8.5 STUDY FLNT61[29]

"A double-blind comparison of fluticasone propionate aqueous nasal spray 100 µg given once daily, fluticasone propionate aqueous nasal spray 100 µg given twice daily and beclomethasone dipropionate aqueous nasal spray 200 µg given twice daily in the treatment of perennial rhinitis in paediatric patients (aged 6 - 11 years) " [sponsor title]

8.5.1 Objectives/Rational

To compare the efficacy and safety FP 100 µg QD and 100 µg BID versus aqueous BDP nasal spray in the treatment of perennial allergic rhinitis in children ages 6 - 11 over a 12 week treatment period.

8.5.2 Design

Eighteen centers (European based: Denmark, France, Iceland and UK), randomized, double-blind, positive-controlled, parallel group study of 12 weeks duration.

Comment

Given that this is a positive, non-placebo control study of PAR, it is not likely to yield helpful efficacy information unless FP consistently or convincingly beats BDP. Otherwise in this variable disease, there is no way to be assured the study "worked." However, given the 12 week design, the results from this study should yield helpful longer term safety and tolerability data.

8.5.3 Summary of the Study Protocol (no amendments given)

8.5.3.1 Population

Inclusions: Male or female patients, 6 - 11 years who have moderate to severe perennial allergic rhinitis with the following symptom requirements:

1 - two or more symptoms (nasal blockage, rhinorrhea, sneezing, or post-nasal drip) on study entry

2 - Daily overall assessment of symptoms (by diary card) scored as being of at least moderate severity (score of at least 2 on 0 - 3 scale) for at least 5 days during the run-in period.

Exclusions: Physical nasal obstruction, serious or unstable concomitant diseases, no infections of the respiratory/nasal tract including candida, contraindication to or history of adverse reactions to corticosteroids, inability to withdraw from treatment of nasal symptoms for the run-in period, nasal surgery in the previous six weeks, systemic or inhaled corticosteroids for the previous month before the start of the study, exposure to inhaled cromolyn or nedocromil within the previous month prior to the study, oral astemizole in the previous (?) weeks [this portion

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of the protocol was mistyped by the sponsor], patients could not have been on immunotherapy in the prior 12 months.

8.5.3.2 Treatment Arms

Fluticasone 100 µg/day - 2 sprays of 25 µg FP in each nostril QAM
2 sprays of matching placebo QPM
Fluticasone 200 µg/day - 2 sprays of 50 µg FP in each nostril BID
Beclomethasone 400 µg/day - 2 sprays of 50 µg BDP in each nostril BID

Comment: *This study will have to be reviewed bearing in mind that this formulation of FP at 25 µg per actuation is not the marketed formulation. This could be particularly important for any impact on local adverse event rates.*

8.5.3.3 Assignment to Treatment

Randomized within each center in a 1:1:1 ratio.

8.5.3.4 Blinding

Double-blinded, with all investigators, study personnel, subjects and monitors blinded to the treatment. Study drug was formulated, packaged and appropriately labeled to disguise treatment assignment, with identical nasal inhalers used for all formulations.

Comment *The floral aroma of BPD AQ and Flonase derives from an excipient used and was presumably present in all three formulations: BPD, FP and placebo. Therefore it is reasonable to assume that subjects would be well masked as to which treatment arm they were in.*

8.5.3.5 Dosing

The study drugs were administered from two different containers BID as above. The times specified were not exact, but rather "morning - 6:00 to 8:00" and "evening - 18:00 to 20:00."

8.5.3.6. Study sequence

Screening visit (visit 1), followed by:

- 14 day run-in period with diary keeping, single-blind placebo nasal spray use, and rescue terfenadine (either tablet or syrup to ≤ 60 mg/day) as needed; followed by
- 12 week treatment period (visits 2 - 6).

To enter into the treatment period, patients must have displayed sufficient symptoms during the run-in period as defined above.

8.5.3.7 Assessments

Screening visit - History (including SAR symptom assessment), physical (including nasopharyngeal exam with rhinoscopy to document any edema, bleeding and the color of the nasal mucosa, as well as the presence of any polyps or anatomic obstruction), laboratories (including a.m. cortisol).

Run-in period - Daily recording of PAR symptoms by the patients or

caretaker surrogate using a 0 - 3 scale rating of overall and individual nasal symptoms (individual domains were nasal blockage on waking, nasal blockage rest of the day, sneezing, rhinorrhea, itching/rubbing), ocular symptoms, and daily rescue medication use. Nasal blockage was scored in the a.m., other parameters were recorded at bedtime. Use of rescue medication, study medication and any other medications was also to be reported on the diary card.

Randomization visit (visit 2) - Diary cards reviewed, nasal exam and investigator symptom assessment, and skin testing to common perennial allergens [house dust mites, animal dander and molds] by prick testing with positive (histamine) and negative controls.

Double Blind period - Patients were scheduled to return at the end of study weeks 6, 10, and 14 (all ± 7 days) for visits 2, 3 and 4. A follow-up post-treatment visit was also conducted at the end of week 16 as necessary to asses any on-going laboratory abnormalities or adverse events.

At all treatment periods, diary cards were to be collected and reviewed. Nasal examinations and investigator symptoms assessments were performed and adverse event assessment was carried out. Note that investigator assessments were similar to the patient ratings - with a 0 - 3 scale (0 - no symptoms, 1 mild, 2 moderate and 3 severe) for nasal blockage, rhinorrhea, sneezing, nasal itching, and post-nasal drip. Additionally, ocular symptoms/signs were to be rated. Adverse event assessment was to be conducted at all visits by both investigator history taking, as well as diary review. Note that adverse events were not explicitly tracked in diary, but such tracking was allowed. Laboratories were only assessed at visit 2 (randomization) and 5 (end of study treatment), with visit 6 as needed. These included routine serum laboratories, urinalysis, and a.m. cortisols.

8.5.3.8 Concurrent Medications Exclusions: All medications which might affect nasal function will be excluded for the entire study period, except for the rescue terfenadine provided.

8.5.3.9 <u>Endpoints</u>

Efficacy parameters:

Efficacy variables included the assessment of patient's rated symptom scores (presumably surrogate in many cases), investigator rated nasal and ocular symptoms, and rescue antihistamine use. The primary analysis was prespecified as the analysis of % of symptom-free days for symptoms of nasal blockage on awakening, nasal blockage during the day and on rhinorrhea, with FP at both dose separately compared to BDP. This was supplemented by an analysis of all days where scores of 1 or

less were recorded. Secondary analyses include assessments of all other nasal component scores, and patients overall assessment, as well as rescue terfenadine use.

Safety Endpoint Parameters:

1. Adverse Events
2. Physical examination / laboratory abnormalities
3. Vital signs assessment

8.5.3.12 Statistical Analysis

The power calculations were based on the percentage of symptom free days by the patient/surrogate's assessment. Based on prior data with FP, Glaxo assumed a SD of 28% and therefore planned the sample size of the study to achieve an 80% power to detect a difference of 12% in the mean % of symptom-free days with an α of 0.05. The target enrollment was 448 subjects into the single blind to achieve 336 randomized patients, 112 in each treatment arm.

Comment

Given that this is a positive control study where the failure to show a difference of FP from BDP would be construed by the sponsor to represent "equal efficacy," an unsatisfactory power is achieved for this study design, despite the ambitious sample size. This planned power means that in a situation where BDP might have worked and FP did not, there would be by design a 20% chance of failing to conclude that an important difference existed. It should be noted that, in fact, a relatively small percent of this target sample size was randomized, so that the true power achieved in this study was clearly substantially less than planned and therefore the chance of committing an important beta error is very high indeed.

1. Efficacy Analysis

   An intent-to-treat analysis was conducted with two populations considered, patients with documented PAR and those with PNAR. Tests for interaction between allergic status and treatments were to be performed. If interactions were found, then only within allergic status assessments were to be made. The efficacy assessment was to be conducted using an ANCOVA allowing for effects due to baseline, rhinitis category, centers and treatments. Poorly recruiting centers were to be combined for analysis purposes.

2. Safety Analysis - was to be focused on clinical adverse events, laboratory tests, physical examination findings (including nasal examinations), and vital signs.

8.5.3.13 Amendments to the protocol

None reported.

8.5.4 **Results**

8.5.4.1 Study population characteristics

The study was conducted was initiated in the winter of 1990/91. A total of 120 subjects were recruited (targeted for 448) into the study: 30 were randomized to FP QD, 35 to FP BID, and 30 to BDP with 25 withdrawing during screening. Actual randomization then was only 95 subjects (target 336). Reasons for non-randomization included insufficient symptoms or drug use (11), non-compliance (1), failure to return (4) and not wishing to continue (9). An additional 8 subjects were not entered into the intent-to-treat analysis by the sponsor because of insufficient baseline data (<4 days), insufficient treatment data (<14 days), or inability to characterize disease status (PAR vs. PNAR). An accounting of subjects failing to adhere to the protocol showed a total of 53 of the 95 subjects failed on at least one category. This included most frequently failing to attend the study visits within the specified time window (55 occasions), as well as the less common noncompliance with study drug use, use of disallowed drugs, or insufficient recording of data.

Demographics revealed reasonable comparability between dosage groups for the reported characteristics.[30] There was reasonable balance in mean age, height and weight, although the FP QD group was somewhat older and therefore heavier and taller on average. There was some imbalance in individual ethnic origin categories, with no blacks in the FP BID arm, but 7% in both of the other arms. Though gender was reasonably comparable across groups, within groups males outnumbered females in the study (67%).

Baseline clinical characteristics related to atopy and allergy history were comparable, including the balance of PAR to PNAR (66% to 28% overall, with 5 not recorded). The majority of subjects who were allergic reacted to skin testing for house dust mites, as well as cats and house dust.

8.5.4.1.1 Concurrent Medication use

The use of concomitant medications was similar between groups.

8.5.4.2 Efficacy Analysis

8.5.4.2.1 *Data set analyzed*

Data analysis was performed on the intent-to-treat population which for efficacy numbered 87 subjects.

8.5.4.2.2 Percentage of Patient Rated Symptom-free days

The percentage of symptom free days is reported for each of the subject's ratings of their component nasal scores. They are presented in both

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30 **table 8 of vol. 1.016, page 46**

absolute terms and relative (to baseline) terms, including mean and median differences. A tabular summary for the protocol designated primary efficacy comparisons of percent symptom free days (i.e., score in that category = 0 for that day) is presented below:

Symptom # subjects in analysis n =	FP QD 28	FP BID 31	BDP 28
Awakening Nasal Blockage			
median % during run-in	0	0	0
median during days 1 - 84	5	8	13
median difference	5	5	5
mean difference	24	19	16
adjusted p value (vs. BDP)	.751	.396	*FP vs. FP p = .604*
Day time Nasal Blockage			
median % during run-in	0	0	0
median during days 1 - 84	7	11	21
median difference	1	6	6
mean difference	28	22	21
adjusted p value (vs. BDP)	.994	.433	*FP vs. FP p = .658*
Rhinorrhea			
median % during run-in	0	20	11
median during days 1 - 84	58	59	46
median difference	12	14	20
mean difference	27	24	20
adjusted p value (vs. BDP)	.399	.316	*FP vs. FP p = .798*

Statistically, there is no separation of any of the treatments on any of the "primary" efficacy variables. This is not surprising given the failure of this study to even come close to the sponsor's planned enrollment. If one looks at median differences in the percent of symptom free days, it appears that numerically BDP is as effective or perhaps for rhinorrhea more effective than either FP dose. For both rhinorrhea and daytime nasal congestion, FP QD appears numerically inferior to FP BID considering the median differences. However, different conclusions on numerical trends would be reached on the mean differences in the symptom free days, with FP appearing more effective than BDP overall

and FP QD appearing more effective than FP BID.

A consideration of the % of symptom free days for the component scores designated as secondary adds little to the above.

8.5.4.2.3 Percentage of Days with Scores less than 2

This analysis adds little to the symptom free day analysis, although on most components, FP appears numerically (though never statistically) superior to BDP.

8.5.4.2.4 Diary Recorded Use of Rescue Terfenadine

The use of rescue antihistamine was tracked in the subject daily diaries. These results were considered an important, though ***not*** primary, indicator of efficacy by the sponsor.

Rescue Terfenadine Use (mean dose; percent of subjects rescuing):

Symptom #subjects in analysis n =	FP QD 25	FP BID 29	BDP 26
Percent of rescue free days			
median during run-in	86	100	100
median during days 1 - 84	100	100	100
median difference	8	0	0
mean difference	17	18	6
adjusted p value (vs. BDP)	**<0.001**	0.043	*FP vs. FP p = .233*
# of daily doses (60 mg)			
median % during run-in	1	0	0
median during days 1 - 84	0	0	0
median difference	-1	0	0
mean difference	-3	-3	-1
adjusted p value (vs. BDP)	**.012**	.043	*FP vs. FP p = .589*

Although "statistical significance" was found in this analysis, a closer review of the data makes any findings on this endpoint a bit suspect. Over half the subjects in the FP BID and BDP arms were not using any rescue on a daily basis at entry, so showing a significant decrease in these two groups would have been difficult. Since it appears that the FP QD group had further to fall in rescue med use than did BDP and hence some important imbalance was present at baseline, these strong p-values are not convincing of any meaningful effect.

8.5.4.2.5 Investigator's Rating of Nasal Symptoms

This analysis essentially added no new information to this review, with no discernable trends appeared in the between group comparisons.

8.5.4.3 Safety Analysis

The safety analysis included all patients who received any study drug, a total of 95 subjects, with 80 subjects completing 84 days of treatment. These 80 were broken down into 24 in the FP QD group, 29 in the FP BID group and 27 in the BDP group.

8.5.4.3.1 Adverse Event Occurrence Rate

Overall, the adverse event profile of the active treatment groups was largely comparable. An abbreviated summary of the overall adverse events is found below (based on those categories where AE's were reported in 3 (10%) or more patients in any treatment group OR categories of potentially expected topical / corticosteroidal effects)[31]:

Adverse Event		FP QD N (%)	FP BID N (%)	BDP N (%)
Total Pt. Numbers		30	35	30
Number of Subjects with events		15 (50)	26 (74)	20 (67)
Total Events reported		31	53	46
ENT	All	11 (37)	16 (46)	11 (27)
	Pharyngitis/sore throat	3 (10)	1 (3)	1 (3)
	Epistaxis	2 (7)	5 (14)	2 (7)
	URTI	5 (17)	8 (23)	6 (20)
	Dysphonia/hoarseness	1 (3)	1 (3)	0 (0)
Neuro	Headache	4 (13)	2 (6)	4 (13)
	psychiatric disorder	0 (0)	3 (9)	0 (0)
Respiratory	All	2 (7)	6 (17)	9 (30)
	Asthma events	1 (3)	2 (6)	5 (17)
	Cough	0 (0)	3 (9)	3 (10)
General	Influenza	0 (0)	3 (9)	3 (10)
	"miscellaneous symptoms"	0 (0)	3 (9)	0 (0)

If one focuses on the comparison of the FP QD group (which is the dosing interval, though not the formulation, included in the proposed labeling) to the BDP AQ group, it appears that on most parameters, the FP is at least as well tolerated as the BDP. Given the small sample size, chance alone could easily play into any differences observed. However, there is no signal from these data that FP administered at a dose of 100 µg once daily is less well tolerated in terms of local/respiratory events than is BPD AQ, which is approved in the pediatric age range for the PAR indication.

31 **taken from table 33, pages 90-93, vol. 1.016**

Of particular note, given the consistent finding in the two US SAR trials regarding asthma events, the number of such events in this study appears to be highest for BDP. This offers some assurance on this matter, though because of small sample sizes and because this study is not of the formulation currently marketed in the US, we cannot reach any firm conclusions on this event rate.

8.5.4.3.2 Adverse Event Severity

There were no serious adverse events reported in this trial. Also, no deaths were reported during this study. There were several subjects withdrawn for adverse events, 2 in the FP QD group, 1 in the FP BID group and 0 in the BDP group.[32] The two events leading to withdrawal in the FP QD groups were an event of epistaxis in an 11 year old female on day 14 of the study, and an acute URTI episode in an 11 year old female beginning on day 28 of the study (symptoms of throat pain, neck edema and runny, congested nose). This subject also experienced a rise in alkaline phosphatase levels which actually led to the study discontinuation. EBV antibodies were detected in this case and this likely was an acute mononucleosis episode. The subject who withdrew from the FP BID group was a 7 year old girl who experienced hyperactivity and sleep disturbances on day 19 that resolved with withdrawal of the medication.

8.5.4.3.3 HPA Axis Effects of FP

HPA axis testing was again conducted with a.m. cortisols, a measure which is neither very sensitive nor specific for adequate HPA axis functioning. Data is only listed for shifts from high or normal to low. Two such subjects occurred in the FP QD group, and 1 each in the FP BID and BDP groups.

Comment - ***Despite the lack of sensitivity of this test, in a 12 week treatment period, one would be more likely to detect a large disparity in effect if one were to exist than in a 2 or 4 week study. However, given all the problems with this study design and execution, these data can offer only limited reassurance, even given that there were no striking disparities between groups.***

8.5.4.3.5 Laboratory Abnormalities / Changes

There were no important signals detected in laboratory examinations when examined by shift tables.[33]. Specifically, there is no signal of overt steroid effect in urinary glucose, or blood eosinophils or lymphocytes. There were no important liver-related chemistry changes (there were scattered infrequent rises in transaminases and particularly alkaline phosphatases, but there was no discernable imbalance).

