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RESEARCH**

APPLICATION NUMBER:

21-247

STATISTICAL REVIEW(S)

Statistical Review and Analysis
Clinical

NDA #: 21,247
Applicant: Forest Labs
Name of Drug: Aerobid (flunisolide hemihydrate) HFA Inhaler
Indication: Treatment of Asthma
Documents Reviewed: Amendment dated February 14, 2001.

I. Background

This amendment refers to the NDA 21247 submission of March 9, 2000. A statistical review on this NDA was issued on March 2, 2001. In an inspection of Site 26 (Dr. Leonard Caputo) in Study ANC-MD-03 (the pediatric study), the data integrity of this site was questioned. The agency notified the sponsor and requested a reanalysis of the data from Study ANC-MD-03, deleting Dr. Caputo's patients. This amendment of February 14, 2001 provides the reanalysis of percent predicted FEV₁ and in-clinic PEF_R with Dr. Caputo's patients deleted. Only the results for percent predicted FEV₁ are presented in this review, because the in-clinic PEF_R was not significant in either submission (with or without Dr. Caputo's patients).

One patient (2614) of Dr. Caputo had already been excluded from the original analyses of the 6-11 years age group in this study, because he was randomized as if he was 4-5 years of age rather than his true age of 6.

II. Sponsor's reanalyses

Dr. Caputo enrolled a total of 22 patients, of which 20 were randomized and 17 were included in the intent-to-treat (ITT) population in the original analyses. Fourteen of his patients were in the 6- to 11-year-old group.

Treatment Means (Standard Deviations) for Percent-Predicted FEV₁ for Patients Aged 6-11 Years with Dr. Caputo's patients deleted. Study ANC-MD-03.

	Baseline	12 Weeks (LOCF)	Change
Placebo (N=93)	84.9 (14.36)	81.7 (17.62)	-3.3 (13.52)
HFA 85 mcg BID (N= 100)	88.8 (12.40)	90.0 (17.44)	1.2 (12.15)
HFA 170 mcg BID (N=100)	87.6 (14.03)	88.0 (18.14)	0.4 (12.18)
CFC 250 mcg BID (N=107)	88.2 (16.11)	88.6 (16.97)	0.5 (13.74)
CFC 500 mcg BID (N=99)	87.6 (14.76)	90.3 (13.53)	2.7 (9.62)

Keywords: Clinical Studies, NDA review

Treatment Effects and P-values from ANCOVA (Pairwise) for Percent -Predicted FEV₁ for Patients Aged 6-11 Years.

Treatment	Trt Effect ^a	P-Value
HFA 85 mcg BID	4.82	0.010
HFA 170 mcg BID	3.99	0.032
CFC 250 mcg BID	4.56	0.015
CFC 500 mcg BID	6.57	<0.001

^a Least squares mean of treatment – least squares mean of Placebo.

III. Reviewer's Comments

This reviewer duplicated the sponsor's results from the datafiles provided with the March 9, 2000 submission. The sponsor did pair-wise comparisons with placebo rather than the more normal combined analysis. These results were similar to the original analysis and lead to the same conclusion that for the primary efficacy analysis both doses of Aerobid HFA were significantly different from placebo. Other efficacy variables did not show significance for the pediatric population.

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Concur: Dr. Wilson

This review contains 2 pages of text.

cc:

Archival NDA 21,247

HFD-570

HFD-570/Dr. Birenbaum

HFD-570/Ms. Barnes

HFD-700/Dr. Anello

HFD-715/Dr. Nevius

HFD-715/Dr. Gebert

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BIOMETRICS

Steve Wilson
3/7/01 09:54:30 AM
BIOMETRICS

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On Original

Statistical Review and Analysis
Clinical

NDA #: 21,247
Applicant: Forest Labs
Name of Drug: Aerobid (flunisolide hemihydrate) HFA Inhaler
Indication: Treatment of Asthma
Documents Reviewed: Data sets and volumes March 9, 2000, volumes 1.92-1.113 dated April 27, 2000, a volume dated May 11, 2000, and a fax dated December 8, 2000.

This review pertains to one study in adults and adolescents and another study in children with asthma.

The Medical Officer for this submission is D. Birenbaum, M.D. (HFD-570), with whom this review was discussed.

