CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:	**20121/S005**
Trade Name:	**Flonase**
Generic Name:	**Fluticsone propionate**
Sponsor:	**Glaxo Wellcome Inc.**
Approval Date:	**October 31, 1997**
Indication:	**Management of nasal symptoms of seasonal and perennial allergic rhinitis in patients 4 to 11 years of age**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20121/S005

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20121/S005

APPROVAL LETTER

NDA 20-121/S-005

OCT 31 1997

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Alison Bowers
Project Director, Regulatory Affairs

Dear Ms. Bowers:

Please refer to your supplemental new drug application dated October 31, 1996, received November 1, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flonase (fluticasone propionate) Nasal Spray, 50 mcg.

We acknowledge receipt of your submissions dated February 24, July 23, August 28, October 6, 27, 28, 29, and 30, 1997. The user fee goal date for this application is November 1, 1997.

The supplemental application, as amended and indicated in the enclosed marked-up draft labeling, provides for the use of Flonase Nasal Spray in pediatric patients 4 to 11 years of age for the management of the nasal symptoms of seasonal and perennial allergic rhinitis.

We have completed the review of this supplemental application including the draft labeling submitted on October 29, 1997, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. These revisions were discussed in a telephone conversation between you and Sandy Barnes of this division on October 31, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling(FPL) must be identical to the enclosed marked-up draft labeling. Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

For administrative purposes, this submission should be designated "FPL for approved supplemental NDA 20-121/S-005." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated October 27, 1997. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports related to these Phase 4 commitments should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include a status summary of each commitment in your annual report to this application. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued

to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Sandy Barnes, Project Manager, at (301) 827-1075.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-121/S-005
HFD-570/Div. files
HFD-570/CSO/S.Barnes
HFD-570/Meyer
HFD-570/Gebert
HFD-570/Conner
HFD-570/Sancilio
HFD-570/Rogers
HFD-101/L.Carter
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80/ (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)

Drafted by: SBarnes/October 28, 1997/N:\Staff\barness\n20121s5.ap
Initialed by:C. Schumaker 10/28/97
Revised: S. Barnes 10/31/97
Initials by: L. Sancilio 10/31/97
G. Poochikian 10/31/97
C. J. Sun 10/31/97
D. Conner 10/31/97
J. Gebert 10/31/97
R. Meyer 10/31/97
final:

APPROVAL (AP) [with Phase 4 Commitments]

10/31/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20121/S005

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	20-121 SE1-005	APPLICATION TYPE:	Efficacy Supplement
SPONSOR:	Glaxo Wellcome	PRODUCT/PROPRIETARY NAME:	Flonase
		USAN / Established Name:	fluticasone dipropionate
CATEGORY OF DRUG:	Nasal corticosteroid	ROUTE OF ADMINISTRATION:	intranasal
MEDICAL REVIEWER:	Robert J. Meyer, MD	REVIEW DATE:	4/16/97

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
10-31-96	11-1-96	Efficacy Supplement	Original submission
12-16-96	12-17-96	Response to IR	Missing data listings
2-24-97	2-25-97	120 Safety Update	one volume amendment

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review:
This is the pediatric supplement for Flonase. Much of these data were originally submitted with the NDA, but this indication was not granted based on inadequate safety data/duration of exposure and lack of convincing data for perennial allergic rhinitis. This current application includes a one-year safety study from the Flovent Rotadisk product which Glaxo claims to be much more bioavailable than Flonase. It also includes some clinical trials with Flonase of longer duration.

Outstanding Issues:

Recommended Regulatory Action: | **N drive location:** \NDA\20121\SE5

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed-

NDAs:

Efficacy / Label Supp.: __X__ Approvable _____ Not Approvable

Signed: **Medical Reviewer:** _____ **Date:** 4/16/97

Medical Team Leader: _____ **Date:** 4/17/97

2.0 TABLE OF CONTENTS

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3.0 MATERIAL REVIEWED / BACKGROUND

3.1 Material Reviewed

The material reviewed as the basis for this Medical Officer's review on sNDA 20 SE2-026 includes:

1. sNDA 20-121 medical officer's copy submitted to FDA on 11-1-96.
2. FDA medical officer's review of Flonase NDA 20-121 from 1994 (Dr. Scheinbaum of HFD-007)

3.2 General Overview:

Flonase (fluticasone propionate) Nasal Spray 0.05% was approved by the Division of Pilot Drugs (HFD-007) on October 19, 1994 for the treatment of seasonal and perennial allergic rhinitis in patients aged 12 and above. In reviewing the NDA itself, the clinical team from Pilot Drugs felt that Flonase was approvable for the treatment of SAR in children at a dose of 100 mcg per day, but did not approve it for treatment of children below the age of 12 because of concerns over safety (primarily lack of medium to long term systemic safety) and over longer term efficacy, primarily in PAR. The requirements for data necessary to support a new pediatric indication for an agent approved in adults was modified by the publication of the Pediatric Rule in Dec. 1994. As it is not generally felt that SAR or PAR are substantially different in children versus adults, nor is it felt Flonase (or any intranasal corticosteroid) would have a substantially different therapeutic action in children versus adults, the main data that the sponsor would need to provide to gain approval for the pediatric use approved in adolescents and adults would be assurance that: 1) an appropriate therapeutic dose is identified, 2) that local toxicity is demonstrated as comparable to that shown in adolescents / adults in the short-term, and 3) that the systemic effects are acceptable, given the benefit expected. Following communication with DPDP (during the review of Flonase, the responsibility for nasal corticosteroids was transferred to DPDP, although Pilot Drugs finished the Flonase review and its launch prior to transfer of this NDA) by the sponsor - Glaxo Wellcome, the Division agreed with the sponsor that given the known low bioavailability of Flonase administered intranasally (<2% claimed) and the higher bioavailability of Flovent Rotadisk DPI (9 - 11% claimed), that the growth and HPA safety study being performed in children with the Rotadisk at comparable nominal daily doses of fluticasone (100 - 200 mcg per day) could support the systemic safety of Flonase.

II. Proposed Indication(s)[1]

Glaxo claims that Flonase Nasal Spray is indicated: "for the management of seasonal *and* perennial allergic rhinitis in adults and pediatric patients

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1 **(vol 1.001, page 20) of SE1-005**

4 years of age and older. Safety and effectiveness of Flonase Nasal Spray in children below 4 years of age have not been adequately established."