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32 **Information taken from appendices 10, 24, and 25 found in vol. 1.016**

33 **Information taken from table 37, found on pages 101-103 in vol. 1.016**

8.5.4.3.6 Vital Signs

Mean values for blood pressure, pulse rate, temperature, and respiratory rate were reported for study entry (visit 1) and visit 5 (last treatment visit) and showed no definable treatment effect.

8.5.4.3.7 Physical Examination

There were no important findings relative to safety from nasal examinations. However, there may be some evidence of relatively better efficacy with FP QD compared with BDP coming from these data in that the occurrence of such pathologic changes as abnormal mucosal coloration, turbinate swelling and post-nasal drainage showed a more substantial decline in the FP group than observed in the BDP treated group.

8.5.5 Conclusions

8.5.5.1 Efficacy Conclusions

There are numerous problems with the design and conduct of this trial:

- There is no placebo control, so without a finding of superiority of FP 100 QD over BDP, there can be no assurance either that the study could have detected a difference between active treatment and placebo, nor is there any comparison by which to gauge the importance of any differences seen between the effects of active treatments.
- The formulation used was a ½ strength formulation and therefore the local safety profile (or systemic profile) and the efficacy results may be substantially different since the concentration of medication in a suspension could in theory impact on all these aspects of the therapeutic characteristics of the drug.
- The study failed to enroll sufficient numbers to even come close to achieving an 80% power. Again, with a positive control study, the beta error is the more crucial error and the meager enrollment inflates this error enormously thereby leading to a high likelihood of assuming equivalence (and in the sponsor's reasoning, equivalent efficacy) when in fact important efficacy and safety differences may have existed.

Therefore, this study does not add much to the review other than very soft supportive conclusions about the role of Flonase in the treatment of SAR. These conclusions take into account that there are some numerical indications of relatively more efficacy with the FP QD group than the BDP group, particularly when rescue medication use is examined (for all that endpoint's caveats) and the mean increases in the percentage of symptom free days.

8.5.5.2 Overall Safety Conclusions

Because of small numbers of subjects and differences in the formulation and dosing regimen, the amount of definitive conclusions that can be drawn on this study are relatively few. However, there certainly are no signals that FP in a total daily dose of 100 µg is less safe than BDP by any measure. In fact, for several adverse event categories, the numerical reporting goes the other direction. There is little indication of any important systemic effects, however, the HPA axis measure used - a.m. cortisols - is the least informative of the standard ways to assess adrenal function.

8.6 STUDY FLD-220[34]

"A Randomized, Double-blind, Parallel-Group, Comparative Trial assessing the long term safety of inhaled fluticasone propionate Rotadisks via Diskhaler 50 mcg BID and 100 mcg BID versus placebo in patients aged 4 to 11 with mild to moderate chronic asthma."

Comment ***As discussed elsewhere in this review, this study is submitted to this sNDA under an agreement made between DPDP and the sponsor that if Glaxo Wellcome could demonstrate that the systemic exposure of the Rotadisk was higher than that of Flonase, then this study (along with safety data from all shorter term pediatric Flonase studies and all relevant adult data - both clinical trials and post-marketing) could serve as the primary study supporting the long term systemic safety of Flonase (as a "worst case" scenario). Being that the primary purpose of reviewing this study for this sNDA is the systemic safety profile of FP, there will be only a minimum representation of and commentary on the efficacy findings and local safety findings of this study.***

8.6.1 Objectives/Rational

To compare the systemic safety of 100 µg per day administered BID and 200 µg a day administered BID (nominal dose of fluticasone propionate delivered as a lactose-blend dry powder from a Diskhaler device versus placebo (lactose) in the treatment of children with mild to moderate chronic asthma over a prolonged period, measuring such variables as growth, standard clinical assessments (history of AE's, laboratories, examinations,...), and tests of HPA axis function. The sponsor also followed Pulmonary Function testing and pharmacoeconomic outcomes [their term] for efficacy.

8.6.2 Design

Nineteen center, randomized, double-blind, placebo-controlled, parallel group study of 1 year duration.

8.6.3 Protocol

8.6.3.1 Population

Inclusions: Males (ages 4 - 11) or premenarchal female patients (ages 4 - 9), with mild to moderate asthma who were at screening (diagnosis of asthma made in accordance with ATS definition, requiring pharmacologic therapy for the preceding 3 months prior to the first visit). For subjects 6 and above, best FEV_1 must have exceeded 60% of predicted. For subjects aged 4 - 5, they either must have met the FEV_1 criterion OR they met the standard definition of asthma under the ATS criteria. If subjects were taking inhaled corticosteroids at the time of enrollment, they must have been on them for at least 3 months and at doses of ≤8 puffs per day for BDP or TAA or ≤4 puffs per day for flunisolide. They also must have demonstrated normal growth velocity with a height within 90% of average (>5% and <95%) and a velocity ≥5th and ≤97th percentile for age. Velocity was to have been determined at the screening visit using one accurate height measurement obtained between 6 and 12 months previously.

Exclusions: History of life-threatening asthma; histological or current evidence of significant disease; substance abuse, including drug and alcohol abuse; significant abnormalities in screening labs or ECG; history of drug allergy to any corticosteroidal drug product or sympathomimetic drug; history of or presence of glaucoma and/or posterior subcapsular cataracts; URTI or LRTI in the previous 2 weeks; any history of tobacco use.

Medication restrictions: No subject could be on oral, intranasal, ophthalmologic, topical or injectable corticosteroid therapy during the month prior to screening. No subject could have received daily or alternate day oral corticosteroid treatment for longer than 2 months total within the last 2 years. For subjects stratified to no prior inhaled steroids (ICS), there could not be any such use for 1 year prior to screen. Upon entering the study, subjects were only allowed to use the following steroidal products: topical hydrocortisone (1% or less), 2 oral corticosteroid bursts of ≤7 days duration during the study, and the ICS required for ICS using subjects during the 2 week lead-in period. Also excluded during the study were the following medications - beta blockers; digitalis; phenothiazines; polycyclic antidepressants; ketoconazole; CNS stimulants (ritalin); and hormone treatments.

8.6.3.2 Treatment Arms

Fluticasone 50 µg BID -	**1 inhalation of 50 µg blister BID**
Fluticasone 100 µg BID -	**1 inhalation of 100 µg blisters BID**
Fluticasone 0 µg BID -	**1 inhalation of 0 µg (Lactose) blisters BID**

8.6.3.3 Assignment to Treatment

Randomized within each center in a 1:1:1 ratio, with a stratified

randomization for prior ICS exposure/use.

8.6.3.4 Blinding

Double-blinded, with all investigators, study personnel, subjects and monitors blinded to the treatment. Study drug was formulated, packaged and appropriately labeled to disguise treatment assignment.

8.6.3.5 Dosing

The study drug was administered via the Diskhaler inhalation device twice daily by patients (at approximately 0800 and 2000 hours).

8.6.3.6 Study sequence

Screening visit (visit 1); followed by

- 14 day single blind run-in period with a placebo Diskhaler, diary keeping, and if the subjects came in on ICS they were to continued with open-label use (ending with visit 2); followed by
- 52 week treatment period (visits 3 -10).

To enter into the randomized treatment period, patients must have displayed relative asthma stability as perceived by the investigator with no use of oral corticosteroids (or ICS for those not previously receiving them), with compliance ≥ 70%, along with demonstrated good Diskhaler technique. They must also have only needed allowed asthma medications (beta agonists, theophylline and cromolyn).

8.6.3.7 Assessments

Screening visit - History, physical, PFT's, 12-lead ECG, clinical laboratory tests, a.m. cortisol, growth measurement, ophthalmologic examination, bone age x-ray of hand and wrist.

Randomization visit - Adverse event and concomitant mediation use assessment, vital signs, patient survey, pulmonary auscultation, oropharyngeal examination, PFTs (optional for 4 - 5 year olds), growth measurements, physician global assessment, 12-hour urinary cortisol.

Double Blind period - Patients were scheduled to return visits 3 - 17 (days 7, 14, 28, 56, 84, 112, 140, 168, 196, 224, 252, 280, 308, 336, 364 ± 2 days for visits 3,4; ± 3 days for visits 5-7 and ± 5 days for the rest of the visits). During this period, subjects were to continue to meet the following continuation criteria:

No use of intranasal or non-study inhaled corticosteroids;
No requirement for more than 2 bursts of oral corticosteroids, having a duration of > 7 days during the study;
Relative asthma stability;
Females would have to remain premenarchal during the study
No use of disallowed asthma medications.

The clinic assessments during the treatment period include:

- Patient survey for adverse events and concomitant medications
- PFT's
- vital signs, pulmonary auscultation, oropharyngeal examinations
- Collect, dispense study medication (blister count)

Additionally, growth measurements were conducted at most treatment visits, along with periodic ophthalmologic examinations, clinical laboratory measures including cortisol assessments. At the mid-point and end of treatment visits, bone age films were done along with global assessments, 12-hour urinary cortisols, ECGs, and full physical examinations.

8.6.3.8 Patient Compliance

Patient compliance was required to be ≥70% compliant with single blind study medication in the screening period to enter in the study. During the screening and study treatment phase, compliance was judged by counting blisters used when study medication was returned at study visits.

8.6.3.9 Patient Withdrawal from the Study

Clinical criteria for patient discontinuation were in place to allow "unstable" patients to be withdrawn from the study. These criteria are outlined above in section 8.6.3.7.

8.6.3.10 Endpoints

Safety Endpoint Parameters with study powered for growth measures:

1. Growth measurements
2. Clinical adverse events
3. Clinical laboratories
4. HPA axis assessment (a.m. cortisols, 12-hour urinary cortisols)
5. Ophthalmologic examinations
6. Physical examination, ECG and vital sign abnormalities

Efficacy was to be determined primarily by spirometry, although this was not the primary intent of the study. There were also various pharmacoeconomic measurements conducted, including an asthma specific QOL instrument. For these latter measures, no discussion was included on study power or pre-specification of domains of interest or on what would constitute a "win" for these instrument measure.

8.6.3.10 Statistical Analysis

Demographic and baseline characteristics will be summarized per treatment assignment. All exposed subjects were to be included in the safety analysis.

Sample Size - Glaxo assumed a standard deviation of growth velocity of

2.7 cm/yr in this age group based on the findings of a recently published paper from the AAAI comparing theophylline and beclomethasone in the treatment of childhood asthma. In this study, a decrease in growth velocity of 1.9 cm/year was found for boys with BDP relative to theophylline and 0.2 cm/year for girls. This one year study had a 75% completion rate. Based on these data, the study under review was planned for 90 subjects in each arm of the study to complete one year of treatment, giving an 80% power of detecting a 1 cm/year difference in growth rate, using a two tailed alpha of 0.05. The targeted enrollment was 120 subjects per arm.

8.6.3.13 Amendments to the protocol

Three protocol amendments were made to the original protocol.

The first allowed for up to 18 months for prior stadiometric measurement of height prior to screening. This amendment also defined the tanner stage of puberty at which a subject would be excluded (SMR of ≥2), it changed the definition of exacerbations which would lead to withdrawal, it removed the exclusion criterion for recent URTI, it removed topical corticosteroids from the list of precluded prior treatments and removed plans for any diary card recordings.

The second had several revisions included. These included a change in the definition of non-ICS subjects to include subjects who had used less than 2 months worth in the prior 2 years, and a change in timing of study medications and visit days.

The third amendment included revisions to add a measure of plasma FP levels at some single time point in the study at 3 centers (either visit 7, 10 or 17). This included a provision to withhold study medications prior to visits in which plasma FP would be determined. Measures were then conducted 20 and 40 minutes post-dosing in the clinic.

8.6.4 **Results**

8.6.4.1 Study population characteristics

The study was conducted between April 20, 1993 and January 13, 1995. A total of 344 patients were screened, with 325 subjects enrolled into the study: 106 were randomized to placebo, 111 to FP 50 BID and 108 to FP 100 . Screening failures were most often due to abnormal ophthalmologic examination, asthma instability, prohibited medication use or failure to meet entry criteria. Randomization was relatively uniform across the 19 centers, although three centers relatively under enrolled: Williams - 1, Schwartz - 8 and Ostrom - 6. Most centers enrolled in the range of 20 subjects.

Demographics revealed overall reasonable comparability of the various characteristics reported across dosage groups, including mean age, height,

weight, and ethnic origin.[35] It should be noted that overall, Caucasians were relatively more represented in this study than in the general US population, and that blacks were less well represented in the active treatment group than placebo (8%, 4% and 11% respectively for FP50, FP100 and placebo). Likewise, girls were very much under represented in the study population (1:3 ratio to boys), likely in part due to the age restrictions, although even in the allowed age range, boys outnumbered girls by roughly a 2:1 margin. However, the gender mix was relatively the same across treatments. These demographic observations are stable for various subgroups, including pre-pubescents and completers.

Comment- *Since much of the difference in growth observed in the aforementioned AAAAI study on BDP and theophylline was observed for boys, this over-representation of males to females will not necessarily lessen the chances of this study finding an overall effect if one should exist. It will, however, lessen the chance of finding a significant difference when the subset of females is separately examined.*

Baseline clinical characteristics related to asthma history (length of diagnosis, predisposing factors, hospitalizations, days of school missed) did not show any important imbalances between treatment groups, including screening PFT's. This study was stratified at randomization for prior ICS use (called "steroid dependant" by the sponsor, although there was no attempt to wean such patients). For the prepubescent completers, this amounted to a 44:66 ratio of ICS versus ICS-naive subjects.

8.6.4.1.1 Concurrent Medication use

Post-randomization subjects in the placebo group more often received rescue steroids, mostly prednisone or a supplemental inhaled steroid (total percentage of subjects exposed to any steroidal preparation during the trial amounted to 71% in placebo, 56% in FP50 and 52% in FP100). Presumably, many of these occurrences apart from the allowed 2 prednisone bursts led to discontinuations. The placebo group had a somewhat higher rate of theophylline use than the active groups (24% vs. 13 and 18%). Otherwise, there appeared to be little important differences between groups in use of concomitant asthma and non-asthma medications.

8.6.4.1.2 Patient Disposition

A total of 62 patients (19%) withdrew prematurely from the study. Although this was below the rate projected in the power calculations, since there was also a lower than planned enrollment, the number of completers came close to the planned number. There was a differential drop-out rate, largely due to differences in withdrawals for lack-of-efficacy, which supports an efficacy claim for the active treatments, but could somewhat confound the results. The reason for this is there are data that indicate that poorly controlled

35 Tables 8 - 19, pages 111 -

asthma itself may retard growth velocity (largely, it is felt, through a delay in puberty that is not felt to impact on adult height).[36] If those subjects who withdrew from placebo were the less well controlled (which is a reasonable assumption), this may have removed from full evaluation a group of subjects who might have displayed lower growth velocities and therefore this differential drop-out could lead to an accentuation of any growth retardation findings for active treatment (i.e., bias against fluticasone). The mean (median) durations of exposure in days were as follows: Placebo 307 (364), FP50 345 (365) and FP100 334 (365). A tabular summary of withdrawals is depicted below:

Number of subjects (%)	Placebo	FP50	FP100	Total
Enrolled	106	111	108	325
Completed	76 (72%)	98 (88%)	89 (82%)	236 (81%)
Withdrawn	30 (28%)	13 (12%)	19 (18%)	62 (19%)
Reason for Withdrawal				
Lack of efficacy	20 (19%)	4 (4%)	4 (4%)	28 (9%)
Adverse Event	2 (2%)	0 (0%)	4 (4%)	6 (2%)
Failed to Return	1 (1%)	2 (2%)	2 (2%)	5 (2%)
Other	7 (7%)	7 (6%)	9 (8%)	23 (7%)

The majority of dropouts for any reason were in the first 6 months (38 subjects) as opposed to the second (24 subjects). Withdrawals for lack of efficacy occurred in much the same pattern, with a majority in the first 6 months (16), but with continuing occurrences in the last 6 months as well (12).

8.6.4.2 Efficacy Analysis

Due to the irrelevance of any efficacy findings from this study to the Flonase application, these data will not be substantially discussed in this review. It is sufficient to say that the study "survival" [see drop outs for lack of efficacy above] and the FEV_1 findings at endpoint support the efficacy of these two doses of Flovent Rotadisk in this population, which along with the adherence data (>90% mean use by blister count) is evidence supporting that those subjects randomized to active treatment did take it and received benefit from it. It should be noted that there were trends towards a dose-response on these two efficacy analyses, but no true statistical separation of the two FP doses when tested in a paired manner.

8.6.4.3 Safety Analysis

The safety analysis included all patients who received any study drug (the

36 **Russell G. Asthma and growth. Arch Dis Child 1993;69:695-8.**

intent-to-treat population). This consisted of 325 patients as outlined above. This review of safety findings will concentrate on the systemic effects tracked in this study, since the local effects of a DPI inhaled formulation of FP have only minor relevance to Flonase applied intranasally from an aqueous formulation. Again, the primary safety parameter for which this study was designed was growth velocity. Other important assessments of systemic action included HPA effects, ocular effects, bone turnover chemistries and physical findings.

