, status of completion, and baseline percent predicted FEV_1 as the covariate.

Table 35 Shows the LS-means and 95% confidence intervals for the mean percent predict FEV_1 changes from baseline.

Table 35. 95% confidence intervals for the mean percent predict FEV_1 changes from baseline (Study FAP30008)

TREATMENT	FEVPCTPREDCHG LSMEAN	95% Confidence Limits	
PlaceboHFA	3.223117	0.871867	5.574367
FP88HFA	8.034501	5.625081	10.443921
FP220HFA	8.208459	5.642238	10.774681
FP440HFA	8.259199	5.772272	10.746125

Source: Data set: Pft30008.sd7, visit: endpoint, patients: ITT

Table 36 shows the test result of the following null hypothesis: There is no difference between the FP treatment groups and the placebo in percent predicted FEV_1 changes from baseline. Multiple comparisons were adjusted using the Dunnett's method to control the overall type-1 error under the 0.05 level. Note that the means here are LS-means.

Table 36. ANCOVA results: Change in percent predicted FEV_1 from baseline at endpoint (Week 12 LOCF) (Study FAP30008)

TREATMENT	FEVPCTPREDCHG LSMEAN	H0:LSMean=Control
		Pr > |t|
PlaceboHFA	3.22311666	
FP88HFA	8.03450053	0.0057
FP220HFA	8.20845922	0.0037
FP440HFA	8.25919885	0.0028

Source: Data set: Pft30008.sd7, visit: endpoint, patients: ITT

The differences in percent predicted FEV_1 changes from baseline between the FP treatments and the placebo are shown to be statistically significant.

The comparisons between FP treatments and placebo, above, can also be expressed in terms of confidence intervals. In Table 24, "j" represent the placebo, and "i=2," FP88HFA; "i=3," FP220HFA; "i=4," FP440HFA.

Table 37. 95% confidence intervals of the differences in percent predicted FEV_1 from baseline between FP treatments and placebo (Study FAP30008)

Least Squares Means for Effect TREATMENT				
i	j	Difference Between Means	Simultaneous 95% Confidence Limits for LSMean(i)-LSMean(j)	
2	1	4.811384	1.167724	8.455044
3	1	4.985343	1.360511	8.610175
4	1	5.036082	1.469469	8.602696

Source: Data set: Pft30008.sd7, visit: endpoint, patients: ITT

For additional information, Table 25 lists key tables from the ANCOVA. The program used to compute the tables is: Anal3000830008.SAS (See SAS Code 2).

Table 38. ANCOVA model (Study FAP30008)

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	80	15941.99246	199.27491	2.34	<.0001
Error	297	25279.53601	85.11628		
Corrected Total	377	41221.52847			

R-Square	Coeff Var	Root MSE	FEVPCTPREDCHG Mean
0.386739	103.0060	9.225849	8.956614

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TREATMENT	3	1326.703513	442.234504	5.20	0.0016
CENTER	75	7243.250217	96.576670	1.13	0.2312
COMPANAL	1	1052.440264	1052.440264	12.36	0.0005
FEVPCTPREDBASE	1	4036.759620	4036.759620	47.43	<.0001

Source: Data set: Pft30008.sd7, visit: endpoint, patients: ITT

Comments on Sponsor's Data

The sponsor applied LOCF approach to fill in the missing observations. For some patients' data, this method was not done as described : The last observations before missing data were not used to carry forward. Instead, numbers other than last observations were used. In Study FAP30007, the number of patients whose data were treated this way is shown in Table 39. A complete list of these patients can be found in the Appendix.

Table 39. Patients with incorrect estimates for missing observations while LOCF was applied (Study FAP30008)

Treatment	Number of Patients
PlaceboHFA	23
FP88HFA	16
FP220HFA	9
FP440HFA	9
All	57

Source: Pftsumm / Computer program: SAS Code 3

Reviewer's Conclusion for Study FAP30008

The statistical results are summarized as follows:

- The differences in percent predicted FEV_1 changes from baseline between the FP treatments and the placebo prove to be statistically significant.
- The same analysis was repeated using Week-12 data alone (without LOCF). It reached the same statistical conclusions.

7 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

Sponsor's Statistical Method

From NDA, FLTA3022.PDF:

5.4.4. Multiple Comparisons and Multiplicity
The protocol stated that a protected (after an overall treatments comparison test) analysis between treatment groups would be used to detect differences and that pairwise treatment testing would be viewed as descriptive when the overall treatment test was not statistically significant. However, this is an older methodology that is not currently the standard approach used in GlaxoWellcome US Clinical Statistics. Instead a sequential approach was used, detailed in the Data Analysis Plan, and described below.

Pairwise comparisons to placebo were performed in a sequential manner, beginning with the FP 880mcg HFA group and the FP 880mcg CFC group. If neither of these comparisons was significantly different from placebo, further p-values were not interpreted, since efficacy relative to placebo was not demonstrated by the test product if the high dose was not different than placebo. If these p-values were significant, comparisons to placebo were interpreted for the FP 440mcg HFA group and the FP 440mcg CFC group.

A comparison to determine whether there was parallelism in doses across propellants was also undertaken to establish whether similar patterns in doses exist for the two propellants. Parallelism here was the condition where the difference between the effects of the two doses was the same for both propellants, i.e. there is no interaction between dose and propellant. Parallelism was assessed in order to justify the combination of doses across propellants and the combination of propellants across doses.

Because the comparisons between propellants were related to equivalency (and not superiority), confidence intervals were used. Since a clinical equivalency criterion was not established a priori, confidence intervals were an informative method to assess clinical comparability/equivalency. If all active group comparisons were significantly different from placebo, and there was evidence for parallelism in dosings across propellants, then the confidence interval comparing both dose groups of HFA propellant to both dose groups of CFC propellant was considered the confidence interval of primary interest. If parallelism was not established, then little emphasis was placed on this confidence interval, since if the high dose of one propellant was more similar to the low dose of the other propellant, then grouping doses within propellants was not justified. (If the parallelism contrast [which can also be seen as an interaction between propellant and dose] was significant, an investigation of the cause was undertaken to assess the degree to which the propellants and doses had an interaction.)

The dose comparisons were made using both confidence intervals and p-values. If the parallelism contrast was not significant (suggesting parallelism holds for this study), then the primary dosing comparison of interest was both high dose groups compared to both low dose groups. If there appeared to be significant interaction between propellant and dose, then the individual treatment groups were compared.

From Protocol and Protocol Amendments, FLTA3022.PDF

5.3.5. Efficacy

The primary measure of efficacy is the mean daily oral prednisone use. Other measures of efficacy include the reduction in oral prednisone dose, the mean dose of prednisone at baseline and endpoint, the mean change from baseline in prednisone dose, duration of study participation, FEV_1, subject-administered PEF, subject-rated daily symptom scores, nighttime awakenings, and inhaled Ventolin® use.

A protected (after an overall treatments comparison test) analysis between treatment groups will be used to detect differences. Pairwise treatment testing will be viewed as descriptive when the overall treatments test is not statistically significant.

1. **Mean Daily Oral Prednisone Use**

   The dose of oral prednisone over the course of the study will be determined for each subject and summarized by treatment group. The total prednisone use will incorporate both regular maintenance doses of oral prednisone as well as those doses taken during the entire period of an oral prednisone burst. Treatment-related effects will be assessed by comparison of the mean daily dose of oral prednisone between treatment groups.

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✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

Concurrence

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