At the present time, we do not have evidence that a significant use of intranasal corticosteroids occurs below age 4 and the statement from the sponsor about lack of evidence to adequately address safety and efficacy in children younger than 4 is accurate, since only limited data from 3 years olds is contained in this supplement.

Proposed Dosage[2]

Proposed starting doses differ for children compared to the currently recommended starting dosing in adults (200 mcg QD). For children and adolescents, the proposed starting dose is 1 spray in each nostril once a day (100 mcg QD) OR with more severe symptoms - 200 mcg QD. Depending upon the patient's response, it is recommended to taper such patients back to 100 mcg QD if started at 200 mcg.

III. Formulation

There are no differences proposed for the formulation for this indication compared with that of the approved formulation.

Foreign Marketing History[3]

Fluticasone propionate aqueous Nasal Spray is approved for the treatment of SAR in pediatric patients in 44 countries, with applications pending in 24 more. The earliest approval was in El Salvador and Hong Kong. Fluticasone propionate aqueous Nasal Spray is approved for the treatment of PAR in pediatric patients in 27 countries, with applications pending in 40 more. There have been no withdrawals of approval in foreign markets for Flonase (a.k.a. - Flixonase in other parts of the word) for any reason.

Comments on the changes in the proposed label are contained in section 11.0 of this review.

4.0 CHEMISTRY / MANUFACTURING CONTROLS

Formulation

The formulation used in the US clinical trials is the marketed formulation of Flonase, with the placebo nasal spray having identical contents of excipients, but no active drug substance. Some of the non-US studies utilized formulations that were clearly different than the one currently marketed in the US. This largely was done by varying the concentration of fluticasone in its vehicle. However, since the relative proportion of excipients to substance could alter the clinical response in terms of safety and efficacy, these situations are noted in the relevant study reviews.

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2 (vol 1.001, page 25 - proposed labeling) of SE1-005

3 (vol. 1.001, pages 48) of SE1-005

5.0 PRECLINICAL PHARMACOLOGY / TOXICOLOGY

Although a review of the completeness of the pharm./tox. data needs to be conducted, there are likely few outstanding issues, since this is a currently approved drug and the pediatric indication is limited to children 4 years old or more.

7.0 CONDUCT OF THE REVIEW

This medical officer review was conducted in the following manner:

a) 45 day review - The issues relevant to filability were reviewed, particularly the structure of the submission, an overview of content and identification of relevant issues for the full NDA review. The 45 day review document by this medical officer was previously submitted to the NDA file on 12-16-96.

b) A full review of the pivotal studies was carried out first of the submitted SAR trials (FLN-320, 321 and FLNT52), and then the PAR trials. A review limited to the relevant portions of study FLD-220 was then conducted. This review focused on the systemic safety aspects of this year long study of the Flovent (inhaled fluticasone) DPI.

c) A review of the ISE was conducted, focusing on the sponsor's claims for their efficacy studies and how these studies related to the indications sought and the Pediatric Rule.

d) A review of the ISS was conducted last, focusing on any changes in the labeling which would need to occur due to information derived from these studies, or relevant post-marketing reports.

d) An audit of the data was performed by the reviewing medical officer using the CRFs included in the sNDA from patients withdrawing for adverse events. These checks by the reviewer did not lead to any defined problems indicating a problem with the integrity of the data.

Abbreviations used: FP - fluticasone propionate; FP100 - 100 mcg of fluticasone/day (unless otherwise noted); FP200 - 200 mcg FP/day; TNSS - total nasal symptom score; NSS - nasal symptom score; SAR - seasonal allergic rhinitis; PAR - perennial allergic rhinitis; PNAR - perennial non-allergic rhinitis; BDP - beclomethason dipropionate; AE - adverse event; DPI - dry powder inhaler (specifically the FP Rotadisk for Diskhaler).

8.0 CLINICAL STUDIES SUPPORTING THE PEDIATRIC ALLERGIC RHINITIS INDICATION FOR FLONASE

8.1 STUDY FLN-320[4]

"A Double-blind, Randomized, Placebo-controlled Study of the Efficacy and Safety of Aqueous Fluticasone Propionate Given Once Daily Versus Placebo for Two weeks in Pediatric Patients with Seasonal Allergic

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[4] vol. 1.005

Rhinitis." [sponsor title]

8.1.1 **Objectives/Rational**

To compare the efficacy and safety FP 100 µg QD and 200 µg QD versus placebo in the treatment of seasonal allergic rhinitis in children ages 4-11 over a 14 day treatment period.

8.1.2 **Design**

Ten center, randomized, double-blind, placebo-controlled, parallel group study of 2 weeks duration.

8.1.3 Summary of the Study Protocol (no amendments given)

8.1.3.1 Population

Inclusions: Male or female (premenarchal or surgically sterile) patients, 4 - 11 years, with at least a 1/3 of subjects ages 4 - 8, who have seasonal allergic rhinitis as defined by 3 criteria:

1 - appearance of nasal mucosa consistent with rhinitis.

2 - presence of a positive skin test reaction to one or more allergens known to be relevant to the August-October season in the geographical region of the study. An acceptable response was a wheal diameter of 3 mm or > using a 1:20 diluent prick test or 1:1000 aqueous extract for intradermal testing.

3 - historical support for the seasonal characteristic of the disease based on a supportive history of the chronological onset and offset of symptoms.

Each subject was to have been sufficiently symptomatic by scoring at least 200 out of 400 in a visual analogue scale for daily nasal symptoms on at least 4 of the 7 days immediately preceding randomization. Subjects also were to need treatment with an intranasal steroid as defined by prior use in other seasons and/or documented history of an unsatisfactory response to other conventional treatments for allergic rhinitis.

Exclusions: Physical nasal obstruction, serious concomitant diseases, no concomitant infections of the respiratory/nasal tract including candida, ability to attend the clinic, consent, and no history of hypersensitivity to steroids or other components of Flonase. Patients could not have received CS in the prior 30 days before the screening visit, and could not be receiving any other concomitant steroids except medium to low potency dermal products. No exposure to intranasal cromolyn was allowed in the prior 2 weeks. Patients could be on immunotherapy, but

only at a steady dose.

8.1.3. Treatment Arms

Fluticasone 100 µg/day -	**2 sprays of 25 µg in each nostril QD**
Fluticasone 200 µg/day -	**2 sprays of 50 µg in each nostril QD**
Fluticasone 0 µg/day -	**2 sprays of 0 µg/vehicle in each nostril QD**

8.1.3.3 Assignment to Treatment

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

8.1.3.4 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.