8.6.4.3.1 Height / Growth Velocities

Standing heights were measured in barefoot subjects at visits 1, 2, 5-17 (and by entry criteria at some visit 6 - 18 months previously) using a Harpenden wall-mounted stadiometer. As often as feasible, this was to be done by the same personnel for each patient. For uniformity's sake, study personnel were trained by video tape on correct height ascertainment. It should be noted that all bone age films were centrally read by radiologists at the Fels Institute in Ohio, and readers were reportedly masked to treatment.

For this analysis, one important subgrouping identified by the sponsor were subjects who did not become pubescent during the study (those with Tanner SMR # 1), since growth velocities accelerate greatly during pubescence. This amounted to a subgroup of 268 subjects, with 87 in placebo, 85 in FP50 and 96 in FP100. However, the differential drop-out was pronounced in this population with only 57 placebo subjects completing compared with 74 and 79 for FP50 and 100 respectively.

A tabular summary of the growth velocities for the intent-to-treat population is found below by cm/year (S.E.) and related statistical testing:

	n	Plac.	n	FP50	n	FP100	Overall	P v FP50	P v FP100	FP50 v FP100
Screening	106	6.11 (0.10)	111	6.15 (0.10)	108	6.15 (0.09)	0.882*	0.854*	0.605	0.758*
Baseline to Wk 28	85	5.97 (0.17)	103	5.76 (0.17)	94	5.62 (0.15)	0.520	0.689	0.227	0.452
Wk 28 to Wk 52	76	6.70 (0.26)	98	6.35 (0.21)	89	5.68 (0.18)	0.099*	0.363	0.031	0.175*
Baseline to Wk 52	**76**	**6.32 (0.17)**	**98**	**6.07 (0.15)**	**89**	**5.66 (0.12)**	**0.095**	**0.465**	**0.031**	**0.123**

** indicates a significant investigator effect exists*

These data show what appears to be good results from the randomization with very similar screening growth velocities. These data suggest that there is a small, but statistically significant suppression of growth velocity apparent when Flovent 100 mcg BID DPI from the Diskhaler is used daily in the control of asthmatic children (0.66 cm/year less than placebo). This effect is apparently smaller than that reported in boys for standard doses of BDP (1.9

cm/year), given the context that the population in this study was predominantly male. Due to drop out of younger patients in the placebo and FP50 group, the mean change in chronologic age was not the same in the three groups over the course of the study, but amounted to 1.03 years in placebo; 1.02 years in FP50 and 0.89 years in FP100, which could confound the findings. [*note that this discrepancy was confirmed by the bone age findings as described below*]. If one looks at the Serono Charts provided by the sponsor, during the period represented by the average age range in this study (between 8 - 10 years), growth velocity *declines* and does not rise again until just pre-puberty - which for boys is age 11 and for girls is age 9.5. Therefore, if the FP100 group became relatively 'younger' compared to the placebo and FP50 group, it appears that this might result in a higher mean growth velocity for the FP100 group irrespective of any treatment effect. This is counter to the sponsor's argument that this difference in change in mean age would have biased the FP100 results towards a lower mean growth velocity for this group. Additionally, the caveat about differential drop out potentially biasing against Flovent in comparison to placebo (where the drop out rate was higher) due to asthma-growth interactions should be borne in mind in considering these data.

Depicted below is a tabular summary of the same measures for the protocol-defined prepubescent population:

	n	Plac.	n	FP50	n	FP100	Overall	P v FP50	P v FP100	FP50 v FP100
Screening	87	6.10 (0.11)	85	6.31 (0.12)	96	6.16 (0.09)	0.368*	0.181*	0.640	0.329*
Baseline to Wk 28	66	5.79 (0.17)	77	5.66 (0.20)	83	5.61 (0.16)	0.804*	0.627	0.513	0.918
Wk 28 to Wk 52	57	6.43 (0.26)	74	6.14 (0.22)	79	5.68 (0.17)	0.250*	0.487	0.080	0.367*
Baseline to Wk 52	57	6.10 (0.17)	74	5.91 (0.16)	79	5.67 (0.13)	0.313	0.446	0.108	0.496

The data represent a somewhat more homogenous population (which is the reason for examining this subgroup) than the overall intent-to-treat population, as evidenced by very similar S.E.'s despite smaller group sizes. The lack of statistical significance from this analysis is not simply due to the smaller sample size, but in part due to a different treatment effect size. The differences in growth velocity for Flovent compared to placebo are 0.19 cm/year for FP50 (as opposed to 0.25 for the ITT) and 0.43 for FP100 (as opposed to 0.66 for the ITT). However, one could make the case that the pubertal age range, where growth velocity is greatly accelerated, would be a more sensitive (though likely more variable) population for assaying growth delay / inhibition and therefore eliminating the pubertal subjects could result

in a less sensitive population (i.e., one less able to detect a difference in growth effects if one does exist). So whether the smaller effect size seen from this analysis is in anyway reassuring is a matter of interpretation.

Finally, in a post-hoc attempt to deal with differential drop-out and its effects on age, the sponsor hired an independent consultant to perform an age matched analysis of pre-pubertal completers. This analysis matched 47 subjects in each treatment arm for age, gender, prior ICS use and skeletal age. The results are depicted below:[37]

	n	Plac.	n	FP50	n	FP100	Overall	P v FP50	P v FP100	FP50 v FP100
Screening	47	6.21 (0.15)	47	6.43 (0.17)	47	6.14 (0.16)	0.488*	0.389	0.712	0.281*
Baseline to Wk 28	47	5.74 (0.21)	47	5.66 (0.19)	47	5.64 (0.20)	0.837*	0.550	0.659	0.664*
Wk 28 to Wk 52	47	6.30 (0.20)	47	5.99 (0.26)	47	5.56 (0.19)	0.224	0.410	0.034	0.777
Baseline to Wk 52	47	6.01 (0.17)	47	5.81 (0.14)	47	5.60 (0.16)	0.321*	0.310	0.116	0.943

This analysis does not add much new information, except perhaps further strengthening the impression that the differences seen in growth velocity in the ITT population are not just due to confounding stemming from the differential aging or differential asthma severities induced by drop-outs. The sponsor points out that there was no significant differences in their summary of this post-hoc analysis. However, there was a p of 0.034 for the FP100 vs. Placebo comparison over the latter 24 weeks, when one might expect to see more of an effect if the growth inhibiting effect of FP is cumulative over long periods (not an improbable assumption). Furthermore, the sample size achieved in this post-hoc analysis is about ½ that called for in the sponsor's power analysis. If these effect sizes were also achieved with a population of 94 patients per arm, it is likely that the baseline to week 52 comparison would be statistically significant - although the actual difference in growth velocity is less than ½ cm/year for both this analysis and the prepubescent analysis above. Again, this is of questionable clinical importance even if it represents a true drug effect and it is smaller than that seen in at least two trials examining the effects of BDP.

8.6.4.3.2 Bone age assessment

Depicted below is a tabular summary of the change in bone age for the intent-to-treat population (with baseline mean bone age given first):

37 **Appendix 10, Vol. 1.019**

	n	Plac.	n	FP50	n	FP100	Overall	P v FP50	P v FP100	FP50 v FP100
Mean Screening bone age	105	8.64 (0.22)	110	8.49 (0.20)	108	8.24 (0.22)	0.348	0.949	0.204*	0.210
Baseline to Wk 28	86	0.53 (0.04)	103	0.61 (0.04)	98	0.45 (0.03)	0.026	0.184	0.173*	0.010
Wk 28 to Wk 52	76	0.65 (0.05)	97	0.59 (0.06)	89	0.50 (0.04)	0.244	0.609	0.050	0.269
Baseline to Wk 52	75	1.18 (0.06)	97	1.19 (0.05)	89	0.95 (0.05)	0.006	0.689	0.008*	0.002

A very similar pattern was seen for the prepubescent sub-group with mean changes in bone age of 1.13 (0.06) for both placebo and FP50 and 0.95 (0.05) years for the FP100 treatment arm. Bearing in mind the differential drop out of younger patients in the FP50 and placebo group which resulted in ≈ 0.14 year higher mean chronologic age for these groups compared with the FP100 group, one would expect findings of a greater change in mean bone age in these two groups compared to the FP100 group regardless of any true treatment effect. Therefore, since these data are not convincingly disparate from the mean chronologic age calculations, one can not conclude that this apparent delay in skeletal maturation by radiologic assessment is a treatment effect, but rather more likely represents a reflection of the chronologic disparity.

8.6.4.3.3 HPA axis assessment

Assessment of hypothalamic-pituitary-adrenal axis function was performed by a.m. cortisol monitoring and by urinary testing of free cortisol and 17-hydroxycorticosteroids (the latter to add to the profiling of adrenal output). Findings for abnormalities occurring in these tests at any post-randomization determination are depicted below:

	Placebo	FP50	FP100	Total
Number of subjects	**106**	**111**	**108**	**325**
Subjects with low a.m. plasma cortisol (< 5 mcg/dL)	14 (13%)	8 (7%)	12 (11%)	34 (10%)
Subjects with low urinary free cortisols (< 0.75 mcg)	16 (15%)	27 (24%)	20 (19%)	63 (19%)
Subjects with low urinary 17-OH-corticosteroids	**80 M 26 F**	**82 M 29 F**	**82 M 26 F**	**244 M 81 F**
Males	29 (36%)	48 (59%)	41 (50%)	118 (48%)
Females	3 (12%)	6 (21%)	5 (19%)	14 (17%)

Although there are no indications from the a.m. cortisol assessments of any definable effect of active treatment, these measures are not to be considered adequately sensitive and specific to be helpful in defining systemic safety. This lack of reliability of a.m. cortisol testing is borne out by the other observations. For both urinary free cortisol and for the 17-hydroxycorticosteroid determinations, there appears to be a treatment effect, albeit not definably dose-related. These data suggest that over a years time, even at a dose of 50 mcg BID, there is some systemic activity of fluticasone when administered by oral inhalation via a dry powder inhaler.

There are a few things worth noting in these data, however. First, these urinary measures were overnight collections since the sponsor argues that it would be in these collections where a differential effect would be most obvious (since there is a normal nadir in cortisol excretion occurring nocturnally and that these data would not then be 'overwhelmed' by daytime excretion - i.e., better signal-to-noise ratio). With a drug dosed BID, this seems to be a credible argument. The collections, however, may not always have been optimal, so the sponsor also checked urinary creatinines to assess adequacy of the collections. This analysis is summarized below for change from baseline to week 52:

Treatment group	**Placebo**			**FD50**			**FP100**		
12 Hour test:	n	$\bar{x}$	(SE)	n	$\bar{x}$	(SE)	n	$\bar{x}$	(SE)
Mean urinary cortisol - baseline (mcg)	99	60.33	(7.52)	102	56.07	(4.46)	103	61.14	(12.1)
Mean urinary cortisol - endpoint (mcg)	75	52.50	(3.75)	97	50.33	(5.53)	89	41.99	(2.61)
mean cortisol/creatinine ratio - baseline	101	0.23	(0.03)	103	0.20	(0.20)	103	0.29	(0.07)
mean cortisol/creatinine ratio - endpoint	75	0.23	(0.05)	97	0.17	(0.02)	89	0.17	(0.01)
change in cortisol (mcg) - baseline to endpoint		- 7.83			- 5.74			- 19.15	
% change in cortisol		- 13.0%			- 10.2%			- 31.3%	
change in cortisol/creatinine ratio - baseline to endpoint		0.00			- 0.03			- 0.12	
% change in ratio		0%			- 15%			- 41%	

Again, these data support that there is likely a true treatment effect on cortisol production, particularly as reflected by the FP100 dosing regimen when tested by 12-hour corrected urinary cortisol excretions. However, since the urinary excretion in the FP100 group - both corrected and

uncorrected - was higher at baseline than in the other two treatment arms, some of the fall demonstrated may have been due to other factors (such as regression towards the mean).

When timing of the occurrence of the urinary free cortisol abnormalities relative to drug exposure is considered, the abnormalities in the placebo group were relatively equally distributed in all time periods (beginning, middle and end) versus that seen with active treatment, which was more clearly clustered towards the end point, again supporting a true treatment effect. For the FP50 group, for instance, of the 27 total abnormalities, 16 occurred exclusively at the end of the study (following at least 2 other normal determinations). For the FP100 group, out of the 20 abnormalities, 14 such 'end of study' abnormalities occurred.

Finally, although a diminished output of urinary cortisol implies some activity of fluticasone systemically upon the HPA axis, these data are not helpful in assessing whether the HPA axis could have responded to stress properly. Certainly there was no clinically overt adrenal insufficiency observed in this study. However, that lack of overt problems also does not assure that there were no subtle, but important abnormalities. In all, the best that can be said of the data available to us is that there indeed appears to be some systemic activity of FP at these doses in this age group when inhaled over long periods. The effects on the adrenal are apparently small, but present, and the clinical importance and relevance of these effects is unknown.

8.6.4.3.4 FP Levels

Fluticasone blood levels were checked around predicted serum peak levels (20 and 40 minutes) in a select subset of individuals. The level of detection of the assay used was 25 pg/ml. These findings are represented below (N[1] = subjects tested; N[2] = subjects with detectable levels):

	Placebo				FP50 BID				FP100 BID			
	N[1]	N[2]	$\bar{x}$	SE	N[1]	N[2]	$\bar{x}$	SE	N[1]	N[2]	$\bar{x}$	SE
20 minutes post-dose	15	1	115.0	-	16	4	69.4	17.1	13	13	71.6	10.7
40 minutes post-dose	15	-	-	-	16	7	97.0	46.7	13	12	72.9	10.6

At a dose of FP100 BID, all patients have detectable levels at 20 minutes post dosing, albeit quite low (mean of 72 picograms/ml). Even at the FP 50 does, some individuals do achieve measurable systemic levels, which is in keeping with the HPA data and bone growth data which were suggestive of effects.

8.6.4.3.5 Ophthalmologic Examinations

Ophthalmologic exams were conducted at baseline and at three additional study visits. A particular focus of these exams was intraocular pressure and

lenticular opacities - looking for glaucoma and subcapsular cataracts. Six subjects developed abnormalities on their ophthalmologic examinations in the course of the study. These included 1 placebo subject, 3 in the FP50 group and 2 in the FP100 group. Most of these represented congenital findings present at baseline and intermittently observed thereafter. There are two notable subjects, however. These two subjects were withdrawn for ocular events. The first was a FP100 subject who developed a trace posterior subcapsular cataract in the left eye at week 24 and was subsequently dropped from the study. This patient had been on beclomethasone (Vanceril) for approximately a year prior to the study, so the relative contribution of FP alone is debatable in this event. The second patient of note was a FP100 patient who entered the study with high baseline intraocular pressure (IOP), but with no visual field testing performed at baseline. At day 173 of the study, the subject had high IOP and visual field deficits consistent with glaucoma and was withdrawn from the study. This subject had a family history of glaucoma. A further subject in the FP50 group had high IOP, but was high throughout the study and did not have baseline measures recorded, so causality is questionable. In summary, there is no clear signal of an important ocular risk from these data, although the subcapsular cataract reported may have been at least in part related to FP exposure and the glaucoma occurrence suggests that subjects with a predisposition to glaucoma may be at risk from exposure to long-term treatment with inhaled FP.

8.6.4.3.6 Other Notable Systemic Findings

The laboratory examinations did not reveal any striking findings. By shift analysis, it appears that only low glucose, high eosinophil counts and low bicarbonates appeared more frequently in an active treatment than placebo, although none were convincing for a treatment related trend (i.e., no dose relationship and inconsistent findings between the two active doses). All three of these are somewhat paradoxical compared what might be pharmacologically predicted for systemic steroid effects.

As far as other data related to potential systemic effects, there was an 11 year old who was noted to have weight gain on day 59 of the study and was finally withdrawn on day 143 for weight gain of 11.5 pounds. There is no mention of a cushingoid appearance, however.

8.6 Conclusions

There are data from separate sources (i.e., not from a single study) that support that the systemic bioavailability for Flovent DPI is in the range of 9 - 20%, while the systemic bioavailability of Flonase is in the range of 2%. Therefore, as previously mentioned, these data from this year long trial represent a "worst case" scenario for the systemic effects of long-term

Flonase.

From these data there appears to be a definite, though small, effect of these doses of inhaled fluticasone on linear growth over a year's time. This effect appears to be similar, if not smaller, than that seen with beclomethasone (400 mcg ex-valve per day) in two previous studies.[38,39] There is a less convincing delay in bone age, since most of the discrepancy noted on the radiologic examinations can be accounted for by differential drop-outs and that impacting on chronologic age. Given the 5 - 10 fold higher bioavailability of the oral inhaled product compared to the nasal spray, it is unlikely that any statistically or clinically significant growth perturbations would result from Flonase use. The rare instances of potentially related ocular, weight or other systemic adverse effects seen in this study, if indeed these were related, would also be even less likely a sequelae of Flonase treatment.