I. Background

Aerobid (flunisolide hemihydrate) MDI with CFC propellant is approved for adults and children with asthma. The recommended dosages are 500-mcg BID or 1000 mcg BID for adults and adolescents and 500 mcg BID for children 6 to 11 years of age. The CFC formulation is a suspension. The HFA formulation of this submission is a solution. A built-in spacer is also used in the HFA device. Aerobid HFA (dose level) and CFC (dose level) will be denoted in the remainder of this review by HFA (dose level) and CFC (dose level), respectively.

The sponsor pre-submitted the datasets with descriptive volumes for this NDA to IND 51,456. This pre-submission was discussed in a statistical review dated April 5, 2000. That review requested information from the sponsor concerning the datasets. The NDA was submitted April 27, 2000. The sponsor's responses to questions about the datasets, requested in the Statistical Review of April 5, 2000, were provided in the May 11, 2000 submission.

II. Study ANC-MD-01

A. Study Design and Method of Analysis

This study was a randomized, parallel group, placebo- and active-controlled study in adolescent and adult asthmatic patients with a 2-week run-in period and a 12-week, double-blind treatment period. To enter the study patients had to have a percent predicted FEV₁ of 45-90% and a 12% increase in their FEV₁ after 2 puffs (180 mcg) of albuterol at or within 2 months prior to screening. During the run-in period patients were on CFC flunisolide 500 mcg BID and albuterol as needed. If patients satisfied inclusion criteria they were randomized to

Keywords: Clinical Studies, NDA review

- Group 1: CFC 250 mcg BID (1 puff at 250 mcg/puff, BID), plus CFC placebo (1 puff, BID), plus 2 HFA placebos (1 puff each, BID)
- Group 2: CFC 500 mcg BID (1 puff from each of 2 CFC canisters at 250 mcg/puff, BID), plus 2 HFA placebos (1 puff each, BID)
- Group 3: CFC 1000 mcg BID (2 puffs at 250 mcg/puff from each of 2 CFC canisters, BID), plus 2 HFA placebos (2 puffs each, BID)
- Group 4: HFA 85 mcg BID (1 puff from HFA canister at 85 mcg/puff, BID), plus HFA placebo (1 puff, BID), plus 2 CFC placebos (1 puff each, BID)
- Group 5: HFA 170 mcg BID (1 puff at 85 mcg/puff from 2 HFA canisters , BID), plus 2 CFC placebos (1 puff each, BID)
- Group 6: HFA 340 mcg BID (2 puffs at 85 mcg/puff from each of 2 HFA canisters, BID), plus 2 CFC placebos (2 puffs from each, BID)
- Group 7: 2 CFC Placebos (1puff from each, BID), plus 2 HFA placebos (1 puff from each, BID)
- Group 8: 2 CFC placebos (2 puffs from each, BID), plus 2 HFA placebos (2 puffs from each, BID).

All patients used 4 canisters (2 HFA and 2 CFC), some taking only one puff from each while others were taking 2 puffs from each. There was a 1-puff placebo group and a 2-puff placebo group in order to blind the study.

The study report states that the doses of HFA 170mcg or 340 mcg BID were chosen on the basis of a pharmacokinetic profile similar to that for the recommended doses of the CFC product. The 85 mcg HFA BID dose was included to evaluate the safety and efficacy of this low dose. The corresponding CFC doses were included in the study. Although not discussed in the protocol, the protocol matches up high, medium and low doses of the CFC and HFA formulations.

Patients during the run-in and treatment period twice daily recorded, in a daily diary, peak flows, asthma symptoms scores for wheeze, cough, shortness of breath, and chest tightness, and number of puffs of albuterol. At the morning the patient also recorded the number of nighttime awakenings that occurred secondary to their asthma and requiring the use of prn albuterol. Each of the 4 asthma symptoms were rated on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). Asthma symptoms were averaged to create an AM average, PM average, and an average Daily score.

Patients did not take their morning dose of medication before Visit 2 (baseline), Visit 3 (3 weeks), Visit 4 (6 weeks), Visit 5 (9 weeks), and Visit 6 (12 weeks). At each of these visits, FEV₁ was measured (highest of three assessments).

The primary efficacy variable was percent predicted FEV₁. The primary analysis was an ANCOVA analysis of the endpoint percent-predicted FEV₁ with baseline value as covariate and treatment effect in the model (no center factor or treatment by center interaction included). The sponsor did numerous analyses with the same model, but dropping some of the treatments from the analyses. (This creates different error terms for

the various comparisons.) The same model was used to compare the two placebo groups to judge poolability. If no significant difference was found at the 0.10 level, the two placebo groups were to be pooled.