8.1.3.5 Dosing

The study drug was administered via the standard Flonase metered spray device once daily by patients or parents/guardians (in an unspecified time frame other than 'morning').

8.1.3.6 Study sequence

Screening visit followed by

- 4 - 14 day run-in period with diary keeping, and open-label chlorpheniramine rescue; followed by
- 2 week treatment period (visits 1-3).

To enter into the treatment period, patients must have displayed sufficient symptoms as defined above in eligibility criteria.

8.1.3.7 Assessments

Screening visit - History (including SAR symptom assessment), physical (including nasopharyngeal exam), skin testing, laboratories (including a.m. cortisol).

Run-in period - Daily recording of SAR symptoms by the patients or caretaker surrogate using a visual analogue scale and rating nasal symptoms (sneezing, rhinorrhea, congestion, itching), ocular symptoms, and daily rescue medication use. Nasal blockage was scored in the a.m., other parameters were recorded at bedtime.

Randomization visit (visit 1) - Diary cards reviewed, nasal exam and symptom assessment, and adverse event assessment.

Double Blind period - Patients were scheduled to return on study days 8, and 15 for visits 2 and 3.

At visit 2, diary cards were collected and reviewed. Nasal examinations and symptoms assessments were performed and adverse event

assessment was carried out. At visit 3, additionally, there was a physical exam performed along with clinical laboratory testing including a.m. serum cortisol determinations.

A post-treatment visit was conducted at day 22, with review of final diary cards, chlorpheniramine use, examination, and laboratory testing as need for abnormalities at visit 5. This visit included a final clinician rating of symptoms. Subjects would only receive on-going assessments thereafter for persistent abnormalities of labs or exam.

8.1.3.8 Concurrent Medications Exclusions: Absolute restrictions on inhaled or systemic corticosteroids. Other antiasthmatics were allowed and recorded on the CRF. No other nasal/allergic medication was allowed except for rescue chlorpheniramine (syrup or tablets), the use of which was to be recorded in the patient daily diary.

8.1.3.9 Endpoints

Efficacy parameters:

Efficacy variables included the assessment of physician rated nasal and ocular symptoms, physician global scoring, patient's rated symptom scores (presumably surrogate in many cases), and rescue antihistamine use. There was no apparent designation in the protocol of the primary assessment, nor was there any discussion of statistical corrections for multiple comparison, given the many efficacy assessments with no designated "primary" comparison. However, in the study report, the nasal symptom scores, rated by the physician (PGA) and the overall global physician scoring were reportedly considered primary.

Safety Endpoint Parameters:

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

8.1.3.12 Statistical Analysis

The primary comparisons were for all exposed subjects (intent-to-treat). There were few enough withdrawals and violators to obviate the need for any "evaluable" analysis.

1. Sample Size - A power analysis was not given in the study protocol. The study report contains a power analysis discussion (seemingly prospective) which states that the standard deviation on the PGA was 91, and in a two-tailed test with alpha of 0.05, there was an 80% power to detect a difference between groups of 40 points or more. There was no discussion of the whether 40 points is clinically detectable / meaningful.

2. Efficacy Analysis

Efficacy analysis was performed on all the 'primary' and 'secondary' variables as listed above with an alpha of 0.05, with two-sided testing. For physician global scores, rescue medication and nasal examinations, Cochran-Mantel-Haenszel tests were performed. For physician rated symptom scores, three differing analyses were performed. These were the van Elteren statistic, F-tests on area under the curve across visits and finally a three-factor model with repeated measures across visits on patient factor.

3. Safety Analysis - was to be focused on clinical adverse events, laboratory tests, physical examination findings (including nasal examinations), and vital signs. Fishers exact test was performed for each of the adverse event tables to detect significant differences.

8.1.3.13 Amendments to the protocol

None reported.

8.1.4 **Results**

8.1.4.1 Study population characteristics

The study was conducted during the fall allergy season of 1989. A total of 250 subjects were enrolled into the study: 85 were randomized to placebo, 84 to FP 100 QD, and 81 to FP 200 QD. The total numbers screened to accrue this treatment population is not clear, nor are the reasons for screening failures provided by the sponsor

A total of 5 patients (2%) withdrew prematurely from the study. This included one in the placebo group who was withdrawn for refusal to comply with dosing regimen, and 2 each in FP100 and FP200 due to adverse events (all at least in part due to asthma flairs, with one also reportedly having sinusitis). The placebo subject who withdrew was also reportedly a protocol violator, as this subject was determined retrospectively to be not sufficiently symptomatic for inclusion in the study. This subject is included in the intent-to-treat analysis, however. See table below for numerical summary.

Demographics revealed reasonable comparability between dosage groups.

Baseline clinical characteristics related to atopy and allergy history were comparable. The majority of subjects (around 70%) were reactive to skin testing with ragweed, with other weeds such as carelessweed and lambs quarter accounting for most of the rest of the predominant weed allergy. The reported presence of a perennial component, seasonality and asthma were similar in all dosage groups.

8.1.4.1.1 Concurrent Medication use

The use of concomitant medications, particularly bronchodilators and anti-allergy compounds was similar between groups.[5]

8.1.4.2 Efficacy Analysis

8.1.4.2.1 *Data set analyzed*

Data analysis was performed on the Intent-to-treat population consisting of all subjects randomized. The intent-to-treat population was 250.

Summary of Patient disposition in all patients randomized to study drug (intent-to-treat population):

	Placebo	FP 100 QD	FP 200 QD	Total
Number Enrolled	**85**	**84**	**81**	**250**
Number (%) withdrawn	**1 (1)**	**2 (2)**	**2 (2)**	**5 (2)**
Reason for withdrawal:				
Lack of efficacy	**0**	**0**	**0**	**0**
Adverse Events	**0**	**2 (2)**	**2 (2)**	**4 (2)**
Other	**1 (1)**	**0**	**0**	**1 (<1)**

Since no subject withdrew due to inadequate treatment (including any in the placebo group), this finding cannot be used as a potential marker of efficacy.

8.1.4.2.2 Clinician-rated Nasal Symptom Scores

This analysis is reported as primary in the study report. It consists of the summary score of all nasal symptoms rated by the investigator (i.e., nasal obstruction, rhinorrhea, sneezing, and itching) each on a 100 point visual analogue scale. The worst possible total nasal symptom score (TNSS) is a 400 and the least possible is a 0.