These data therefore offer reasonable assurance that Flonase could be used long-term in the age range at a comparable daily dose with little in the way of systemic effects. Given the low levels of FP documented in this study by PK sampling, it seems unlikely that Flonase would yield measurable systemic levels when given at comparable nominal doses (i.e., 100 and 200 mcg / day). These data from FLD-220, combined with the local safety data available elsewhere in this submission, should provide adequate information for yielding an assessment of the risk/benefit ratio of Flonase for the pediatric population.

9.0 INTEGRATED SUMMARY OF EFFICACY (ISE)

This section submitted by the sponsor is rather brief and does not necessarily integrate the efficacy data to any large degree, but rather summarizes the findings of the various studies reviewed above. In part this is due to the disparity of disease-state studied (SAR, PAR), duration, assessment methods, as well as other considerations. However, this review follows the sponsors ISE submission and will comment on that submission as well as comment on the integrate review of efficacy.

9.1 Efficacy in Seasonal Allergic Rhinitis

Three main studies support this indication for the 4 - 11 year old age range: studies FLN-320, 321 and FLNT52. Each of these examined both 50 mcg per nostril Q a.m. and 100 mcg per nostril Q a.m. (100 and 200 mcg daily respectively). However, FLNT52 used a different formulation to achieve the 200 mcg daily dose. The data derived from these studies, considered

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38 **Doull, Freezer and Holgate. "Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate." Am J Respir Crit Care Med. 1995; 151:1715-9**

39 **Tinkleman, Reed, Nelson and Offord. "Aerosol beclomethasone dipropionate compared with Theophylline as primary treatment of chronic mild to moderately severe asthma in children." Pediatrics. 1993; 92:144-6**

together, offer reasonable evidence of efficacy for both doses, with studies FLN-320 and FLNT52 more strongly supporting the FP100 dose and the 321 study supporting the 200 mcg daily dose. No study gave clear evidence of a reliable dose response for efficacy, nor was there a titration component (either upward for non-response or downward for good response) to any of these trials. The US trials suffer from a no apparent *a priori* definition of primary efficacy variables and no pre-planned analyses. However, the results are broad enough even given these deficiencies that there is reasonable evidence of effectiveness. The most convincing trial in many respects, though it can only be considered supportive of the FP200 efficacy (due to the formulation issue), is FLNT52. This trial under enrolled and there was demographic imbalance which appeared to bias against the FP100 group, yet clear efficacy was found, including on the *a priori* designated components of the NSS.

Finally, when the two US trials were submitted to the original NDA, there was a Pilot Drug requested analysis of high pollen count day data, which despite eliminating roughly half the subjects, showed "statistical significance." These data were not presented for our review with this supplement.

None of these studies was well designed to address issues of onset of action. However, from study FLN-320, it appears that efficacy was noted in patient diary data by 4 - 7 days (by day 3 for the a.m. nasal obstruction endpoint), a reasonable time frame for intranasal corticosteroids.

9.2 Efficacy in Perennial Allergic Rhinits

Studies FLNT60 and 61 were submitted to support this claim. The latter suffers from numerous problems, not the least of which is that it is a positive control trial of a variable disease in which a large placebo response commonly observed. On top of that concern, this study was underpowered, which further complicates an active control equivalency trial. Study FLNT60 was placebo controlled and of reasonable design and execution (other than the different formulation used for the FP200 group, as in FLNT52). However, this study failed to demonstrate significance on 2 of the 3 sponsor defined primary endpoints (though the study plans were without clear cut plans for needing "wins" on all three, there was also no correction for multiple comparisons). The investigator evaluations (which were secondary) were somewhat more convincing, but still were not consistently positive.

All that being stated, by the pediatric rule we should be able to conclude efficacy based on well controlled adult data under circumstances where the disease processes and the response to the medications do not differ significantly between adults and children, as long as we can be convinced that the proper dose has been identified. Given that the proposed doses of Flonase 100 mcg and 200 mcg daily have been demonstrated to be effective in SAR in children and SAR and PAR in adults, and given that the main difference between PAR and SAR is the type of allergen and the duration of

symptoms (but not the pathophysiology), and given the modest support of efficacy coming from FLNT60, it is reasonable to conclude efficacy of Flonase 100 mcg and 200 mcg daily for PAR in children ages 4 - 11. This is especially so given that the Division has seen other instances where reasonably designed and conducted trials in the allergic rhinitides have failed in children with a regimen that we later, based on other data, have concluded were efficacious.

9.3 Efficacy of Flonase in Subsets of the Population

Meaningful ethnic origin comparisons could not be performed by the sponsor due to the paucity of non-Caucasians in these trials, particularly the European based studies.

Analysis of gender differences for the two US SAR trials showed no convincing trend towards a different therapeutic response between the two genders.

9.4 Drug-Disease and Drug-Drug Interactions

Other than atopic diseases, this population was relatively devoid of other conditions and therefore meaningful statements about drug-disease interactions for any non-atopic process is impossible. The one drug-disease interaction worth comment will be discussed in the ISS and that is whether Flonase is associated with wheezing/bronchospasm.

There were also few concomitant medications given to these children other than rescue H1 antagonists and asthma medications. No striking interaction would be expected, however, given the low systemic levels of FP likely to be achieved by these doses in children when administered intranasally from the aqueous preparation.

9.5 Evidence of Long-term Efficacy

Long term data are not available in this age group to support a finding of lack of tolerance and persistent benefit. However, this has been reasonably been demonstrated out to the six month time frame for the adolescent/adult age range through studies submitted to NDA 20-121 (FLN-311,310 found in volumes 1.107 and 1.129).

In this application, there is a component of the studies assessing the efficacy variables beyond the active treatment phase. These data support that there is no rebound observed. In fact, there is the observation that the placebo subjects convincingly worsen after treatment is stopped, where the active treatment groups remain stable (largely seen in the US SAR trials).

10.0 Integrated Summary of Safety

Note: Unless otherwise noted in this ISS review, the data referred to will be from the clinical studies of Flonase, not to Flovent.

10.1 Characterization of Pediatric Exposure

10.1.1 Study Drug Exposure

The controlled clinical trials experience provided in this document of aqueous formulations of fluticasone propionate (though not necessarily the U.S. formulation and not all receiving active treatment) was 1,152 subjects by the sponsor's reporting, consisting of children ranging in age from 3 to 14 years. These data are depicted below by dosage and study:

	Placebo	FP100 QAM	FP100 BID	FP200 QAM	BDP 200 BID	Total
Seasonal						
FLN-320	85	84	0	81	0	250
FLN-321	83	83	0	83	0	249
FLNT52	50	47	0	*46*	0	143
Total Seasonal	218	214	0	210	0	642
Perennial						
FLNT60	141	138	0	*136*	0	415
FLNT61	0	30	*35*	*0*	30	95
Total Perennial	141	168	*35*	*136*	30	510
Total Patients	**359**	**382**	**35**	**346**	**30**	**1152**

Subtracting out the placebo and BDP patients, there were 763 subjects exposed to intranasal aqueous suspensions of fluticasone. Of these, 546 were exposed to formulations and dosing schedules that were either similar or identical to the U.S. formulation and dosing recommended in the proposed labeling (that is, 182 subjects were exposed to 200 mcg formulations which were 0.1% rather than 0.05% and 35 subjects were treated with BID dosing - see italicized numbers in graph above).

10.1.2 Duration of Exposure (Pediatric)

The duration of exposure was predominantly short-term, consistent with the fact that three of these trials were SAR trials. Excluding the Flovent study, there were only data from 12 subjects beyond 90 days.

Duration in days	1 - 15	16 - 30	31 - 60	61 - 90	>90	NA
Number of subjects	143	428	124	41	12	7

As can be seen from the above table, of the more than 750 subjects exposed in the pediatric age group during these clinical trials, the large majority of these exposures were between 16 - 30 days in duration, with only 53 being exposed for more than 60 days.

10.2 **Demographics of Study Participants**

10.2.1 Age of Exposed Individuals

	Treatment Group			
Age (years)	**FP 100 BID**	**FP 100 QD**	**FP 200 QD**	**ALL**
3	0	2 (<1)	0	**2 (<1)**
4	0	15 (4)	17 (5)	**32 (4)**
5	0	28 (7)	22 (6)	**50 (7)**
6	6 (17)	36 (9)	32 (9)	**74 (10)**
7	5 (14)	45 (12)	49 (14)	**99 (13)**
8	6 (17)	57 (15)	51 (15)	**114 (15)**
9	8 (23)	46 (12)	47 (14)	**101 (13)**
10	6 (17)	83 (22)	60 (23)	**149 (20)**
11	4 (11)	64 (17)	66 (19)	**134 (18)**
12 - 14	0	6 (2)	3 (1)	**9 (1)**
ALL	35	382	347	**764**

There were 72 subjects under the age of 6 exposed to FP. This is significant because this 4 - 6 year old age range is younger than the current labeling for some of the corticosteroid nasal products. Within the 6 - 11 age groupings, the distribution was fairly even. There were only 9 subjects above their 12th birthday, a population group that is already included in the current indication for this product.

10.2.2 Other Demographic Summary Data

US study population:

	Placebo	FP100 QD	FP 200 QD
N	168	167	165
Age in years (SE)	8.7 (0.1)	8.6 (0.1)	8.7 (0.1)
Range	4-11	4-11	4-11
Male:Female (%:%)	95:73 (57:43)	122:45 (73:27)	100:57 (66:34)
Ethnic origin			
White	145 (86%)	152 (91%)	141 (86%)
Black	10 (6%)	7 (4%)	7 (4%)
Other	13 (8%)	8 (5%)	17 (10%)

As noted in the individual trial reviews, these demographics are weighted toward caucasian males compared with to entire indicated population in the US. One reason for the male predominance is the need to exclude post-menarche girls, so that the 10 - 11 year old age group was heavily represented by boys. However, this lack of full demographic balance should

not affect the findings from the safety data, as there are not known definable differences in these populations which would bias the safety results.

Non-US study population:

	Placebo	FP100 QD	FP100 BID	FP 200 QD	BDP200 BID
N	191	215	35	182	30
Age in years (SE)	8.1 (2.3)	8.3 (2.3)	8.5 (1.7)	8.1 (2.4)	8.7 (1.7)
Range	4-12	3-14	6-12	4-13	6-11
Male:Female (%:%)	123:68 (64:36)	137:78 (64:36)	24:11 (69:31)	120:62 (66:34)	21:30 (70:30)
Ethnic origin					
White	177 (93%)	194 (90%)	32 (91%)	171 (94%)	27 (90%)
Black	1 (1%)	2 (1%)	0 (0%)	2 (1%)	2 (7%)
Other	12 (6%)	19 (9%)	3 (9%)	9 (5%)	1 (3%)

Like the US exposed population, this population is also weighted towards Caucasian males, although the female representation is a bit more balanced. There were relatively few blacks studied. The 'other' category in this study represented primarily Asians (not otherwise specified).

10.2.3 Withdrawals as an indicator of Safety

There were relatively few withdrawals in these studies for any reason, particularly in the US studies (which were shorter-term). A summary of these data is found in the following table (details in table D1 of ISS, vol. 1.045):

			Number withdrawn		
	Number randomized	Number completed (%)	Adverse Event	Treatment Failure	Other
US studies					
Placebo	168	166 (98.8%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
All FP	331	321 (97.0%)	7 (2.1%)	0 (0.0%)	3 (0.9%)
Non-US studies					
Placebo	191	180 (94.2%)	3 (1.6%)	2 (1.0%)	7 (3.7%)
All FP	432	386 (89.4%)	8 (1.9%)	6 (1.4%)	35 (8.1%)
BDP	30	27 (90.0%)	0 (0.0%)	0 (0.0%)	3 (10.0%)

Even though the non-US studies were of longer duration (a likely reason why the observed drop-out rate for other reasons was higher), the drop-outs in active treatment with FP reported as due to adverse events was in each population close to 2%. This appears to be somewhat in excess of the placebo group, but not inordinately so. The number of treatment failure withdrawals was also quite low, though not convincingly different between

active FP or BDP and placebo.

10.3 Adverse Event Summary

10.3.1 US study results

The number and character of the most frequent/important adverse events is shown in tabular summary below. Depicted are all events which occurred more frequently than 2% in any treatment group or which are salient to nasal corticosteroid use as a class (note that shaded rows represent events where event occurrences for FP overall exceeded the occurrences in placebo by >1%):

Adverse Event Term	FP Overall	Placebo	100 QD	200 QD
N (%)	(N = 332)	(N = 168)	(N = 167)	(N = 165)
Any Adverse Event	**143 (43.1%)**	**66 (39.3%)**	**68 (40.7%)**	**75 (45.5%)**
Nasal Burning	8 (2.4%)	2 (1.2%)	4 (2.4%)	4 (2.4%)
Nasal Congestion	4 (1.2%)	0 (0%)	0 (0%)	4 (2.4%)
Epistaxis	20 (6.0%)	9 (5.4%)	10 (6.0%)	10 (6.1%)
Pharyngitis	14 (4.2%)	8 (4.8%)	10 (6.0%)	4 (2.4%)
Nausea/vomiting	13 (3.9%)	4 (2.4%)	8 (4.8%)	5 (3.0%)
Gastritis	7 (2.1%)	3 (1.8%)	3 (1.8%)	4 (2.4%)
Asthma Symptoms	26 (7.8%)	6 (3.6%)	12 (7.2%)	14 (8.5%)
Wheeze	7 (2.1%)	2 (1.2%)	4 (2.4%)	3 (1.8%)
Cough	16 (4.8%)	2 (1.2%)	6 (3.6%)	10 (6.1%)
Headache (see below)	17 (5.1%)	14 (8.3%)	11 (6.6%)	6 (3.6%)

One problem with these sort of data is that for much of this population, it is likely that the reporting was by proxy (parental / care giver reports) which may not be a true reflection of medication tolerance. That caveat stated, note that overall the rate of adverse events with active treatment was only somewhat higher than with placebo. The events which were reported are mostly expected, except for the higher incidence of cough and asthma symptoms, along with nausea and vomiting. These will need some mention in labeling, if not already addressed. It is notable that the rate of epistaxis does not appear to be significantly higher with active treatment than with placebo, although the length of these trials must be kept in mind (14 and 28 days for the two US SAR studies). Epistaxis, being an observable sign rather than a symptom is likely less subject to proxy under reporting. Finally note that for headaches, there appears to be a negative relationship between dose and occurrence, suggesting that Flonase has some efficacy against headaches occurring in the setting of SAR in this population.

10.3.2 Non-US Study Results

The number and character of the most frequent/important adverse events from the Non-US SAR and PAR trials are shown in tabular summary below. It must be borne in mind that these studies were of longer duration on average than the US studies. Also bear in mind that only the FP100 QD and the BDP would be expected to hold direct relevance to the US formulation and dosage regimen proposed. Depicted are all events which occurred more

frequently than 2% and in more than 1 subject in any treatment group or which are salient to nasal corticosteroid use as a class (events where the rate in the FP100 QD group exceeded placebo by more than 1% are shaded):

Adverse Event N (%)	Placebo (N = 191)	FP100 QD (N = 215)	FP100 BID (N = 168)	FP200 QD (N = 167)	BDP200 BID (N = 165)
Any Event	**80 (42%)**	**98 (46%)**	**26 (74%)**	**70 (39%)**	**20 (67%)**
Otitis	2 (1.0%)	6 (2.8%)	1 (2.9%)	4 (2.2%)	0 (0.0%)
Pharyngitis	5 (2.6%)	6 (2.8%)	1 (2.9%)	5 (2.7%)	1 (3.3%)
Rhinitis symps.	5 (2.6%)	3 (1.4%)	4 (11.4%)	0 (0.0%)	1 (3.3%)
URTI	15 (7.9%)	26 (12.1%)	6 (17.1%)	15 (8.2%)	6 (20.0%)
Epistaxis	4 (2.1%)	12 (5.6%)	5 (14.3%)	2 (1.1%)	2 (6.7%)
Flu symptoms	2 (1.0%)	5 (2.3%)	3 (8.6%)	4 (2.2%)	3 (10.0%)
Bronchitis	6 (3.1%)	6 (2.8%)	2 (5.7%)	2 (2.2%)	1 (3.3%)
Asthma symps.	16 (8.4%)	14 (6.5%)	1 (2.9%)	6 (3.3%)	5 (16.7%)
Cough	9 (4.7%)	13 (6.0%)	3 (8.6%)	8 (4.4%)	3 (10.0%)
Headache	8 (4.2%)	10 (4.7%)	2 (5.7%)	7 (3.8%)	4 (13.3%)

The only shared event highlighted between these studies (focusing on the relevant treatment group as being the FP100 QD) and the US studies was cough. The apparent excess in otitis would be surprising and paradoxical, given that the treatment of allergic rhinitis should lead to more eustachian tube patency. Given the small number of subjects involved, this observation could well be spurious. The observation with excess epistaxis in the trial with active treatment differs from the findings in the US trials. However, given the longer duration of exposure in these trials, these data could be accurate reflections of both data sets. Although in these studies the asthma symptom reporting had a negative relationship to active study drug exposure, "upper respiratory tract infections" or URTIs had a positive relationship. It is conceivable that some of this discrepancy may be due to differences in coding and how symptoms get recorded.

10.3.4 Serious Adverse Events

There were no deaths in these trials, either domestically or abroad. There were 4 serious adverse events reported from these trials, two of these were in subjects receiving active treatment. Note that in the safety update, there were no additional study-related serious adverse events in children.