For the diary variables, the sponsor calculated the means of the diary variable for the week (last 7 non-missing days) before each clinic visit. [The statistical analysis plan says that for diary variables, if the patient had insufficient data (not defined by the sponsor) to produce a reliable mean for the last visit, the data would be imputed using LOCF.]

The sponsor chose the sample size to show comparability of the averaged HFA doses (170 mcg BID and 340 mcg BID) with the averaged CFC doses (500 mcg BID and 1000 mcg BID). These combined doses were to have 180 patients for each formulation. [This reviewer questions the relevance of such a comparison.] The sponsor increased the sample sizes to 100 per dose level with only 50 in each of the two placebo groups (for logistic reasons) in generating randomization codes. The sponsor's study report states that 100 patients per group would have 90% power to detect a 5% difference in changes from baseline in percent predicted FEV₁ between an HFA dose group and placebo (assuming a 0.05 significance level and a 11% standard deviation). The randomization was carried out using a block size of 26. Each randomization block included 2 patients in the 2 puffs placebo group, 2 patients in the 4 puffs placebo group, and 3, 4, and 4 patients in each of the low, medium, and high dose groups of HFA and CFC flunisolide, respectively.

There was no discussion of multiple comparison issues in the protocol or study report. The study report mentioned the use of Tukey's method to analyze for dose response (using both dose and log dose in a covariate model.) The sponsor analyzed the primary efficacy variable using this method.

B. Results

There were 863 patients enrolled into the study at a total of 33 investigator sites. Of these patients, 669 were randomized into the study (104 placebo, 75 HFA 85 mcg BID, 100 HFA 170 mcg BID, 113 HFA 340 mcg BID, 76 CFC 250 mcg BID, 103 CFC 500 mcg BID, and 98 CFC 1000 mcg BID). There were 548 (70 placebo, 63 HFA 85 mcg BID, 85 HFA 170 mcg BID, 100 HFA 340 mcg BID, 59 CFC 250 mcg BID, 90 CFC 500 mcg BID, and 81 CFC 1000 mcg BID) patients who completed the study. Eight patients (3 placebo, 2 HFA 85 mcg BID, 1 CFC 250 mcg BID, 2 CFC 1000 mcg BID) were not included in the ITT analyses because they had no post-baseline efficacy data.

The treatment groups were comparable in baseline efficacy variables. The population's asthma was mild with a mean percent-predicted FEV₁ of 72.4 at screening. There were significant differences at baseline in mean weight and mean height. Such differences are unlikely to affect efficacy. [They didn't have any appreciable affect on the primary efficacy variable when used as covariates by this reviewer.]

The mean changes from baseline in percent-predicted FEV₁ were similar ($p=0.929$) for the two placebo groups which justifies pooling.

Tables 1 and 2 below provide treatment means and p-values compared to placebo for the primary efficacy variable: changes from baseline in percent-predicted FEV₁ at Endpoint.

TABLE 1

Treatment Means (Standard Deviations) for Percent-Predicted FEV₁ for Adults and Adolescents

	Baseline	12 Weeks (LOCF)	Change
Placebo (N=101)	83.6 (12.0)	79.1 (16.4)	-4.5 (12.2)
HFA 85 mcg BID (N= 73)	81.8 (14.3)	79.1 (15.3)	-2.6 (11.3)
HFA 170 Mcg BID (N= 100)	79.2 (15.2)	79.2 (18.4)	0.0 (12.0)
HFA 340 mcg BID (N=113)	80.6 (14.7)	81.0 (16.1)	0.4 (9.8)
CFC 250 mcg BID (N=75)	81.1 (16.4)	75.2 (20.1)	-5.9 (14.9)
CFC 500 mcg BID (N=103)	79.7 (15.5)	79.6 (18.1)	-0.1 (11.1)
CFC 1000 mcg BID (N=96)	79.5 (17.6)	81.3 (18.8)	1.7 (10.8)

TABLE 2

Least Squares Means (LSM) and P-values* from ANCOVA for Percent-Predicted FEV₁ for Adults and Adolescents

Treatment	LSM Placebo	LSM Treatment	Difference	P-Value
HFA 85 mcg BID	-4.369	-2.816	1.553	0.389
HFA 170 mcg BID	-4.247	-0.190	4.057	0.012
HFA 340 mcg BID	-4.247	0.332	4.579	0.003
CFC 500 mcg BID	-4.251	-0.221	4.029	0.012
CFC 1000 mcg BID	-4.251	1.536	5.786	0.000

*Pairwise for placebo and HFA 85 mcg, within HFA+ placebo for HFA comparisons or CFC+placebo for CFC comparisons. P-values are not corrected for multiple comparisons.