Table of Investigator rated TNSS on over the two week treatment period (0 - 400 scale):

5 **Table 8, page 101 of volume 1.005**

TNSS	Placebo			FP100			FP200			p values		
	N	mean	SE	N	mean	SE	N	mean	SE	P vs FP100	P vs FP200	FP100 vs FP200
Day 1	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

Although both doses were statistically better than placebo at day 8, only the FP100 dose achieved statistical superiority over placebo at day 15 (though the 200 dose was numerically superior). Therefore, the FP200 dose did not display a consistent, statistically significant effect over the entire 2 week treatment period on this analysis, which the sponsor designated as primary in the study report. Pairwise comparisons between active doses did not show any predictable dose-related differences between the treatment groups at any time point, and any "trend" towards a dose-response goes the wrong way, with the numerical effect of FP100 > FP200 at day 15.

When examined as individual symptoms scores, there were statistically significant differences compared to placebo for some individual components of the clinician rated scoring at both 1 and 2 weeks for both active treatments. This was particularly true of the nasal obstruction rating (significant at both time points at both doses). The rhinorrhea rating was significant for both active treatment arms at week 1 but for neither at week 2. Sneezing ratings only reached statistically significant levels for the FP200 dose at week 1, and no other time point/dose group. Nasal itching was significant only in the FP100 group, but at both time points. Eye symptoms, not included in the above TNSS, were not surprisingly insignificant numerically and statistically in all comparisons.[6] Again, for the most part, there was little discernable difference in efficacy between the 100 and 200 mcg dosing with little data suggesting improved efficacy with the 200 mcg dosing.

8.1.4.2.3 Clinician-rated Overall Assessment

Clinicians were instructed at the end of the study to evaluate the effectiveness of the treatment and record the patient's response in terms of the following classifications of symptoms: significant improvement, moderate improvement, mild improvement, no change, mildly worse, moderately worse, significantly worse or not evaluable. The results of this analysis were conducted by the Mantel-Cochran-Haenszel test, with the following categories assigned: 1=significant improvement, 2=moderate

6 **taken from table 12 on page 105, vol. 1.005**

improvement, 3=mild improvement, 4=all other categories. The table below depicts the findings of these ratings:

Overall Assessment	Placebo	FP100	FP200
Number of baseline patients	85	84	81
Number of evaluable patients	85	84	80
Significant improvement	8 (9%)	24 (29%)	17 (21%)
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

FP100 vs placebo - p<.001; FP200 vs. placebo - p = .002; FP100 vs FP200 - p = .564

This analysis supports the difference of both active doses from with placebo, which on review does appear to be due to an upward shift of the active treatments into greater degrees of improvement. It is again notable that no evidence of superior efficacy of the higher dose comes out of this analysis. Indeed, the number of subjects rated as achieving a "significant improvement" [*sponsor's wording*] is higher in the FP100 group by 25% relative to the FP200 group.

8.1.4.2.4 Patient Rated Symptom Scores

Patients and/or their parent/guardian also evaluated their nasal symptoms on a visual analog scale identical to the one used by the investigators. It should be remembered that this scoring was done in the evening.

Tabular summary of patient (surrogate) rated TNSS on over the two week treatment period (0 - 400 scale):

	Placebo			FP100			FP200			p values		
TNSS	N	mean	SE	N	mean	SE	N	mean	SE	P vs FP100	P vs FP200	FP100 vs FP200
Day 3 - 0	85	272	6.6	84	276	5.8	81	262	4.7	.638	.119	**.045**
Day 1 - 3	85	239	8.1	84	222	8.1	81	210	7.4	.066	.106	.874
Day 4 - 7	85	221	9.7	84	192	9.0	80	180	9.7	**.017**	**.048**	.756
Day 8 - 10	84	201	9.8	84	165	10.0	80	157	10.1	**.022**	.109	.546
Day 11 - 14	83	196	11.1	83	155	11.0	80	154	9.9	**.027**	.193	.402
Day 15 - 17	83	203	10.7	82	170	10.8	79	163	9.8	**.034**	.231	.395

There are a few notable things in this analysis. First is that the subjects and their surrogates (parents/guardians) rate their symptoms worse at baseline than the investigators did and the relative movement over the course of treatment in the subject/surrogate rated scores is much less. Secondly, there was a baseline significant difference between the FP100 and FP200 group, with the FP200 group being less symptomatic at baseline by this analysis (which was not the case with the investigator ratings). By this analysis, there is statistical improvement in the FP100 and FP200 group by 7 days. However, this is only consistently maintained in the FP100 group to the end of the study (day 15). Again, for many of the subcomponents of the TNSS there were occasional significant treatment differences observed. However, these were only consistently and convincingly demonstrated for both FP100 and FP200 in nasal obstruction, with less consistent improvement in the rhinorrhea and sneezing scoring for the FP100 group and no other significant findings for the FP200 group.

8.1.4.2.5 AM nasal obstruction rating (Patient measured)

Subjects were also to rate their morning nasal obstruction, which in some ways reflects a "trough" measure of efficacy. The tabular summary for these results is found below (0-100 scale):

	Placebo			FP100			FP200			p values		
AM nasal obstruction	N	mean	SE	N	mean	SE	N	mean	SE	P vs FP100	P vs FP200	FP100 vs FP200
Day 3 - 0	85	76.3	2.2	84	79.8	1.6	81	78.0	1.4	.118	.641	.297
Day 1 - 3	85	76.2	2.1	84	73.2	1.8	81	71.8	2.0	**.012**	.056	.594
Day 4 - 7	85	70.2	2.3	84	64.0	2.6	80	61.6	2.4	**.005**	**.006**	.925
Day 8 - 10	84	65.7	2.4	84	58.0	2.9	80	54.4	2.9	**.020**	**.036**	.891
Day 11 - 14	83	63.6	2.7	83	53.7	3.0	80	53.2	3.0	**.009**	.052	.560
Day 15 - 17	83	65.9	2.8	82	56.8	3.1	80	55.0	2.9	**.002**	**.042**	.349

By this endpoint analysis, there is efficacy for the FP100 dose by day 3, with no clear evidence of any dose-response and certainly no evidence of more rapid relief with FP20 by this or the previous endpoint analysis.