- An 8 year old male receiving FP200 QD had a serious asthma attack that required hospitalization, after receiving only 2 doses of FP. The subject was withdrawn from the study.
- An 8 year old male receiving FP100 was admitted to the hospital following a fall.
- The two placebo subjects were trauma/surgical related and had no reasonable relation to study participation.

Of the spontaneously reported adverse events post-marketing worldwide up to Jan 1, 1997, only two such serious events were reported for a person

under the age of 12. The first was for convulsions in an 8 year old female subject, with unknown relationship to Flonase treatment. The second was new onset diabetes mellitus in a 3 year old given Becloforte and Flonase. The diabetes persisted despite withdrawal of corticosteroidal medications.

Of note in the ≥ 12 year old population, there was a dyspnea episode in a 20 year old that the reporter felt was almost certainly related to Flonase, which may relate to some of the asthma-like occurrences seen in the US pediatric studies. There is a more clear cut case of increased asthma symptoms occurring in relation to Flonase treatment in a 66 year old asthmatic female, but she was also being overdosed at 200 mcg TID. There were 2 anaphylactic reactions and a benzalkonium reaction, the latter in a subject with known sensitivity. There were 3 nasal septal perforations in users who had received over 2 years of Flonase, 3 months of Flonase and six days respectively. There were also some cases of parosmia.

10.3.5 Adverse Event Summary

The current and proposed labeling will be reviewed with regard to the events noted above and the adverse event tables for both the US and non-US study groups. It should be noted that the 2 US trials and at least some of the foreign data were available for the original NDA review and, in fact, were included in the original approved labeling. Anaphylaxis and nasal septal perforation episodes were the subject of a memo to the sponsor requesting changes in the labeling specific to these events occurring in the post-marketing setting with this agent. These changes were contained in a labeling supplement s-004 and were approved in Dec. 1996. Of particular note, any labeling approved as a result of this pediatric supplement will need to specifically refer to the potential for increase in asthma symptoms/wheezing with Flonase use in asthmatics.

10.4 Cortisol / HPA axis Data

For the Flonase studies, there cortisol data available is predominantly a.m. cortisols, although there was also assessment of urinary cortisols in the US 28 day study. The a.m. cortisol data, which would be expected to lack sufficient sensitivity and specificity for subtleties in the adrenal axis / output, showed comparably few occurrences of abnormality in any group, active or placebo. However, the assessment of corrected urinary output (corrected for creatinine) suggests a potential mild effect in the FP200 group from the US 28 day study. These results are summarized by means below:

Cortisol/creatinine (mcg/g)	Placebo	FP100 QD	FP200 QD
Pretreatment			
N	83	81	81
Mean (SE)	30.6 (1.68)	33.4 (1.40)	33.0 (2.54)
Final study day			
N	72	80	75
Mean (SE)	31.1 (1.79)	33.2 (2.23)	27.2 (1.67)
Net Change	*+ 0.5*	*- 0.2*	*- 5.8*

The mean cortisol either stayed steady or rose slightly in the placebo and FP100 group, however, it fell by a mean of 5.8 mcg/g in the FP200 group. Again, this supports the possible association of the FP200 dose with a small mean effect on cortisol production with short-term use in this age range. Extrapolating from these results of the mean, one might expect that a small minority of sensitive subjects have the potential to display more important systemic effects of this dose. Again, this needs consideration in labeling.

The systemic data available from the same nominal daily doses in this age range with the more bioavailable Flovent DPI is discussed below in 10.7.

10.5 Laboratory Findings Related to Safety

A close review of these data, presented in the individual study reports and again in the ISS with both shift tables and reports of significant abnormalities does not demonstrate any consistent unexpected or expected findings related to active drug treatment. There were some sporadic abnormalities, including abnormalities in liver-related chemistries, but taken as a whole, there is no convincing relation to active treatment. This includes an examination of shifts that might indicate a systemic response to the fluticasone (e.g., high glucose, low lymphocytes or eosinophils,...).

10.6 Vital Signs

There were no important signals either in the US or non-US trials of any trend in vital signs during treatment. Particularly, since systemic corticosteroids can elevated blood pressure, there was essentially no change in mean systolic and diastolic blood pressure during active treatment compared to baseline in either of the data sets.

10.7 Systemic Safety

These data, as previously mentioned, were obtained by a year long study of the same nominal dose using the more bioavailable formulation/route of the inhaled Flovent DPI product. Although the sponsor concludes from this study that no statistical effect on growth was demonstrated, for the overall population (not just the prepubescent upon which they focus) there is a statistically significant decrease in growth velocity with the 100 mcg of FP/day dose, although the change is clinically small and compatible if not

smaller than that seen in previously cited studies with BDP. The sponsor argues that since there was a differential drop-out in the placebo and FP50 groups leading to a larger mean change in chronologic age in the active treatment group, that this may have biased against FP100 in terms of finding a growth velocity retarding effect. However, given the mean age of the population examined, if one considers the growth velocity charts provided by the sponsor, growth velocity is ***decreasing*** with advancing age in this age range. Therefore, the effect of the larger change in mean chronologic age in the FP100 treatment group may have actually biased against showing a treatment effect of retarding growth velocity. In any case, the evidence from the inhaled route is that any effect of fluticasone on growth velocity is small, and likely negligible with the nasal product.

As discussed in the study review, there does also seem to be a small effect of FP treatment by the Flovent DPI on cortisol production, when corrected for creatinine. While the clinical significance of this association is not known for the inhaled product, it is even less certain for the intranasal product. However, as previously stated, even the nasal product shows some apparent effect on urinary excretion of cortisol when corrected for creatinine.

Finally, study of the long-term effects of inhaled fluticasone (at these nominal doses in the population) on other aspects of systemic safety showed two ocular findings of note, a case of increased ocular pressure/glaucoma in a child with a family history of glaucoma, and a cataract. Both of these occurrences can rarely be linked to inhaled glucocorticoid. The relevance for Flonase is less certain, although sporadic case reports have been reported by the sponsor from post-marketing experience in the US and abroad.

10.8 Demographic - Safety Information

No presentation of such data is presented by the sponsor in the ISS, other than for gender with adverse events. However, given the homogeneity of the population (i.e., almost exclusively Caucasian), it is unlikely that any meaningful statement on other demographics and safety could be made. The adverse event data shows no discernable pattern of differences in toleration/safety of Flonase by gender.

10.9 Overall Safety Conclusions

The data available support that the safety of Flonase is acceptable for the given indications. The local (i.e., upper respiratory tract) tolerance of Flonase in this population is quite good, with only some nasal irritation/pain, cough appearing to stand-out as treatment related adverse events overall, with nausea, asthma symptoms and URI-like symptoms appearing possibly related. As with all nasal corticosteroids, there are some important caveats which need to be placed in the labeling about systemic effects in susceptible individuals. Although little direct comparative data are available in this supplement for either local or more importantly systemic effects, there is little evidence that the effects of fluticasone are inordinately different than

currently marketed intranasal corticosteroids. Given the findings of the FLD-220 Flovent DPI studies, it is likely that any systemic effects would be on average small to negligible, with only very rare individuals who might display consequences in terms of adrenal function, growth, ocular findings, or other systemic effects.

11.0 Comments on Proposed Labeling[40]

The proposed labeling provided gives revision to the labeling which was in place at submission and therefore prior to approval of S-004 (approved 12-6-96), which included the addition of specific references to nasal septal perforation and to anaphylaxis due to occurrences noted in the spontaneous adverse events database. However, my comments on the labeling presumes the labeling as approved in S-004 will serve as the basis for the revisions proposed by the sponsor. Comments will be given in sequential order below:

- In the clinical trials section, reference to the two US SAR trials submitted as a part of this package is added. In line 97, reference is made to nasal basophil and eosinophil reductions. Since these data do not come from the studies of children ages 4 - 11, this should be amended to specifically state that the data come from adolescents and adults.
- In line 102, there is a reference to 6 trials that failed to show a significant dose response. Since FLN-320 and 321 also did not demonstrate a separation of these two doses, this statement should be amended to add these two trials (i.e., 8 total trials) and to indicate that the 8 trials referred to include the two US pediatric.
- Since there are no controlled data to support the dosing recommendations in lines 112-117 (and there is no reference to this recommendation provided in the proposed labeling) and no clear evidence of a dose response to Flonase, the recommendation to start more severe child patients at doses of 200 mcg QD should be removed to avoid excessive dosing in subjects who might well respond to 100 mcg QD. In its place should be added the caveat that in any subject controlled at 200 mcg QD, an attempt at dose reduction should be made.
- There is a list of general severe reactions which have been reported with intranasal corticosteroids in lines 157-160. This paragraph should end with "..., including fluticasone propionate." since adverse reaction reports from spontaneous reporting and clinical trials confirm these rare associated occurrences with Flonase.
- Reference to the Flovent study (FLD-220) is included in the

40 **Proposed revisions to the package insert are found on page 17-31 in volume 1.001. Note that line numbers refer to enumerated lines in the proposed labeling.**

precautions section in lines 165 - 170. This section needs to be rewritten to better reflect the data from that study which we feel shows a clinically small, but statistically significant growth effect of the 100 mcg BID dose in the intent-to-treat analysis. Therefore, lines 165 - 168 should be amended to read: "In a US study of 325 children aged 4 to 11 years given inhaled fluticasone propionate 50 mcg powder formulation at doses of 0 mcg (placebo), 50 mcg, and 100 mcg twice daily for 52 weeks, there was a small, but statistically significant effect on growth velocity with the 100 mcg twice daily dose as measured by stadiometry. Although the intranasal administration of Flonase Nasal Spray 0.05% is substantially less systemically bioavailable than the inhaled dry powder formulation, physicians should closely...."

- Lines 174-175 should be amended to read: "When used at higher than recommended doses, or in rare individuals at recommended doses, systemic glucocorticoid effects such as hypercorticism and adrenal suppression may appear."
- Lines 183 - 184 should be amended to read: "Flonase Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculosis infection; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infection; or ocular herpes simplex.
- Lines 237 - 239 should be amended to read: "Oral and, to a less certain extent, inhaled glucocorticoids have been shown to have the potential to cause a reduction in growth velocity in children and teenagers with extended use."
- The adverse event section should be reconstructed to include a table characterizing the most frequent adverse events which occurred more often in active treatment than placebo from the pivotal US studies, including FLN-320 and 321. This could be done in separate tables for the $\geq$ 12 versus 4 - 11 population, or done in one summary table. Which ever the choice, for the pediatric data, it appears from our review that the events which need to be captured include nasal burning, nasal congestion, nausea/vomiting, asthma symptoms and cough.
- Also in the adverse event section, the list of events reported in the postmarketing experience should be amended to include cataracts and increased ocular pressure/glaucoma.
- The dosage recommendation in lines 295 through 299 should be modified to be consistent with the previous comment on dose titration, removing the reference to using the 200 mcg dose to start in more severe patients, and recommending that any patient controlled on 200 mcg QD should have an attempt made to reduce their dose.

cc: NDA 20-121
HFD-570/Div file/NDA 20-121
HFD-570/Medical Officer/Meyer
HFD-570/Chemistry Reviewer/Rogers
HFD-570/Pharm - Tox Reviewer/Sancilio
HFD-570/Project Manger/Barnes
HFD-570/Medical Officer/Purucker

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20121/S005

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

	1. ORGANIZATION HFD-570 DPDP	2. NDA NUMBER 20-121
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Glaxo Wellcome, Inc. Research Triangle Park, NC 27709		4. AF NUMBER
		5. SUPPLEMENT (S) NUMBER(S) DATES(S) SE1-005 10/31/96
6. NAME OF DRUG Flonase® Nasal Spray	7. NONPROPRIETARY NAME fluticasone propionate nasal suspension	
8. SUPPLEMENT PROVIDES FOR: Extend the approved use of this product to the pediatric population of 4 - 11 years of age.		9. AMENDMENT(S), REPORT(S), ETC. SE1-005 (BC) 7/23/97
9. PHARMACOLOGICAL CATEGORY glucocorticosteroid with anti-inflammatory and anti-allergic properties for treatment of seasonal and perennial allergic rhinitis	10. HOW DISPENSED RX X OTC __	11. RELATED IND/NDA/DMF
12. DOSAGE FROM(S) Metered nasal pump spray (suspension)	13. POTENCY 50 µg per actuation through the nasal adapter	
14. CHEMICAL NAME AND STRUCTURE S-Fluoromethyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate (for structure see USAN)		15. RECORDS AND REPORTS CURRENT YES__NO__ REVIEWED YES__NO__

16. COMMENTS:

cc:
Orig. NDA #20-121
HFD-570/div. File
HFD-570/BDRogers/7/25/97
HFD-570/GPoochikian
HFD-570/SBarnes
HFD-570/RMeyer
R/D Init. by: GP 8/5/97
F/T by: BDRogers/7/25/97
doc # 20121.S05

17. CONCLUSIONS AND RECOMMENDATIONS: The supplement is APPROVABLE from a CMC perspective pending adoption, by the applicant,

18. REVIEWER NAME:	SIGNATURE	DATE COMPLETED
Brian D. Rogers, Ph.D.	Brian D. Rogers	7/25/97

Project Manager Review of Environmental Assessment

NDA 20-770 Flovent (fluticasone propionate) Rotadisk Inhalation Powder

NDA 20-121/S-005 Flonase (fluticasone propionate) Nasal Spray

Submission date: August 28, 1997

Sponsor: GlaxoWellcome

This submission contains a request to withdraw the Environmental Assessments which were submitted as part of the original submission for NDA 20-770 and 20-121/S-005 and replace them with Statements of Categorical Exclusions.

The categorical exclusions are submitted under 21 CFR § 25.31(b). There is no information that indicates that additional environmental information is warranted.

Sandy Barnes
Project Manager
Division of Pulmonary Drug Products

ccNDA 20-770
NDA 20-121/S-005
Div Files
HFD-570/B. Rogers 9/25/97
HFD-570/D. Koble 9/25/97
HFD-570/S. Barnes/9-24-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20121/S005

PHARMACOLOGY REVIEW(S)

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Label Review

NDA: 20-121, Supplemental Application

Date of Submission: 10/31/96

Information to be Conveyed to Sponsor: Yes (X), No ( )

Reviewer: Lawrence F. Sancilio, Ph.D.

Date Review Completed: 10/17/97

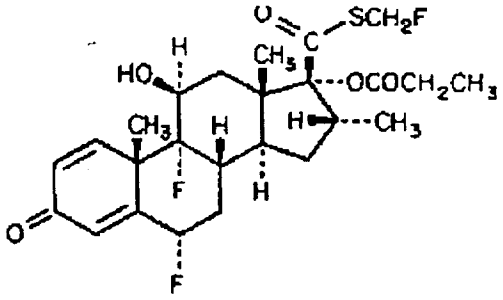
Sponsor: Glaxo Inc.
5 Moore Drive
Research Triangle Park, NC 27709

Drug Name: Fluticasone propionate

Chemical Name: S-fluoromethyl 6 , 9 -difluoro-11 -hydroxy-16 - methyl-3-oxo- 17 - propionyloxyandrosta-1,4-diene-17 -carbothioate

CAS No. 80474-14-2

Structure:



Molecular Weight and Formula: 500.6 ($C_{25}H_{21}F_3O_5S$)

Class: Glucocorticoid

Indication: Management of seasonal and perennial allergic rhinitis in patients 4-11 years old and adults.

Formulation: Aqueous suspension of 0.05% microfine fluticasone propionate containing microcrystalline methylcellulose, carboxymethylcellulose sodium, dextrose, 0.02% benzalkonium chloride, polysorbate 80 and 0.25% w/w phenylethyl alcohol.

Route of Administration and Daily Dose: 100-200 mcg intranasally.

Summary and Evaluation

This supplement of ND A20-121 is for fluticasone propionate to be administered by nasal inhalation as a spray for the management of seasonal and perennial allergic rhinitis in patients 4-11 years old. The maximum human daily inhalation dose is 200 mcg day. This formulation of fluticasone propionate has already been approved for this indication in adults. The Pharmacology and Toxicology of fluticasone propionate have been studied in depth (see the review of the pharmacologic and toxicologic studies submitted in the original NDA and in NDA 20-770).

Labeling Review

The following changes in the label regarding preclinical data are recommended. Deletions are highlighted with a ~~strikeout~~ and additions are highlighted in [redacted]. Relationship of the preclinical dose to the maximum recommended human nasal inhalation dose based on body surface were calculated using km factors of 6 for rats, 3 for mice, 12 for rabbits, 37 for Adults and 24 and for Children.

RECOMMENDATIONS

This NDA is for fluticasone propionate to be administered intranasally by inhalation for the treatment of allergic rhinitis in children and adults. From a preclinical standpoint, this NDA supplement is approvable.

The proposed changes in the label for the preclinical areas are recommended.