Significant differences from placebo were seen for HFA 170 mcg BID and HFA 340 mcg BID for the primary efficacy analysis. Dose response is suggested by both the HFA and CFC Least Squares Means. The HFA 170 mcg dose was roughly comparable to the CFC 500 mcg dose with slight suggestion that the CFC 1000 mcg dose may be more effective than the HFA 340 mcg dose. Although the sponsor did numerous statistical comparisons of the CFC and HFA products, they will not reported here since only relative comparability is needed.

The sponsor found a significant dose response using either dose or log dose for HFA and

CFC, if the placebo dose was included, but no significance was found if the placebo dose was not included in the analyses for each formulation.

Significant differences between the two higher doses of HFA and placebo were seen in the 12 week LOCF analyses of AM PEFr, AM Asthma score, PM Asthma score and mean Daily Asthma score, and Nocturnal Awakenings. The HFA 340 mcg BID dose was also significantly different from placebo for prn Albuterol Use (puffs/day) at 12 Weeks (LOCF).

C. Reviewer's Comments

This reviewer duplicated the sponsor's primary efficacy analyses from the datafiles provided.

This reviewer checked whether there was any indication of treatment-by-center interaction for the primary analysis and found no indication of such interaction ($P>0.44$).

This sponsor's pairwise or within formulation analyses (HFA or CFC) are somewhat unorthodox. They do not use all the data to provide estimates of error variability. The sponsor provided no justification of why such analyses were done or needed. This reviewer does not think such analyses were needed and the sponsor would be led to the same conclusions from an overall analysis with pairwise p-values computed.

Although dose response is suggested for the HFA and CFC formulations with placebo excluded, the sample size was not adequate to show dose response. The study was powered to show a 5% difference and the difference between doses was much lower than this. This sample size is not adequate to demonstrate whether the 340 mcg HFA dose is different from the 1000 mcg CFC dose.

III. Study ANC-MD-03

A. Study Design and Method of Analysis

This study was similar to Study ANC-MD-01 with the following major exceptions: It was in children 4-11 years of age rather than adults. The doses studied were placebo, HFA 85 mcg BID, HFA 170 mcg BID, CFC 250 mcg BID, and CFC 500 mcg BID. The primary efficacy analysis of percent-predicted FEV₁ was restricted to children 6-11 years of age. In-clinic PEFrS were performed in all children. The children 4 and 5 years of age used the Aerochamber on their CFC inhalers. Randomization was stratified by age group: 4-5 years, and 6 -11 years. Because the higher doses of Study ANC-MD-01 were not administered, there was no need for a 2-puff placebo group. (All children used 4 canisters, 2 HFA and 2 CFC).

B. Results

There were 653 patients enrolled into the study at a total of 51 investigator sites. Of these patients, 583 were randomized into the study (116 placebo, 114 HFA 85 mcg BID, 117 HFA 170 mcg BID, 123 CFC 250 mcg BID, 113 CFC 500 mcg BID). There were 477 (89 placebo, 94 HFA 85mcg BID, 98 HFA 170 mcg BID, 105 CFC 250 mcg BID, 91 CFC 500 mcg BID) patients who completed the study. Twelve patients (4 placebo, 2 HFA 85 mcg BID, 2 HFA 170 mcg BID, 1 CFC 250 mcg BID, 3 CFC 500 mcg BID) were not included in the ITT analyses because they had no post-baseline efficacy data. There were 61 randomized patients in the 4 and 5 year old subgroup.

The treatment groups were comparable at baseline in demographic and baseline efficacy variables. Greater than 89% of all ITT patients were compliant with their dosing at all visits. The population's asthma was very mild with a mean percent-predicted FEV₁ of 81.2 at screening.

Tables 3 and 4 below provide treatment means and p-values compared to placebo for the primary efficacy variable changes from baseline in percent-predicted FEV₁ at Endpoint.

TABLE 3

Treatment Means (Standard Deviations) for Percent-Predicted FEV₁ for Patients Aged 6-11 Years.