8.1.4.2.6 Use of Rescue Chlorpheniramine

The use of rescue antihistamine was tracked in the subject daily diaries. These results were considered an important indicator of efficacy by the sponsor. However, the results were not terrifically convincing of a treatment effect, as summarized below. Note that a dose of chlorpheniramine was 1 mg for 4 - 5 year olds (2.5 ml syrup) and 2 mg for 6 - 11 year olds (5 ml syrup or ½ of a 4 mg tablet):

Rescue Chlorpheniramine Dosing (mean dose; % of subjects rescuing):

	Placebo			FP100			FP200			p values		
	mean	n/N	%	mean	n/N	%	mean	n/N	%	p vs 100	p vs 200	100 vs 200
week -1	3.3	49/85	58%	2.7	50/84	60%	3.8	52/81	64%	.812	.360	.476
week 1	2.5	47/84	56%	2.3	34/84	40%	2.2	36/81	44%	**.050**	.157	.572
week 2	2.2	33/83	40%	1.9	30/84	36%	1.9	29/80	36%	.581	.662	.910

In one respect, although the study largely failed on this endpoint, these results make the other determinants of efficacy less confounded, since any large differential in use of rescue medication (either in mean dose/patient or in percent of subjects using rescue) could be expected to alter the subjective reporting of the symptom scores.

8.1.4.3 Safety Analysis

The safety analysis included all patients who received any study drug, a total of 250 subjects, with 245 completing 14 days of treatment. These 245 were broken down into 84 in the placebo group, 82 in the FP100 group, and 79 in the FP200 group. Adverse events were apparently not tracked in the daily diary and therefore were ascertained retrospectively at clinic visits. It is quite likely that much of this reporting for the younger population was surrogate reporting.

8.1.4.3.1 Adverse Event Occurrence Rate

Overall, the adverse event profile of the active treatment groups was largely comparable to placebo, except for the expected side-effects of the inhaled corticosteroids. No obvious idiosyncratic reaction is detectable. An abbreviated summary of the overall adverse events is found below **(based on those categories where AE's were reported in > 1% of patients OR categories of potentially expected topical / corticosteroidal effects)**[7]:

7 **taken from table 21, pages 125-128, vol. 1.005**

Adverse Event		Placebo N (%)	FP100 QD N (%)	FP200 QD N (%)
Total Pt. Numbers		85	84	81
All Events		26 (31)	34 (40)	26 (32)
ENT	All	13 (15)	20 (24)	11 (14)
	Pharyngitis/sore throat	2 (2)	7 (8)	3 (4)
	Epistaxis	4 (5)	4 (5)	3 (4)
	URTI	2 (2)	1 (1)	2 (2)
	Burning in nose	0 (0)	3 (4)	1 (1)
Neuro	Headache	8 (9)	6 (7)	1 (1)
Respiratory	All	2 (2)	9 (11)	9 (11)
	Asthma attack	0 (0)	4 (5)	3 (4)
	Cough	0 (0)	1 (1)	5 (4)
Teeth	Any disorder	2 (2)	1 (1)	2 (2)
GI	All	1 (1)	6 (7)	3 (4)
	stomach ache	1 (1)	2 (2)	0 (0)
	vomiting	0 (0)	5 (6)	2 (2)

Overall, the adverse event experience is in keeping with a topically applied medicine for SAR. It is notable that GI upset, particularly vomiting, appears to be active treatment-related from these data. It is also notable that asthma "attacks," presumably bronchospasm, appear to be active treatment-related from these data. The 4 withdrawals from the active treatment groups, in fact, were all due at least in part to asthma flairs.[8]

8.1.4.3.2 Adverse Event Severity

No deaths were reported during this study. Only 1 patient experienced a serious adverse event. This event was in an 8 year old assigned to FP200 and who received two doses of study medication before developing an asthma exacerbation that required hospitalization and withdrawal from the study (included in previous discussion).[9]

8.1.4.3.3 HPA Axis Effects of FP

HPA axis testing was only conducted with a.m. cortisols, a measure which is neither very sensitive nor specific for HPA axis functioning. Only two measures were conducted, a baseline and a test at the final treatment

8 **Narratives in study report found on pages 83-84, vol. 1.005**

9 **Narrative on pages 82, vol. 1.005**

visit (day 15). Abnormalities of cortisol testing are summarized below[10]:

	Placebo	FP100 QD	FP200 QD
Subjects, N	**85**	**84**	**81**
Subjects with any abnormal a.m. cortisol at day 15 or repeat	**14 (16)**	**9 (11)**	**7 (9)**
Subjects with a.m. cortisol < 7µg/dl	**14 (16)**	**8 (10)**	**6 (7)**
Subjects with a.m. cortisol > 25 µg/dl	**0 (0)**	**1 (1)**	**1 (1)**

By this measure, there appears to be no definable cortisol suppression of HPA axis function with active treatment in that placebo has the highest rate of abnormally low a.m. cortisols and FP200 the lowest rate. However, these data are not too reassuring given the insensitivity and non-specificity of this measure *and* the very brief duration of exposure.

Comment - ***The HPA axis effects, as far as a "worst case scenario" will be better ascertained from FLD-220, the year long study with the more bioavailable inhaled formulation of fluticasone, which measured urinary free cortisol.***

8.1.4.3.5 Laboratory Abnormalities / Changes

There were no important signals detected in laboratory examinations (which were conducted only at screening and day 15). This includes examination of mean data as well as shift tables. Specifically, there was no signal of overt steroid effect on serum glucose, on eosinophils or lymphocytes. There were no important liver-related chemistry changes.

8.1.4.3.6 Vital Signs

Mean values for blood pressure, pulse rate, temperature, and respiratory rate were reported for study entry and endpoint and showed no definable treatment effect.

8.1.4.3.7 Physical Examination

There were no important findings relative to safety from serial physical examinations. It is notable, however, that wheezing was noted on the exams of 7 subjects, four in the FP100 group, 3 in the FP200 group and none in the placebo group.

8.1.5 Conclusions

8.1.5.1 Efficacy Conclusions

It appears by both measures of physician and patient/surrogate rated symptom scoring that FP100 is effective in this age group for the treatment of SAR. This difference may be noticeable by day 3 (if one considers the a.m. nasal obstruction scoring by patients/surrogates). The

10 **taken from table 13, page 122, vol. 1.066**

FP200 dose, though it trends towards numerical superiority over placebo, is less convincingly effective in this study. Certainly, there is no indication of increased efficacy with increased dose coming from this study, despite the proposed label instructions that a 200 µg dose should be used in more severe patients. Despite the lack of prespecified primary endpoints and analyses, all the efficacy variables are supportive of the FP100 dose being effective, with most of them showing that this effect starts relatively early (3 - 7 days) and lasts throughout the trial. This study, however, not only failed to show a dose-response characteristic for FP in this age group, but the FP200 dose failed to meet significance criteria on most efficacy parameters. This apparent paradox will need to be examined more fully in latter studies.