APPEARS THIS WAY
ON ORIGINAL

Lawrence F. Sancilio 10/17/97
Lawrence F. Sancilio, Ph.D.
Pharmacologist/Toxicologist

Oct. 17, 1997

cc. /Division File, NDA 20-121 HFD-570
/RMeyer, HFD-570
/C.S.O., HFD-570
/LFSancilio, HFD-570
/JSun, HFD-570

N:\NDA\20121\pharm\96-10-31.re2

Approved by J. Sun

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20121/S005

STATISTICAL REVIEW(S)

APR 30 1997

Statistical Review and Evaluation

NDA #: 20-121/SE1-005

Applicant: Glaxo Wellcome

Name of Drug: Flonase (Fluticasone propionate) Nasal Spray

Indication: Seasonal and Perennial Allergic Rhinitis

Documents Reviewed: Volumes 1.1-1.15 dated October 31,1996.

This review pertains to two studies in seasonal allergic rhinitis and one study in perennial allergic rhinitis is children 4-11 years of age.

The medical reviewer for this submission is R. Meyer, M.D. (HFD-570), with whom this review was discussed.

I. Background

Studies FLN-320 and FLN-321 of this submission were reviewed in a statistical review dated April 25, 1994. That review found both doses of Flonase to be significantly different from placebo for clinician-rated symptoms and patient-rated nasal symptoms. These analyses were on a set of 14 days that were of highest pollen count. The sample sizes in the review indicated that it covered only slightly more than half the patients. This reviewer feels that too much data had been excluded in those analyses. [The analyses in the statistical review of April 25, 1994 were not resubmitted with this submission.] This reviewer will, therefore, discuss only the analyses presented in this submission.

Although Flonase was approved for the adult population by the Pilot Drug Division (HFD-007) on October 19,1994; Flonase was not approved for the pediatric population (ages 4-11) because no long term safety data in children was provided in the original submission. Long term safety and efficacy data were provided in this submission.

II. Study FLN-320

A. Study Description and Method of Analyses

This was a parallel group, double-blind, randomized, seasonal allergic rhinitis trial comparing Flonase (FP) 100mcg QD, FP 200mcg QD and placebo in children 4-11 years of age. The treatment period was two-weeks. There was a four-day to two-week run-in period. There was a one week post-treatment phase.

To enter the study, the child had to have a total nasal score

above 200 of 400 possible points (using 100-point analog scales on 4 nasal symptoms) on 4 of the seven days immediately preceding entry into the trial. This corresponds to a mild to moderate patient population.

During the two weeks of treatment, the patient or guardian evaluated the patient's symptoms of nasal obstruction, rhinorrhea, sneezing, nasal itching, and eye symptoms. These were evaluated in the PM, with an additional AM nasal obstruction assessment. These were also evaluated using 100-point analog scales.

At clinic visits the physician rated nasal obstruction, rhinorrhea, sneezing, nasal itching and eye symptoms using 100-point analog scales.

A derived total nasal symptom score was calculated by adding the nasal obstruction, rhinorrhea, sneezing and nasal itching score. This was calculated for both physician assessments and patient diary PM assessments.

Treatment was given as two sprays per nostril in the morning.

The protocol states that the efficacy variables include (1) the physician-rated nasal and ocular symptom scores, (2) the physician's overall evaluation, (3) the patient's self-rating symptom scores and (4) extent of chlorpheniramine use. The protocol further states that the baseline symptom scores are defined as those determined at the end of the run-in phase. The sponsor stated that between treatment group symptom scores would be examined for treatment differences. The Cochran-Mantel-Haenszel test would be used to compare physician's overall evaluations. No justification of sample size was given, therefore, no indication of the primary efficacy variable or method of analysis was specified by the protocol. Except for physician's overall evaluation, no methods of analysis are specified in the protocol.

The sponsor in their study report states that 1) nasal symptom scores assessed by the physician at each study visit and 2) overall clinical evaluation, recorded by the investigator, were considered primary efficacy variables because they were taken in a controlled setting. [The medical division usually gives more weight to patient assessed symptoms. Here, however, since the patients are children (or their guardian) using a unfamiliar analog scale and having undefined assessment intervals, there is more justification for treating physician's evaluations as being more important.]

The sponsor analyzed physician rated symptom scores by three types of analyses. This reviewer will only discuss the analyses

using the Cochran-Mantel-Haenszel test controlling for investigators. Because this analysis was done at each clinic visit, a subjective evaluation must be made as to whether these results demonstrate efficacy.

[The other two tests for physician's assessments are not appropriate from a statistical point of view. One used a repeated measures test which had four time points (Day 1 {Pre-treatment}, Day 8, Day 15, Day 22 {post-treatment}), while the other used area under the curve using values between Day 1 (pre-treatment) and Day 22 (7 days post treatment). Since, in the repeated measures analysis there is a treatment-by-time interaction and some of these time points are not on-treatment, this analysis is clearly not appropriate. The area under the curve analysis equally weighs the 14 on-treatment days to the 7 days after stopping treatment. Clearly that is not appropriate. In fact it should be biased against Flonase. This reviewer also had problems understanding how the sponsor calculated area under the curve. Study FLN-321 which had many more days of treatment had very similar area under the curve treatment means.]

Since the sponsor did not state how multiple comparisons would be handled this reviewer will say a treatment is significant only if $p<0.025$. [This represents a Bonferonni adjustment.] Such a rule is more than reasonable in that there are also multiple endpoints which the sponsor did not prioritize in his protocol. Although using a 0.025 rule is subjective, some rule must be used in order not to indicate too many significant results.

The diary data were grouped over 3 day intervals including a 3 day baseline, with the exception of rescue medication usage, which was grouped over 7 day intervals.

Rescue medication usage was analyzed as the percentage of patients taking rescue medication over the weekly intervals. A Cochran-Mantel-Haenszel test was used stratifying by investigators.

Patient-rated symptoms were analyzed as changes from pretreatment using an analysis of variance F-test according to the Sponsor's Table 17 footnote. No indication is given as to what factors were in the model.

B. Results

There were 250 children (85 placebo, 84 FP 100mcg QD, and 81 FP 200mcg QD) entered into the trial at 10 centers.

The treatment groups were comparable at baseline in demographic variables except for sex and height. Both differences were caused by more males in the FP 100mcg QD group. The treatment groups

were comparable in baseline symptoms, except for patient-rated sneezing.

Only 5 patients (1 placebo and 2 in each FP group) discontinued the trial without completion.

Sponsor's Table 12 (FLN-320) contains the p-values comparing treatments for the physician's assessments at clinic visits. Significant differences favoring both FP doses over placebo ($p<0.025$) were seen in total nasal symptom score at Day 8, for nasal obstruction at Days 8 and 15, and for rhinorrhea at Day 8. Significant differences favoring only the FP 100mcg QD dose over placebo ($p<0.025$) were seen in total nasal symptom at Day 15, and nasal itching at Days 8 and 15. Significant differences ($p<0.025$) favoring only the FP 200mcg QD dose over placebo were seen in nasal obstruction at Day 22.

Sponsor's Table 16 (FLN-320) contains the p-values comparing treatments for the overall clinical evaluations. Both FP doses gave significantly more improvement ($p<0.025$) than placebo.

Sponsor's Table 17 (FLN-320) compares treatments over 3 day intervals for patient rated symptom data. FP 100mcg QD was significantly better ($p<0.025$) than placebo for total nasal symptoms at Days 4-7 and Days 8-10, for nasal obstruction at Days 15-17, for sneezing at Days 4-7, and for AM nasal obstruction at Days 1-3, Days 4-7, Days 8-10, Days 11-14, Days 15-17 and Days 18-21. FP 200mcg QD was significantly better ($P<0.025$) than placebo for nasal obstruction at Days 1-3, Days 4-7, Days 8-11, and Days 15-17, and for AM nasal obstruction at Days 4-7.

No significant differences ($p<0.025$) were seen in rescue medication usage.

C. Reviewer's Comments

Although the sponsor did not provide any analyses by gender in the FLN-320 study report, it is unlikely that the sex difference in the treatment groups would have an effect on efficacy because Flonase efficacy is due to its topical effect.

Since the sponsor did not specify the primary efficacy analyses in the protocol and efficacy of the drug is not overwhelming, efficacy must be judged using a subjective gestalt assessment.

This reviewer thinks that this study has demonstrated efficacy for Flonase in children. Efficacy was seen for both doses in the overall clinical evaluation. This was the only efficacy variable for which the analysis was specified in the protocol. Efficacy was seen for both FP doses in the investigator's evaluation at Day 8 for total nasal system. The sponsor chose a non-parametric

analysis which usually is the less powerful type of analysis. Therefore, this analysis showed efficacy. Efficacy was seen also in patient-rated AM nasal obstruction. This scale was the only variable that is assessing end-of-dosing interval efficacy.

This study is showing numerically more efficacy for the 100mcg QD dose of Flonase than the 200mcg QD dose.

III. Study FLN-321

A. Study Description and Method of Analysis

This study was similar to study FLN-320, with the exception that the treatment period was 4 weeks rather than 2 weeks.

The repeated measures and area under the curve analyses of physician rated symptoms are, again, not considered appropriate. [There were now 6 time points in the repeated measures analyses- only four of which were on-treatment assessments.

The diary data were grouped over 7 day intervals, including a 7 day baseline period.

B. Results

There were 249 children (83 per treatment group) entered into the trial at 10 centers.

The treatment groups were comparable at baseline in demographic variables. The treatment groups were comparable in baseline symptoms.

Only 7 patients (1 placebo and 3 in each FP group) discontinued the trial without completion.

Sponsor's Table 12 (FLN-321) contains the p-values comparing treatments for the physician's assessments at clinic visits. Significant differences favoring both FP doses over placebo ($p<0.025$) were seen in nasal obstruction at Day 22. Significant differences favoring only the FP 100mcg QD dose over placebo ($p<0.025$) were seen in nasal obstruction at Day 15. Significant differences ($p<0.025$) favoring only the FP 200mcg QD dose over placebo were seen in total nasal score at Days 8 and 22, nasal obstruction at Day 8, and eye symptoms at Days 8 and 22.

Sponsor's Table 16 (FLN-321) contains the p-values comparing treatments for the overall clinical evaluations. Both FP doses gave significantly more improvement ($p<0.025$) than placebo.

Sponsor's Table 17 (FLN-321) compares treatments over 7 day

intervals for patient rated symptom data. Significant differences favoring both FP doses over placebo ($p<0.025$) were seen in total nasal score at Days 22-28, in nasal obstruction at Days 15-21, Days 22-28 and Days 29-35. Only FP 200mcg QD was significantly better ($p<0.025$) than placebo for total nasal symptoms at Days 1-7, Days 8-14 and Days 15-21, for nasal obstruction at Days 1-7, Days 8-14, for rhinorrhea at Days 1-7 and Days 22-28, for sneezing at Days 8-14 and Days 15-21, for nasal itch at Days 15-21 and Days 22-28. and for AM nasal obstruction at Days 1-7 and Days 8-14.

Sponsor's Table 18 (FLN-321) compares treatments with respect to use of rescue medication. Significant differences ($p<0.025$) favoring both FP doses over placebo were seen at Days 1-7 and Days 22-28 in the percentage of patients who used such medication. A significant difference ($p<0.025$) favoring only FP 200mcg QD over placebo was seen at Days 15-21.

C. Reviewer's Comments

Since the sponsor did not specify the primary efficacy analyses in the protocol and efficacy of the drug is not overwhelming, efficacy must be judged using a subjective gestalt assessment.

This reviewer thinks that this study has demonstrated efficacy for Flonase in children. Efficacy was seen for both doses in the overall clinical evaluation. This was the only efficacy variable for which the analysis was specified in the protocol. Efficacy was seen for both FP doses in patient-rated nasal obstruction and AM nasal obstruction at Days 15-21, Days 22-28 and Days 29-35 (off-treatment).

This study is showing numerically more efficacy for the 200 mcg QD dose of Flonase than the 100 mcg dose. The 200mcg QD dose of Flonase was significantly different from placebo ($p<0.025$) in all weekly periods for patient-rated total nasal symptom score, nasal obstruction and AM nasal obstruction.

IV. Study FLNT60

A. Study Description and Method of Analysis.

This is a parallel group, double-blind, randomized, international perennial allergic rhinitis trial comparing Flonase 100mcg QD, FP 200mcg QD and placebo in children 4-11 years of age. The treatment period was four-weeks. There was a four-day to two-week run in period.

The primary analysis was based on the analyses of the percentage of symptom-free days during Days 1-28 for symptoms of nasal blockage on waking, nasal blockage during the rest of the day and

rhinorrhoea. The analyses of percentage of symptom-free days was carried out by the Wilcoxon rank sum test, using the van Elteren extension to adjust for center and rhinitis category. Centers were pooled for statistical analyses. All the Danish, Finnish, and Icelandic patients were pooled into one grouping and the Greek, Italian and Spanish patients into another grouping. There were separate groupings of patients in Israel, South Africa and the United Kingdom.

Symptoms were assessed on a four-point scale rather than the 100-point analog scale.

B. Results

Sponsor's Table 34 provides the mean and median percentages of symptom-free days and p-values comparing treatments for the van Elteren analysis. Of the analyses considered primary only rhinorrhoea showed significant differences ($p<0.025$) from placebo for both doses of FP. The FP 200mcg QD dose was also significantly different ($p<0.025$) for overall assessment.

C. Reviewer's Comments

This study is only demonstrating weak evidence of efficacy. Of the three variables considered primary, only rhinorrhoea showed efficacy for percentage of symptom-free days. No efficacy was seen in nasal obstruction which was the assessment showing most efficacy in Studies FLN-320 and FLN-321.

V. Overall Conclusions

The previous statistical review had found both doses of Flonase significantly different from placebo in the treatment of seasonal allergic rhinitis using the 14 highest pollen days in Studies FLN-320 and FLN-321. This analysis used data from only about half of the patients. The present submission did not discuss that analysis.

This reviewer, also, found that Flonase was significantly different from placebo in Studies FLN-320 and FLN-321. This conclusion had to be made from a subjective judgement because the protocols did not specify the method of analysis (except for clinician's overall assessment). Both doses of Flonase were significantly different for clinician's overall assessment in both studies. Significant differences (at the $p<0.025$ level) were seen in nasal blockage and AM nasal blockage in these studies. Numerically, the best dose of Flonase was 100mcg QD in Study FLN-320 and 200mcg QD in Study FLN-321. This makes the proper dose recommendation somewhat problematic.

Flonase only showed weak evidence of efficacy in the perennial

rhinitis Study FLNT60. Only rhinorrhoea showed significant differences of Flonase from placebo for the three stated variables that were to be primary variables in assessing differences in symptom-free days.

James R. Gebert

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

Concur: Dr. Wilson SCW 4/29/97

This review contains 8 pages of text and 20 pages of tables.

cc:
Orig NDA 20-121/SE1-005
HFD-570
HFD-570/Dr. Meyer
HFD-570/Ms. Barnes
HFD-344/Dr. Lisook
HFD-715/Div. File
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson
Chron

Table 12

SYMPTOMS OF RHINITIS: CLINICIAN RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
TOTAL NASAL SYMPTOM SCORE[3]												
Day 1(pre-treatment)	85	234	8.4	84	235	7.9	81	237	7.1	.857	.625	.699
Day 8	84	183	10.6	82	131	9.2	80	130	9.7	<.001	<.001	.756
Day 15	85	148	9.5	84	117	9.1	81	127	9.7	.008	.079	.764
Day 22(post-treatment)	84	167	9.4	82	157	9.7	78	163	9.7	.509	.744	.752
NASAL OBSTRUCTION												
Day 1(pre-treatment)	85	72.9	2.5	84	77.3	2.0	81	77.1	2.1	.310	.322	.846
Day 8	84	57.4	3.0	82	46.3	3.1	80	42.7	3.3	.002	<.001	.250
Day 15	85	56.1	3.1	84	47.3	2.9	81	46.2	3.1	.001	.002	.966
Day 22(post-treatment)	84	61.3	2.9	82	56.7	3.0	78	56.5	3.3	.264	.016	.450

continued

Table 12 (Continued)

SYMPTOMS OF RHINITIS: CLINICIAN RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
RHINORRHEA												
Day 1 (pre-treatment)	85	65.1	3.0	84	63.5	3.2	81	64.9	3.1	.680	.944	.988
Day 8	84	50.7	3.6	82	36.0	3.4	80	35.7	3.6	.014	.010	.717
Day 15	85	42.2	3.7	84	31.8	3.4	81	36.3	3.6	.160	.592	.475
Day 22 (post-treatment)	84	47.6	3.5	82	45.3	3.8	79	45.9	3.8	.687	.886	.970
SNEEZING												
Day 1 (pre-treatment)	85	40.0	3.6	84	34.9	3.6	81	36.5	3.9	.470	.987	.531
Day 8	84	32.6	3.6	82	18.4	2.6	80	17.8	2.9	.054	.047	.799
Day 15	85	17.3	2.7	84	14.5	2.5	81	16.5	2.8	.862	.536	.960
Day 22 (post-treatment)	84	21.2	2.8	82	22.1	3.2	79	22.0	3.1	.219	.325	.644

continued

Table 12 (Continued)

SYMPTOMS OF RHINITIS: CLINICIAN RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
NASAL ITCHING												
Day 1(pre-treatment)	85	56.2	3.4	84	58.9	3.4	81	58.8	3.4	.468	.489	.843
Day 8	84	41.9	3.8	82	30.6	3.4	80	33.5	3.6	.004	.085	.524
Day 15	85	32.9	3.4	84	23.5	3.3	81	28.2	3.3	.011	.096	.532
Day 22(post-treatment)	84	36.7	3.6	82	32.6	3.4	79	39.1	3.9	.503	.802	.412
EYE SYMPTOMS												
Day 1(pre-treatment)	84	39.6	3.2	84	42.1	3.6	81	42.4	3.4	.820	.784	.514
Day 8	84	30.1	3.4	82	26.0	3.2	80	27.0	3.4	.525	.199	.868
Day 15	85	21.7	2.7	84	20.4	3.0	80	24.2	3.0	.648	.803	.718
Day 22(post-treatment)	84	26.0	3.1	82	22.2	2.9	79	29.2	3.5	.617	.895	.440

FP100 QD=Fluticasone propionate aqueous nasal spray 100 mcg once daily
FP200 QD=Fluticasone propionate aqueous nasal spray 200 mcg once daily
[1] Symptom scores are based on visual analogue scale from 0 (absent) to 100 (most severe).
[2] P-values are based on mean scores for Day 1 and on differences from baseline (Day 1) for subsequent days using the van Elteren statistic. P-values are not adjusted for multiple comparisons.
[3] TOTAL NASAL SYMPTOM SCORE = NASAL OBSTRUCTION + RHINORRHEA + SNEEZING + ITCHING.