	Baseline	12 Weeks (LOCF)	Change
Placebo (N=95)	85.0 (14.31)	81.6 (17.57)	-3.4 (13.41)
HFA 85 mcg BID (N= 103)	88.6 (12.45)	89.8 (17.52)	1.2 (12.03)
HFA 170 mcg BID (N=103)	87.7 (13.87)	87.9 (18.02)	0.2 (12.18)
CFC 250 mcg BID (N=110)	88.2 (15.94)	88.7 (16.80)	0.5 (13.68)
CFC 500 mcg BID (N=102)	87.5 (14.61)	90.2 (13.34)	2.6 (9.59)

TABLE 4

Least Squares Means (LSM) and P-values from ANCOVA (Pairwise) for Percent - Predicted FEV₁ for Patients Aged 6-11 Years.

Treatment	LSM Placebo	LSM Treatment	Difference	P-Value
HFA 85 mcg BID	-3.55	1.32	4.87	0.008
HFA 170 mcg BID	-3.53	0.35	3.88	0.034
CFC 250 mcg BID	-3.83	0.84	4.67	0.012
CFC 500 mcg BID	-3.70	2.94	6.64	0.0001

*Within HFA+ placebo for HFA comparisons or CFC+placebo for CFC comparisons. P-values are not corrected for multiple comparisons.

Significant differences from placebo were seen for HFA 85 mcg BID and HFA 170 mcg BID for the primary efficacy analysis as well as for the CFC doses. Dose response is suggested for the CFC Least Squares Means but not the HFA Least Squares Means.

There were no significant differences between the HFA treatments and placebo for endpoint in-clinic PEFrs or diary variables.

The sponsor provided the results of the in-clinic PEFr observed cases analysis at 12 Weeks in in-text Table 20.

Sponsor's In-text TABLE 20
Comparison of HFA Flunisolide 170 mcg bid Doses to Placebo: Change From Baseline in IN-clinic PEFr (L/min) After 12 Weeks of Treatment- Observed Cases

	LSM Placebo	LSM 170 mcg BID	Difference	P-Value
4-11 years old	3.54	18.93	15.39	0.023
6-11 years old	2.73	20.38	17.65	0.018

C. Reviewer's Comments

In checking the sponsor's analysis, this reviewer could not duplicate the sponsor's results. The data file indicated 102 patients 6-12 years of age in the 85 mcg HFA group and 104 patients 6-12 years of age in the 170 mcg HFA group, whereas the sponsor reported 103 patients in each of these two groups. This reviewer asked the sponsor for a clarification, which was supplied in the December 8, 2000 fax from the sponsor. One patient (#1508), who was only one-week before his 6th birthday, was randomized into the HFA 85 mcg group by using the randomization scheme for the 6-11 age group. Another patient (#2614) who was 6 years old was placed in the HFA 170 mcg treatment group by using the scheme for the 4-5 age group. The sponsor stated that for the ITT analyses, these two patients were grouped according to the randomization scheme that was applied to them instead of their actual age. This reviewer duplicated the sponsor's primary efficacy analyses from the datafiles provided with these two modifications. [An analysis without making these two modifications yielded similar results.]

This reviewer checked whether there was any indication of treatment-by-center interaction for the primary analysis and found no indication of such interaction (P>0.41).

This sponsor's pairwise analyses are somewhat unorthodox. They do not use all the data to provide estimates of error variability. The sponsor provided no justification of why such analyses were done or needed. This reviewer does not think such analyses were needed and the sponsor would be led to the same conclusions from an overall analysis with pairwise p-values computed.

Although the sponsor did not state how multiple comparison issues would be handled, since both doses of the HFA formulation were significantly different from placebo using pairwise tests and for suspected comparability of the 170 mcg dose with the approved CFC dose for children (making this comparison the primary comparison of interest) both HFA doses should be considered significant for the primary efficacy variable in children 6-11 years of age. No efficacy in children 4 and 5 years of age has been established.

The sponsor's analysis of the 12 Weeks observed cases analysis of in-clinic PEFrs doesn't add much to the efficacy already shown. It is a post-hoc analysis and the shift in the treatment means, when the children 4 and 5 years old are added, is a further indication that efficacy in the 4 and 5 year old patients has not been demonstrated.

IV. Conclusions

Efficacy was seen in the primary efficacy analysis of changes from baseline in percent-predicted FEV₁ for the Aerobid HFA 170 mcg BID and Aerobid HFA 340 mcg BID in adults and adolescents and for Aerobid HFA 85 mcg BID and Aerobid HFA 170 mcg BID in children aged 6-11 years. Efficacy was also seen in secondary efficacy parameters for the adults and adolescents but not in children aged 4-11 years of age. No efficacy in children 4 and 5 years of age has been established.

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

Concur: Dr. Wilson

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