When looked at in individual scoring of nasal symptom components, the most convincing effect is on nasal obstruction, followed by sneezing, nasal itching and lastly and least convincingly rhinorrhea. There was no clear indication of eye symptom relief, although there was a trend towards some effect with the FP100 dose.

There is little convincing support for Flonase leading to a meaningful decrease in rescue medication use coming from this study, despite the effectiveness noted in the symptom scores.

8.1.5.2 Overall Safety Conclusions

Flonase 100 and 200 µg per day administered intranasally to 4 - 11 year olds is well tolerated for 14 days duration, with little evidence of important adverse events. Safety issues which will be borne in mind in reviewing the other studies submitted will include the apparent active treatment-related vomiting and bronchospasm noted in this study. The latter signal came from several different areas, including adverse event coding, withdrawal narratives and physical examination recordings.

8.2 STUDY FLN-321[11]

"A Double-blind, Randomized, Placebo-controlled Study of the Efficacy and Safety of Aqueous Fluticasone Propionate Given Once Daily Versus Placebo for Two weeks in Pediatric Patients with Seasonal Allergic Rhinitis." [sponsor title]

8.2.1 Objectives/Rational

To compare the efficacy and safety FP 100 µg QD and 200 µg versus placebo in the treatment of seasonal allergic rhinitis in children ages 4-11 over a 28 day treatment period.

8.2.2 Design

[11] **Volume 1.009, page 1**

Ten center, randomized, double-blind, placebo-controlled, parallel group study of 4 weeks duration.

8.2.3 **Summary of the Study Protocol (final version, no amendments given)**

Since this protocol differs little from that of FLN-320, save for length, only differences outside the 28 day length will be explicitly mentioned. The numbering system for the sections of the review will be preserved, however, for ease of cross-reference to the previous review. Differences will be underlined.

8.2.3.7 Assessments

Unlike the shorter-term FLN-320, this study included a more extensive use of clinical studies to assess HPA axis function, including urinary cortisols and 17-ketogenic steroids in addition to the a.m. cortisol assessment.

Screening visit - History (including SAR symptom assessment), physical (including nasopharyngeal exam), skin testing, laboratories (including a.m. cortisol, *24-hour urine collection*).

Run-in period - Daily recording of SAR symptoms by the patients or caretaker surrogate using a visual analogue scale and rating nasal symptoms (sneezing, rhinorrhea, congestion, itching), ocular symptoms, and daily rescue medication use. Nasal blockage was scored in the a.m., other parameters were recorded at bedtime.

Randomization visit (visit 1) - Diary cards reviewed, nasal exam and symptom assessment, and adverse event assessment.

Double Blind period - Patients were scheduled to return on study days 8, *15, 22, and 29 for visits 2 - 5*. At *visit 2 - 4*, diary cards were collected and reviewed. Nasal examinations and symptoms assessments were performed and adverse event assessment was carried out. At *visit 5*, additionally, there was a physical exam performed along with clinical laboratory testing with a.m. serum cortisol determinations and 24 hour urines for cortisol and ketogenic steroids.

A post-treatment visit was conducted at day *36*, with review of final diary cards, chlorpheniramine use, examination, and laboratory testing as need for abnormalities at visit 5. This visit included a final clinician rating of symptoms.

8.2.3.9 Endpoints

Efficacy parameters:

The same endpoints are assessed in this protocol as in 320, and again there are no prespecified designations of exact statistical methods or primary endpoints.

Safety Endpoint Parameters:

4. Adverse Events
5. Physical examination / laboratory abnormalities
6. HPA axis assessments (24 hour urines)
7. Vital signs assessment

8.2.3.12 Statistical Analysis

As above; there are no important differences in this aspect of the protocol between this trial and trial 320.

8.2.3.13 Amendments to the protocol

None reported.

8.2.4 **Results**

8.2.4.1 Study population characteristics

The study was also conducted during the fall allergy season of 1989. A total of 249 subjects were enrolled into the study, with equal numbers in all three treatments of 83. The total numbers screened to accrue this treatment population is not clear, nor are the reasons for screening failures provided by the sponsor

A total of 7 patients (3%) withdrew prematurely from the study. This included one in the placebo group who was withdrawn for sinusitis (also reportedly failed to meet entry criteria), and 3 each in FP100 and FP200. In the FP100 group, one was withdrawn due to failure to meet symptom requirement, and the other two withdrew due to asthma-related adverse. In FP200, two withdrew for reasons other than adverse events (advice against participation by the subject's pediatrician in one and failure to return for visit 4 in the other). The last patient in this group also withdrew due to asthma symptoms. See table below for numerical summary.

Demographics revealed reasonable comparability between dosage groups of the reported characteristics.[12] There was some imbalance with the FP100 group being slightly younger, which was also reflected in the weight and in height. As in FLN-320, there was also some imbalance in gender, with more males overall in the study (65%) and with a comparative excess of males in the FP100 group (66%) and even more so in the FP200 group (72%) compared with placebo (55%). Again, the gender subsets of efficacy and safety data in the ISE and ISS will need to be considered to determine if such an imbalance might have had a definable effect on the study findings.

Baseline clinical characteristics related to atopy and allergy history were comparable. The majority of subjects (around 70%) were reactive to skin

12 **table 4 of vol. 1.009, page 88**

testing with ragweed, with other antigens such as cockleburr and "other weeds" accounting for most of the rest of the predominant weed allergy.

8.2.4.1.1 Concurrent Medication use

The use of concomitant medications, particularly bronchodilators and anti-allergy compounds was similar between groups, although the active treatment groups did seem to have a higher percentage of subjects using bronchodilators and allergy medications at baseline, perhaps arguing for more prominent atopy/asthma.[13]

8.2.4.2 Efficacy Analysis

8.2.4.2.1 *Data set analyzed*

Data analysis was performed on the intent-to-treat population consisting of all subjects randomized. The intent-to-treat population was 249.

Summary of Patient disposition in all patients randomized to study drug (intent-to-treat population):

	Placebo	FP 100 QD	FP 200 QD	Total
Number Enrolled	83	83	83	249
Number (%) withdrawn	1 (1)	3 (3)	3 (3)	7 (3)
Reason for withdrawal:				
Lack of efficacy	0	0	0*	0
Adverse Events	1	2 (2)	1 (1)	4 (2)
Other	0	1 (<1)	2 (2)	1 (<1)

*Note that since one subject failed to show for visit 4 in this group, lack of efficacy cannot be excluded. However, even with this assumed to be due to lack of efficacy, there is no signal that this represents a "trend" suggestive of an efficacy problem.