Supporting data listing in Appendix 7.14, Volume 6, Page 366.
12MAY90

Table 16

OVERALL CLINICAL EVALUATION
Investigator: All Investigators
Frequency[1]

CLINICAL RESPONSE TO THERAPY	PLA-CEBO	FP100 QD	FP200 QD	P-VALUES[2] PLA VS FP100	PLA VS FP200	FP100 VS FP200
Number of patients at Baseline Visit	85	84	81			
Number of evaluable patients	85	84	80			
Significant Improvement	8 (9%)	24 (29%)	17 (21%)	<.001	.002	.564
Moderate Improvement	25 (29%)	24 (29%)	31 (39%)			
Mild Improvement	19 (22%)	20 (24%)	13 (16%)			
No Change	30 (35%)	12 (14%)	17 (21%)			
Mildly Worse	1 (1%)	3 (4%)	1 (1%)			
Moderately Worse	2 (2%)	1 (1%)	1 (1%)			
Significantly Worse	0 (0%)	0 (0%)	0 (0%)			

FP100 QD=Fluticasone propionate aqueous nasal spray 100 mcg once daily
FP200 QD=Fluticasone propionate aqueous nasal spray 200 mcg once daily
[1] Percentages are based on the number of evaluable patients.
[2] P-values based on Cochran-Mantel-Haenszel test for categories scored as: 1=significant improvement; 2=moderate improvement; 3=mild improvement, and 4=no change or mildly worse or moderately worse or significantly worse. P-values are not adjusted for multiple comparisons.
Supporting data listing in Appendix 7.29, Volume 7, Page 430.
06JUN90

Table 17

SYMPTOMS OF RHINITIS: PATIENT RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
TOTAL NASAL SYMPTOM SCORE[3]												
Day -3 - Day 0	85	272	6.6	84	276	5.8	81	262	4.7	.638	.119	.045
Day 1 - Day 3	85	239	8.1	84	222	8.1	81	210	7.4	.066	.106	.874
Day 4 - Day 7	85	221	9.7	84	192	9.0	80	180	9.7	.017	.048	.756
Day 8 - Day 10	84	201	9.8	84	165	10.0	80	157	10.1	.022	.109	.546
Day 11 - Day 14	83	196	11.1	83	155	11.0	80	154	9.9	.027	.193	.402
Day 15 - Day 17	83	203	10.7	82	170	10.8	79	163	9.8	.034	.231	.395
Day 18 - Day 21	83	209	10.5	82	191	10.2	78	189	9.6	.283	.960	.282
NASAL OBSTRUCTION												
Day -3 - Day 0	85	73.3	2.3	84	77.8	1.6	81	76.6	1.4	.100	.092	.920
Day 1 - Day 3	85	65.9	2.5	84	63.5	2.4	81	59.4	2.4	.105	.007	.242
Day 4 - Day 7	85	60.2	2.9	84	56.2	2.7	80	50.1	3.1	.053	.005	.324
Day 8 - Day 10	84	56.3	2.9	84	48.3	3.0	80	44.8	3.0	.029	.011	.648
Day 11 - Day 14	83	54.0	3.0	83	45.6	3.1	80	44.3	3.1	.032	.068	.802
Day 15 - Day 17	83	58.8	2.9	82	50.6	3.0	79	49.2	3.1	.004	.023	.609
Day 18 - Day 21	83	61.4	2.8	82	57.2	2.9	78	55.1	3.0	.085	.169	.775

continued

Table 17 (Continued)

SYMPTOMS OF RHINITIS: PATIENT RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
RHINORRHEA												
Day -3 - Day 0	85	69.4	2.0	84	70.1	2.0	81	66.1	2.0	.867	.092	.129
Day 1 - Day 3	85	60.3	2.5	84	55.6	2.7	81	54.1	2.5	.081	.236	.618
Day 4 - Day 7	85	56.6	2.8	84	47.7	2.7	80	46.5	3.1	.045	.093	.808
Day 8 - Day 10	84	51.0	2.8	84	41.8	3.0	80	39.5	3.1	.104	.322	.569
Day 11 - Day 14	83	49.6	3.2	83	38.8	3.2	80	39.1	2.9	.107	.336	.553
Day 15 - Day 17	83	50.6	3.3	82	44.9	3.2	79	40.3	2.7	.424	.632	.770
Day 18 - Day 21	83	52.1	3.2	82	49.9	3.1	78	47.8	2.9	.878	.656	.557
SNEEZING												
Day -3 - Day 0	85	63.1	2.3	84	60.9	2.4	81	55.2	2.6	.614	.016	.056
Day 1 - Day 3	85	54.9	2.7	84	46.9	2.5	81	42.4	2.5	.285	.465	.762
Day 4 - Day 7	85	52.7	2.7	84	41.0	2.6	80	36.9	2.6	.016	.078	.590
Day 8 - Day 10	84	47.1	2.8	84	35.3	2.7	80	32.0	2.7	.048	.323	.363
Day 11 - Day 14	83	46.6	3.1	83	32.2	2.9	80	31.8	2.6	.048	.377	.305
Day 15 - Day 17	83	45.2	3.1	82	35.7	3.0	79	32.3	2.8	.218	.499	.609
Day 18 - Day 21	83	46.6	3.1	82	40.5	3.0	78	38.7	2.7	.806	.554	.412

continued

Table 17 (Continued)

SYMPTOMS OF RHINITIS: PATIENT RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
NASAL ITCHING												
Day -3 - Day 0	85	66.0	2.5	84	66.8	2.3	81	63.8	2.1	.576	.245	.090
Day 1 - Day 3	85	58.3	2.7	84	56.2	2.7	81	54.2	2.8	.135	.545	.401
Day 4 - Day 7	85	51.1	3.0	84	47.2	2.7	80	46.9	3.1	.097	.774	.193
Day 8 - Day 10	84	46.9	3.1	84	39.7	3.0	80	41.2	3.0	.061	.429	.314
Day 11 - Day 14	83	45.5	3.2	83	37.8	3.2	80	38.4	2.9	.066	.453	.307
Day 15 - Day 17	83	47.8	3.1	82	38.5	3.1	79	40.8	3.0	.027	.554	.124
Day 18 - Day 21	83	49.3	3.2	82	43.4	3.1	78	46.9	3.0	.145	.672	.071
EYE SYMPTOMS												
Day -3 - Day 0	85	49.5	3.0	84	54.1	3.1	81	51.2	2.9	.316	.627	.630
Day 1 - Day 3	85	44.9	3.1	84	44.8	3.0	81	41.5	3.2	.319	.174	.691
Day 4 - Day 7	85	42.3	3.0	84	37.9	2.9	80	40.5	3.4	.077	.599	.244
Day 8 - Day 10	84	37.2	3.1	84	33.9	3.1	80	34.8	3.2	.132	.815	.227
Day 11 - Day 14	83	36.4	3.1	83	32.8	3.3	80	33.0	3.0	.138	.595	.368
Day 15 - Day 17	83	37.7	3.2	82	33.2	3.3	79	32.5	3.2	.132	.451	.484
Day 18 - Day 21	83	37.8	3.2	82	39.3	3.2	78	34.9	3.2	.792	.587	.775

continued

Table 17 (Continued)

SYMPTOMS OF RHINITIS: PATIENT RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
A.M. NASAL OBSTRUCTION												
Day -3 - Day 0	85	76.3	2.2	84	79.8	1.6	81	78.0	1.4	.118	.641	.297
Day 1 - Day 3	85	76.2	2.1	84	73.2	1.8	81	71.8	2.0	.012	.056	.594
Day 4 - Day 7	85	70.2	2.3	84	64.0	2.6	80	61.6	2.4	.005	.006	.925
Day 8 - Day 10	84	65.7	2.4	84	58.0	2.9	80	54.4	2.9	.020	.036	.891
Day 11 - Day 14	83	63.6	2.7	83	53.7	3.0	80	53.2	3.0	.009	.052	.560
Day 15 - Day 17	83	65.9	2.8	82	56.8	3.1	80	55.0	2.9	.002	.042	.349
Day 18 - Day 21	83	69.1	2.4	82	61.7	2.9	78	61.9	2.9	.003	.136	.168

FP100 QD=Fluticasone propionate aqueous nasal spray 100 mcg once daily
FP200 QD=Fluticasone propionate aqueous nasal spray 200 mcg once daily
[1] Symptom scores are based on visual analogue scale from 0 (absent) to 100 (most severe).
[2] P-values are based on mean scores for pretreatment and on differences from pretreatment for subsequent periods using the F-test. P-values are not adjusted for multiple comparisons.
[3] TOTAL NASAL SYMPTOM SCORE = NASAL OBSTRUCTION + RHINORRHEA + SNEEZING + ITCHING.

Supporting data listing in Appendix 7.32, Volume 8, Page 2.
!1MAY90

Table 12

SYMPTOMS OF RHINITIS: CLINICIAN RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
TOTAL NASAL SYMPTOM SCORE[3]												
Day 1(pre-treatment)	83	253	8.6	83	237	8.0	83	242	9.0	.049	.299	.529
Day 8	82	188	8.0	82	146	9.7	82	142	9.4	.092	.016	.344
Day 15	83	161	8.4	80	133	9.0	82	121	8.2	.432	.060	.310
Day 22	83	162	9.2	79	118	9.8	81	109	9.5	.107	.019	.232
Day 29	82	143	10.0	82	110	9.3	83	109	9.2	.575	.162	.294
Day 36(post-treatment)	82	166	10.2	80	154	11.3	80	151	11.5	.970	.561	.637
NASAL OBSTRUCTION												
Day 1(pre-treatment)	83	78.3	2.3	83	77.8	2.2	83	75.8	2.5	.562	.428	.288
Day 8	82	58.7	2.7	82	47.5	3.1	82	45.1	2.8	.035	.023	.538
Day 15	83	52.1	2.9	80	39.2	2.7	82	40.0	2.8	.018	.029	.719
Day 22	83	52.2	2.9	79	34.7	3.1	81	36.2	3.0	<.001	.005	.521
Day 29	82	46.1	3.2	82	35.2	2.8	83	36.3	3.0	.032	.185	.643
Day 36(post-treatment)	82	52.8	3.0	80	48.3	3.2	80	46.2	3.5	.423	.295	.709

continued

Table 12 (Continued)

SYMPTOMS OF RHINITIS: CLINICIAN RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
RHINORRHEA												
Day 1(pre-treatment)	83	65.6	3.2	83	60.8	3.0	83	62.0	3.2	.122	.435	.286
Day 8	82	49.6	3.0	82	37.5	3.3	82	38.1	3.2	.366	.123	.681
Day 15	83	39.5	3.1	80	34.9	3.1	82	35.2	3.0	.984	.717	.802
Day 22	83	43.7	3.1	79	29.5	3.2	81	29.2	3.2	.125	.041	.374
Day 29	82	39.9	3.4	82	27.6	3.1	83	31.5	3.3	.189	.223	.546
Day 36(post-treatment)	82	41.0	2.9	80	40.9	3.3	80	36.8	3.3	.186	.494	.261
SNEEZING												
Day 1(pre-treatment)	83	45.2	3.1	83	39.2	2.8	83	44.2	3.5	.180	.980	.134
Day 8	82	31.9	2.8	82	26.4	2.7	82	23.3	2.7	.918	.517	.374
Day 15	83	29.2	3.0	80	25.1	2.9	82	19.1	2.4	.886	.423	.114
Day 22	83	23.4	2.9	79	22.6	2.5	81	17.0	2.5	.123	.660	.063
Day 29	82	22.9	2.8	82	19.4	2.6	83	17.3	2.5	.604	.387	.076
Day 36(post-treatment)	82	30.7	3.0	80	29.5	3.4	80	27.9	3.2	.404	.514	.171

continued

Table 12 (Continued)

SYMPTOMS OF RHINITIS: CLINICIAN RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
NASAL ITCHING												
Day 1(pre-treatment)	83	63.7	3.0	83	59.0	3.2	83	59.5	3.3	.419	.288	.742
Day 8	82	48.1	3.4	82	34.9	3.3	82	35.7	3.3	.134	.317	.983
Day 15	83	40.6	3.3	80	33.7	3.4	82	26.2	2.7	.916	.141	.229
Day 22	83	42.5	3.3	79	31.0	3.3	81	26.9	3.2	.214	.035	.464
Day 29	82	33.6	3.3	82	28.1	3.1	83	24.3	2.9	.853	.474	.211
Day 36(post-treatment)	82	41.7	3.4	80	35.2	3.3	80	40.3	3.7	.615	.514	.352
EYE SYMPTOMS												
Day 1(pre-treatment)	83	42.0	2.8	83	41.5	3.1	83	44.9	3.1	.762	.729	.369
Day 8	82	35.3	3.3	82	30.0	3.3	82	28.4	3.0	.493	.023	.130
Day 15	83	29.8	3.3	80	25.8	3.1	82	23.7	2.9	.397	.058	.219
Day 22	83	30.5	3.2	79	23.9	3.2	81	21.4	2.9	.207	.017	.401
Day 29	82	24.9	2.8	82	23.0	2.8	83	22.2	2.9	.839	.067	.160
Day 36(post-treatment)	82	33.1	3.3	80	26.2	3.0	80	27.3	3.4	.335	.158	.685

FP100 QD=Fluticasone propionate aqueous nasal spray 100 mcg once daily
FP200 QD=Fluticasone propionate aqueous nasal spray 200 mcg once daily
[1] Symptom scores are based on visual analogue scale from 0 (absent) to 100 (most severe).
[2] P-values are based on mean scores for Day 1 and on differences from baseline (Day 1) for subsequent days using the van Elteren statistic. P-values are not adjusted for multiple comparisons.
[3] TOTAL NASAL SYMPTOM SCORE = NASAL OBSTRUCTION + RHINORRHEA + SNEEZING + ITCHING.
Supporting data listing in Appendix 7.14, Volume 11, Page 145.
06JUN90

Table 16

OVERALL CLINICAL EVALUATION
Investigator: All Investigators
Frequency[1]

CLINICAL RESPONSE TO THERAPY	PLA-CEBO	FP100 QD	FP200 QD	P-VALUES[2] PLA VS FP100	PLA VS FP200	FP100 VS FP200
Number of patients at Baseline Visit	83	83	83			
Number of evaluable patients	82	80	81	.001	<.001	.267
Significant Improvement	9 (11%)	23 (29%)	28 (35%)			
Moderate Improvement	17 (21%)	21 (26%)	21 (26%)			
Mild Improvement	26 (32%)	18 (23%)	18 (22%)			
No Change	26 (32%)	16 (20%)	12 (15%)			
Mildly Worse	3 (4%)	2 (3%)	1 (1%)			
Moderately Worse	1 (1%)	0 (0%)	1 (1%)			
Significantly Worse	0 (0%)	0 (0%)	0 (0%)			

FP100 QD=Fluticasone propionate aqueous nasal spray 100 mcg once daily
FP200 QD=Fluticasone propionate aqueous nasal spray 200 mcg once daily
[1] Percentages are based on the number of evaluable patients.
[2] P-values based on Cochran-Mantel-Haenszel test for categories scored as: 1=significant improvement; 2=moderate improvement; 3=mild improvement, and 4=no change or mildly worse or moderately worse or significantly worse. P-values are not adjusted for multiple comparisons.
Supporting data listing in Appendix 7.29, Volume 12, Page 363.
31JUL90