8.2.4.2.2 Clinician-rated Nasal Symptom Scores

This analysis is again reported as primary in the study report. It consists of the summary score of all nasal symptoms rated by the investigator (i.e., nasal obstruction, rhinorrhea, sneezing, and itching) each on a 100 point visual analogue scale. The worst possible total nasal symptom score (TNSS) is a 400 and the least possible is a 0.

Table of Investigator rated TNSS on over the two week treatment period (0 - 400 scale)

13 **Table 9, page 92 of volume 1.005**

TNSS	Placebo			FP100			FP200			p values		
	N	mean	SE	N	mean	SE	N	mean	SE	P vs FP100	P vs FP200	FP100 vs FP200
Day 1	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	.561	.294

As opposed to the proceeding study, these results are not supportive of efficacy of the FP100 dose at anytime point. It is notable, however, that there was a baseline disparity in symptoms, with the FP100 group being on average the least symptomatic of all and statistically different from placebo at baseline. The FP200 group showed more convincing efficacy compared with placebo, albeit inconsistently - with no separation statistically at days 15 and 29. The latter finding, that the FP200 (and FP100) dose does not separate out from placebo at day 29, may arguably be due to the study's duration exceeding the peak of the allergy season. Note that numerically, both doses still display more of a fall from baseline at day 29 than does placebo.

When examined as individual ratings of the symptoms scores,[14] the most convincing evidence came from the nasal obstruction, where both doses separated from placebo at day 8 and remained consistently superior to placebo for the entire treatment period, with the exception of the FP200 group on day 29 (p=0.185). Few of the other comparisons of symptom score components and time periods convincingly supported efficacy. However, all these comparisons of components should be regarded as supportive evidence (as was true of the previous study) since they were not prespecified as important, nor were multiple comparison and power issues addressed for these TNSS component analyses.

When the TNSS is displayed by categorical analysis, it appears that the largest component of the difference between FP100 and placebo came from one category - there were more placebo patients whose symptoms increased. In the FP200 group, there is a more convincing broad difference in this analysis - more patients achieved reductions in scores of > 150 points in (47%) vs. placebo (35%).

14 **Table 12, page 96 of volume 1.009**

Change in TNSS from day 1 to 29	Placebo		FP100 QD		FP200 QD	
Number of subjects	82		82		83	
	mean	%	mean	%	mean	%
< -250	9	11%	9	11%	13	16%
- 250 to -151	20	24%	25	30%	26	31%
- 150 to - 51	31	38%	27	33%	24	29%
- 50 to 50	14	17%	18	22%	15	18%
> 50	8	10%	3	4%	5	6%

8.2.4.2.3 Clinician-rated Overall Assessment

Clinicians were instructed at the end of the study to evaluate the effectiveness of the treatment and record the patient's response in terms of the following classifications of symptoms: significant improvement, moderate improvement, mild improvement, no change, mildly worse, moderately worse, significantly worse or not evaluable. The results of this analysis were conducted by the Mantel-Cochran-Haenszel test, with the following categories assigned: 1=significant improvement, 2=moderate improvement, 3=mild improvement, 4=all other categories. The table below depicts the findings of these ratings:

Overall Assessment	Placebo	FP100	FP200
Number of baseline patients	83	83	83
Number of evaluable patients	82	80	81
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	1 (1%)
Significantly worse	0	0	0

FP100 vs placebo - p = .001; FP200 vs. placebo - p <.001; FP100 vs FP200 - p = .267

While this analysis supports the difference of both active doses from with placebo (which convincingly is due to an upward shift of the active treatments into greater degrees of improvement), it does not match very well the categorical analysis of symptom scoring presented above, where there appeared little difference in the FP100 vs. placebo groups and where there appeared to be more subjects who worsened than is described here. Also notable is that in this analysis, the active

treatments appear very similar (and tested out as being statistically no different).

8.2.4.2.4 Patient Rated Symptom Scores

Patients and/or their parent/guardian evaluated their nasal symptoms on a visual analog scale in the evening.

Tabular summary of patient (or surrogate) rated TNSS on over the two week treatment period (0 - 400 scale):

TNSS	Placebo			FP100			FP200			p values		
	N	mean	SE	N	mean	SE	N	mean	SE	P vs FP100	P vs FP200	FP100 vs FP200
Day 6 - 0	83	277	5.2	83	261	5.0	83	273	5.6	.253	.496	.624
Day 1 - 7	83	237	8.4	82	204	7.9	83	199	8.9	.148	**.008**	.255
Day 8 - 14	83	194	10.1	82	164	9.2	82	145	10.0	.323	**.005**	.081
Day 15 - 21	83	184	10.4	80	147	9.8	82	134	10.7	.070	**.003**	.280
Day 22 - 28	83	175	11.2	80	131	9.0	82	118	10.9	**.024**	**<.001**	.280
Day 29 - 35	82	180	10.8	80	153	10.7	80	146	10.9	.152	**.030**	.503

As opposed to the clinician rated symptom score, there is not a statistical imbalance at baseline in this analysis between the FP100 group and placebo. There is only statistical separation of FP100 from placebo at one time point, which given the multiple comparisons made in this testing is not at all convincing of a true, significant drug effect. However, the FP200 group, as in the clinician rated TNSS, is convincingly superior to placebo at all time points, with the earliest testing for separation from placebo coming at 7 days. Again, as in the other measures, there is no statistical separation of the two active treatments suggestive of a clear dose response from the pairwise comparison. However, the observation that FP200 separates statistically from placebo and FP100 does not implies some increased efficacy with the higher dose (albeit FLN-320 showed the opposite). Also note that with this measure as opposed to the clinician rating, the statistical superiority of FP200 is durable out to 28 days of treatment and beyond.

8.2.4.2.5 AM nasal obstruction rating (Patient measured)

Subjects were also to rate their morning nasal obstruction, which in some ways reflects a "trough" measure of efficacy. The tabular summary for these results is found below (0-100 scale):

AM nasal obstruction	Placebo			FP100			FP200			p values		
	N	mean	SE	N	mean	SE	N	mean	SE	P vs FP100	P vs FP200	FP100 vs FP200
Day 6 - 0	83	76.7	2.2	83	75.2	1.6	83	78.9	1.4	.941	.239	.266
Day 1 - 7	83	73.9	2.1	82	66.5	1.8	83	68.1	2.0	.068	**.002**	.227
Day 8 - 14	83	65.5	2.3	82	55.8	2.6	82	52.1	2.4	**.039**	**<.001**	**.045**
Day 15 - 21	83	62.0	2.4	80	49.7	2.9	82	50.0	2.9	**.005**	**<.001**	.406
Day 22 - 28	83	58.2	2.7	80	46.9	3.0	82	43.8	3.0	**.020**	**<.001**	.127
Day 29 - 35	82	59.6	2.8	80	49.2	3.1	80	46.5	2.9	**.011**	**<.001**	.108

By this endpoint analysis, there is efficacy for the FP200 dose by day 7, but not for the FP100 dose until the second week. While there is no clear evidence of any dose-response, there is a hint of some superiority of the FP200 dose (though again, multiple comparisons make any one week's p value comparison of < 0.05 suspect for indicating any real difference).