Table 17

SYMPTOMS OF RHINITIS: PATIENT RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
TOTAL NASAL SYMPTOM SCORE[3]												
Day -6 - Day 0	83	277	5.2	83	261	5.0	83	273	5.6	.253	.496	.624
Day 1 - Day 7	83	237	8.4	82	204	7.9	83	199	8.9	.148	.008	.255
Day 8 - Day 14	83	194	10.1	82	164	9.2	82	145	10.0	.323	.005	.081
Day 15 - Day 21	83	184	10.4	80	147	9.8	82	134	10.7	.070	.003	.280
Day 22 - Day 28	83	175	11.2	80	131	9.0	82	118	10.9	.024	<.001	.280
Day 29 - Day 35	82	180	10.8	80	153	10.7	80	146	10.9	.152	.030	.503
NASAL OBSTRUCTION												
Day -6 - Day 0	83	78.3	1.6	83	74.9	1.7	83	80.3	1.7	.574	.383	.161
Day 1 - Day 7	83	65.3	2.2	82	58.1	2.2	83	57.2	2.6	.198	.002	.079
Day 8 - Day 14	83	54.3	2.8	82	45.8	2.6	82	42.3	3.0	.083	<.001	.097
Day 15 - Day 21	83	53.5	2.8	80	40.8	2.7	82	41.1	3.2	.003	<.001	.670
Day 22 - Day 28	83	52.2	3.1	80	36.2	2.7	82	36.0	3.1	<.001	<.001	.648
Day 29 - Day 35	82	53.6	2.9	80	42.2	2.9	80	42.7	3.1	.002	<.001	.771

continued

Table 17 (Continued)

SYMPTOMS OF RHINITIS: PATIENT RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
RHINORRHEA												
Day -6 - Day 0	83	69.9	2.1	83	67.8	2.0	83	67.9	1.9	.924	.417	.380
Day 1 - Day 7	83	60.4	2.4	82	51.7	2.5	83	48.9	2.6	.058	.018	.701
Day 8 - Day 14	83	48.8	2.9	82	41.3	2.6	82	37.3	2.8	.214	.061	.570
Day 15 - Day 21	83	46.3	3.0	80	38.3	2.8	82	34.0	3.1	.063	.036	.875
Day 22 - Day 28	83	44.5	3.1	80	35.3	2.6	82	28.7	3.0	.035	.004	.487
Day 29 - Day 35	82	44.8	3.2	80	40.7	3.0	80	35.1	2.9	.302	.089	.539
SNEEZING												
Day -6 - Day 0	83	61.4	2.1	83	55.9	2.2	83	58.8	2.2	.175	.209	.884
Day 1 - Day 7	83	55.1	2.7	82	44.7	2.5	83	43.2	2.5	.300	.032	.299
Day 8 - Day 14	83	45.1	2.9	82	36.2	2.5	82	30.5	2.6	.674	.014	.052
Day 15 - Day 21	83	41.6	2.8	80	32.5	2.7	82	27.4	2.7	.545	.016	.088
Day 22 - Day 28	83	36.8	2.9	80	28.6	2.3	82	24.7	2.6	.403	.047	.282
Day 29 - Day 35	82	39.6	2.9	80	33.4	2.9	80	30.5	2.6	.739	.181	.337

continued

Table 17 (Continued)

SYMPTOMS OF RHINITIS: PATIENT RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
NASAL ITCHING												
Day -6 - Day 0	83	67.6	2.2	83	62.7	2.2	83	66.5	2.3	.301	.758	.460
Day 1 - Day 7	83	56.3	2.7	82	49.5	2.5	83	50.0	2.9	.588	.204	.494
Day 8 - Day 14	83	45.5	3.0	82	40.1	2.8	82	35.0	3.1	.964	.054	.057
Day 15 - Day 21	83	43.0	3.0	80	35.4	2.9	82	31.5	3.0	.440	.015	.117
Day 22 - Day 28	83	41.1	3.2	80	30.8	2.6	82	28.2	3.1	.245	.004	.112
Day 29 - Day 35	82	41.9	3.2	80	36.2	3.0	80	37.4	3.4	.607	.318	.651
EYE SYMPTOMS												
Day -6 - Day 0	83	57.1	2.8	82	50.7	2.8	83	52.6	3.2	.143	.241	.731
Day 1 - Day 7	83	48.4	2.9	82	42.7	2.8	83	39.7	3.0	.626	.369	.178
Day 8 - Day 14	83	38.1	3.1	82	34.7	2.9	82	30.3	2.9	.413	.578	.177
Day 15 - Day 21	83	34.7	3.1	80	31.1	3.0	82	25.3	2.8	.545	.478	.201
Day 22 - Day 28	83	30.9	2.9	80	28.7	2.9	82	20.7	2.9	.503	.253	.079
Day 29 - Day 35	82	31.4	3.0	80	31.2	2.9	80	26.2	3.2	.373	.882	.300

continued

Table 17 (Continued)

SYMPTOMS OF RHINITIS: PATIENT RATED[1]
Investigator: All Investigators

	PLACEBO			FP100 QD			FP200 QD			P-VALUES[2]		
	N	MEAN	SE	N	MEAN	SE	N	MEAN	SE	PLA VS FP100	PLA VS FP200	FP100 VS FP200
A.M. NASAL OBSTRUCTION												
Day -6 - Day 0	83	76.7	1.7	83	75.2	1.7	83	78.9	1.7	.941	.239	.226
Day 1 - Day 7	83	73.9	2.0	82	66.5	2.2	83	68.1	2.1	.068	.002	.227
Day 8 - Day 14	83	65.5	2.5	82	55.8	2.6	82	52.1	2.9	.039	<.001	.045
Day 15 - Day 21	83	62.0	2.7	80	49.7	2.9	82	50.0	3.1	.005	<.001	.406
Day 22 - Day 28	83	58.2	2.9	80	46.9	2.9	82	43.8	3.3	.020	<.001	.127
Day 29 - Day 35	82	59.6	2.8	80	49.2	2.9	80	46.5	3.0	.011	<.001	.108

FP100 QD=Fluticasone propionate aqueous nasal spray 100 mcg once daily
FP200 QD=Fluticasone propionate aqueous nasal spray 200 mcg once daily
[1] Symptom scores are based on visual analogue scale from 0 (absent) to 100 (most severe).
[2] P-values are based on mean scores for pretreatment and on differences from pretreatment for subsequent periods using the F-test. P-values are not adjusted for multiple comparisons.
[3] TOTAL NASAL SYMPTOM SCORE = NASAL OBSTRUCTION + RHINORRHEA + SNEEZING + ITCHING.

Supporting data listing in Appendix 7.32, Volume 12, Page 396.
13JUN90

Table 18

USE OF RESCUE MEDICATION
Investigator: All Investigators
Summary Statistics

	PLACEBO MEAN n/N	(%) [1]	FP100 QD MEAN n/N	(%)	FP200 QD MEAN n/N	(%)	P-VALUES [2] PLA VS FP100	PLA VS FP200	FP100 VS FP200
Day -6-0 (run-in)	4.0 53/83	(64%)	3.2 45/83	(54%)	3.1 42/83	(51%)	.172	.094	.603
Day 1-7	3.0 45/83	(54%)	1.5 27/82	(33%)	1.5 28/83	(34%)	.007	.010	.918
Day 8-14	2.0 30/83	(36%)	1.7 29/82	(35%)	1.0 20/82	(24%)	.893	.096	.087
Day 15-21	2.9 37/83	(45%)	1.2 24/80	(30%)	1.2 21/82	(26%)	.047	.007	.546
Day 22-28	2.3 34/83	(41%)	1.1 19/80	(24%)	1.2 19/82	(23%)	.017	.011	.852
Day 29-35 (post-trt.)	2.8 31/82	(38%)	1.8 26/80	(33%)	1.7 23/80	(29%)	.394	.189	.666

FP100 QD=Fluticasone propionate aqueous nasal spray 100 mcg once daily
FP200 QD=Fluticasone propionate aqueous nasal spray 200 mcg once daily
[1] MEAN=mean number of chlorpheniramine maleate doses taken per seven day period.
n=number of patients using chlorpheniramine maleate at least once.
One dose equals 1 mg (2.5 ml syrup) for patients 4 or 5 years of age.
One dose equals 2 mg (5 ml syrup or one-half 4 mg tablet) for patients 6-11 years of age.
N=number of patients, (%) = n/N times 100%.
[2] P-values are based on n/N using the Cochran-Mantel-Haenszel test, adjusting for investigators.
P-values are not adjusted for multiple comparisons.

Supporting data listing in Appendix 7.32, Volume 12, Page 396.
07SEP90

3 pages
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20121/S005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 26 1997

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20,121

FLONASE® (FLUTICASONE PROPIONATE) NASAL SPRAY 0.05%

GLAXOWELLCOME
FIVE MOORE DRIVE
RESEARCH TRIANGLE PARK, NC 27709

SUBMISSION DATE:
31 OCTOBER 1996

REVIEWER:
DALE P. CONNER, PHARM.D.

TYPE OF SUBMISSION: SUPPLEMENTAL NDA

Background

Fluticasone propionate (S-fluoromethyl 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate) is an anti-inflammatory corticosteroid, approved as a metered-dose inhaler for the treatment of asthma (NDA 20-548) and as a nasal spray for the treatment of symptoms of seasonal and perennial allergic rhinitis (NDA 20-121). The molecular weight is 500.6. It is nearly insoluble in water, slightly soluble in methanol and 95% ethanol, and freely soluble in DMSO and dimethylformamide. Oral bioavailability of the corticosteroid fluticasone propionate is very low, probably due to presystemic metabolism by CYP3A4 in the gut and liver. The Rotadisk® via Diskhaler® dry powder formulation of fluticasone propionate is currently under review for the maintenance treatment of asthma in adults (NDA 20-549) and adolescents (NDA 20-770).

This NDA was submitted to extend the recommended age range for the fluticasone propionate nasal spray to the pediatric population (ages 4 to 11 years) at doses of 100 µg and 200 µg once daily.

Summary

This NDA does not contain any new pharmacokinetic studies with the fluticasone propionate nasal spray. This NDA contains one new pharmacokinetic study in the pediatric age group. The study was also included in NDA 20-770 and reviewed for that submission. This study was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study in patients aged 4 to 11 years with chronic, non-seasonal, mild to moderate, stable asthma. Two doses of fluticasone propionate (50 µg and 100 µg BID) inhalation powder formulation and a placebo were studied. A subset of patients (n=16 low dose and n=13 high dose) had measurements for plasma fluticasone propionate performed at 20 and 40 minutes after dosing at one study visit. Most of the plasma concentrations from the 50 µg dose group were below the level of quantitation (BLQ) of the assay. The mean of the maximum plasma concentrations from the 100 µg treatment group was 58.7 pg/mL. This was slightly higher than the maximum plasma concentrations from 100 µg of fluticasone propionate given to

adult patients in Study FLD 230. This difference, based on a cross-study comparison of small numbers of patients, is probably not clinically significant.

Recommendation

Although this supplemental NDA contains no new data in the pediatric age group (4-11 years) using the nasal spray, this NDA is approvable from a Clinical Pharmacology perspective. The systemic exposure in adults from the nasal spray is much smaller than the inhalation dosage forms and comparable exposures can be expected in the proposed pediatric patient population.

Dale P. Conner 6/26/97
Dale P. Conner, Pharm.D.
Team Leader
Div. of Pharmaceutical Evaluation II

for
Mei-Ling Chen, Ph.D. 6/26/97
Division Director

cc:
HFD-570 (NDA 20,770, Division File, Barnes, Meyer)
HFD-870 (MChen, Conner)
HFD-850 (Lesko)
HFD-340 (Viswanthan)
CDR (Barbara Murphy)

APPENDIX

TITLE: A randomized, double-blind, parallel-group, comparative trial assessing the long term safety of inhaled fluticasone propionate Rotadisks® Via Diskhaler® 50mcg BID and 100mcg BID versus placebo in patients aged 4 to 11 years with mild to moderate chronic asthma (FLD-220)

OBJECTIVES

To compare the long term safety and pharmacoeconomic outcomes of fluticasone propionate (FP) 50mcg BID, 100mcg BID and placebo BID.

STUDY DESIGN

This was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study in male (n=244) and female (n=81) patients aged 4 to 11 years with chronic, non-seasonal, mild to moderate, stable asthma. A subset of patients (n=16 low dose and n=13 high dose) had measurements for plasma fluticasone propionate performed at 20 and 40 minutes after dosing at one study visit. Following a two week placebo (in addition to their normal asthma medications) lead-in period, patients were randomly assigned to one of three treatments for a 52 week treatment period. Treatments were:

Treatment A: Fluticasone propionate 50mcg BID from the Rotadisk® via Diskus® dry powder inhaler

Treatment B: Fluticasone propionate 100mcg BID from the Rotadisk® via Diskus® dry powder inhaler

Treatment C: Placebo BID from the Rotadisk® via Diskus®

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The sampling scheme and low plasma concentrations resulting from normal doses of fluticasone propionate do not allow calculation of pharmacokinetic parameters.

RESULTS

Plasma concentrations were very low at the 50 µg BID dose. Eight of 16 patients had plasma concentrations below the level of quantitation (BLQ) of the assay (25 µg/mL) at both timepoints sampled. At 100 µg BID, most patients had plasma concentrations above the lower limit of the assay.

Table 1. Median (range) maximum plasma concentrations of fluticasone propionate in pediatric patients

	50 µg BID	100 µg BID	Adult 100 µg BID*
n	16	13	8
Age (y)	8 (4-11)	8 (6-10)	31 (23-56)
C_{max} (pg/mL)	BLQ	58.7	39.5

* *Study FLD-230 after 1 week*

COMMENTS

The sampling strategy of this study does not give an accurate estimate of C_{max}. At best, the plasma concentrations at these timepoints can be compared across studies with adult data. The maximum (measured) concentrations in children appear slightly higher than those in adults. This difference is probably not clinically significant.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20121/S005

ADMINISTRATIVE DOCUMENTS

I. PATENT INFORMATION

Amendment to Patent Information for FLONASE® NASAL SPRAY NDA 20-121

The following submission of patent term expiration information is made subsequent to the decisions rendered by the United States District Court, Eastern District of Virginia (*Merck & Co. v. Kessler*, 903 F. Supp. 964, 38 U.S.P.Q.2d (BNA) 1727, 1995) and the United States Court of Appeals for the Federal Circuit (*Merck & Co. v. Kessler*, 80 F.3d 1543, 38 U.S.P.Q.2d (BNA) 1347, 1996).

By action of the Uruguay Round Agreements Act, Public Law 103-465, signed by the President on 8 December, 1994, the expiration date of United States Patent, 4,335,121, is 13 February, 2001.

The undersigned attests the above-listed patent was in force 8 June, 1995 without the benefit of any patent extension derived under 35 USC § 156.

Beyond the 13 February, 2001 date, Applicant has obtained a 1004-day extension under the Hatch-Waxman Amendments (35 USC § 156) bringing the expiration date of United States Patent, 4,335,121, to 14 November, 2003. This is less than the 14-year cap of the Hatch-Waxman Amendments.

The undersigned further attests that the above-listed patent covers the formulation, composition, or method of use of FLONASE® NASAL SPRAY. A new drug Application for this product has been approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

Date: 26 July, 1996

Charles E. Dadswell
Attorney for Applicant
Registered Patent Attorney
Registration No. 35,851

II. MARKETING EXCLUSIVITY

NDA 20-121

Flonase® (fluticasone propionate) Nasal Spray 0.05% w/w

Request for Marketing Exclusivity

Pursuant to Section 505(c)(3)(D)(iv) and 505(j)(4)(D)(iv) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.108(b)(4), Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval of Flonase (fluticasone propionate) Nasal Spray, 0.05% w/w for the management of seasonal and perennial allergic rhinitis in children 4 to 11 years of age.

We hereby certify as to the following:

Section 7, Item VI.C. of this application contains a list of published studies or publicly available reports of clinical investigations known to Glaxo Wellcome through a literature search that are relevant to the use of Flonase Nasal Spray in children 4 to 11 years of age for the management of seasonal and perennial allergic rhinitis. Literature searches reveal no publications which in our opinion provide sufficient basis for the approval of this application.

Thus, Glaxo Wellcome Inc. is entitled to exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and sponsored by Glaxo Wellcome Inc. The following investigation is "essential to the approval of the application" in that there are no other data available that could support FDA approval of the application.

UCR/95/024 A Randomized, Double-Blind, Parallel-Group Comparative Trial Assessing the Long Term Safety of Inhaled Fluticasone Propionate Rotadisk via Diskhaler 50mcg BID and 100mcg BID versus Placebo in Patients Aged 4 to 11 Years with Mild to Moderate Chronic Asthma (FLD-220).

This clinical investigation is defined as "new" because it has not been relied on by the FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication, or of safety for a new patient population, and does not duplicate the results of another investigation that was relied on by FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug application. In this regard, it is noted that data from studies FLN-320, FLN-321, GRP/91/050, GRP/92/008, and GRP/92/009 were previously filed to NDA 20-121 but to the best of our knowledge, were not relied upon by FDA for approval of that NDA.

Each of these investigations was "conducted or sponsored by Glaxo Wellcome" in that Glaxo Wellcome Inc. was the sponsor of the investigational new drug applications (IND) under which UCR/95/024, FLN-320, and FLN-321 were conducted and sponsored the conduct of GRP/91/050, GRP/92/008, and GRP/92/009 outside the United States.

Alison Bowers
Project Director, Regulatory Affairs

III. DEBARMENT CERTIFICATION

In accordance with the certification provision of the Generic Drug Enforcement Act of 1992 as outlined in correspondence dated July 29, 1992, from Daniel L. Michels, Office of Compliance, Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.