8.2.4.2.6 Use of Rescue Chlorpheniramine

The use of rescue antihistamine was tracked in the subject daily diaries. As opposed to FLN-320, there was more indication of efficacy on this endpoint from this trial as summarized below:

Rescue Chlorpheniramine Dosing (mean dose; % of subjects rescuing):

Period	Placebo			FP100			FP200			p values		
	mean	n/N	%	mean	n/N	%	mean	n/N	%	p vs 100	p vs 200	100 vs 200
week - 1	4.0	53/83	64%	3.2	45/83	54%	3.1	42/83	51%	.172	.094	.603
week 1	3.0	45/93	54%	1.5	27/82	33%	1.5	28/83	34%	**.007**	**.010**	.918
week 2	2.0	30/83	36%	1.7	29/82	35%	1.0	20/82	24%	.893	.096	.087
week 3	2.9	37/83	45%	1.2	24/80	30%	1.2	21/82	26%	**.047**	**.007**	.546
week 4	2.3	34/83	41%	1.1	19/80	24%	1.2	19/82	23%	**.017**	**.011**	.852

With the exception of one aberrant week, this analysis supports efficacy of both doses, starting within the first week. Both in terms of dose and percentage of subjects requiring rescue, there appears to be no important differences of the two active treatment doses, with the exception of the week 2 period, which again appears otherwise aberrant.

8.2.4.3 Safety Analysis

The safety analysis included all patients who received any study drug, a total of 249 subjects, with 242 completing 28 days of treatment. These 242 were broken down into 82 in the placebo group, 80 in the FP100 group, and 80 in the FP200 group. As in the previous study, adverse events were ascertained retrospectively at clinic visits.

8.2.4.3.1 Adverse Event Occurrence Rate

Overall, the adverse event profile of the active treatment groups was largely comparable to placebo, except for the expected side-effects of the inhaled corticosteroids. No obvious idiosyncratic reaction is detectable. An abbreviated summary of the overall adverse events is found below (based on those categories where AE's were reported in > 2% of patients OR categories of potentially expected topical / corticosteroid effects)[15]:

Adverse Event	Placebo N (%)	FP100 QD N (%)	FP200 QD N (%)
Total Pt. Numbers	83	83	83
All Events	40 (48)	34 (41)	49 (59)
ENT All	28 (34)	19 (23)	24 (29)
Epistaxis/bloody discharge	6 (7)	6 (7)	9 (11)
Otitis Media	3 (4)	0 (0)	3 (4)
Pharyngitis/sore throat	6 (7)	3 (4)	1 (1)
URTI	4 (5)	2 (2)	3 (4)
Ulcers of nasal septum	1 (1)	2 (2)	2 (2)
Burning in nose	2 (2)	1 (1)	3 (4)
Neuro Headache	5 (6)	4 (5)	5 (6)
Respiratory All	11 (13)	17 (20)	18 (22)
All Asthma symptom coding*	6 (7)	8 (10)	13 (16)
All coding under "Cough"**	2 (2)	5 (6)	6 (7)
GI All	6 (7)	3 (4)	10 (12)
stomach ache/cramps	1 (1)	0 (0)	5 (6)
vomiting	3 (4)	1 (1)	3 (4)

** Includes wheezing, asthma, nocturnal asthma, acute asthma and asthma attack.*
*** includes cough, dry cough and bronchial cough*

Overall, the adverse event experience is in keeping with a topically applied medicine for SAR. It is notable that GI upset again appears to be active treatment related, at least for the FP200 group compared to placebo. It is also again notable that these data appear to confirm the data from FLN-320 regarding asthma events, presumably bronchospasm, appear to be active treatment related, showing a dose-response. There were 3 withdrawals from the active treatment groups that were due to asthma flairs, 2 in the FP100 group, one in the FP100 group - although in

15 **taken from table 21, pages 117-121, vol. 1.009**

reading the cases, causality cannot be ascribed to treatment.[16] However, the overall pattern emerging from these two studies is that FP treatment is related to asthma symptoms in some patients, and that FP treatment *may* predispose to exacerbations.

It is interesting that in contrast to FLN-320, pharyngitis appears in this study not to result from active treatment, but to be ameliorated by active treatment. Also in contrast to FLN-320, epistaxis appears more clearly active treatment related in this study, at least for the FP200 dose.

8.2.4.3.2 Adverse Event Severity

No patients experienced serious adverse events in this study, nor were any deaths reported during this study.

8.2.4.3.3 HPA Axis Effects of FP

HPA axis testing was conducted with a.m. cortisols (a measure which again is neither very sensitive nor specific for adequate HPA axis functioning - but in a 4 week study may be more likely to show an effect than the previous 2 week study), as well as 24 hour urines for cortisol and 17-ketosteroid. Only two measures were conducted, a baseline and a test at the final treatment visit (day 28). Abnormalities of a.m. serum cortisol testing are summarized below[17]:

	Placebo	FP100 QD	FP200 QD
Subjects, N	**82**	**83**	**83**
Subjects with any abnormal a.m. cortisol at day 29 or on repeat	**6 (7)**	**8 (10)**	**12 (14)**
Subjects with a.m. cortisol < 7µg/dl	**5 (6)**	**8 (10)**	**11 (13)**
Subjects with a.m. cortisol > 25 µg/dl	**1 (1)**	**0 (0)**	**1 (1)**

By this measure, there appears to be some evidence of an effect over the 4 weeks of this study, with an increasing incidence of low cortisols with increasing dose. Although some of these subjects were low or borderline low at screening and remained low at day 29 (particularly represented by cases in placebo), there were only 6 subjects where the a.m. cortisol fell by more than 10 mcg/dl from screen to end-of-treatment, all were in active treatment - 3 in FP100, 3 in FP200.

Urinary free cortisols (and urinary cortisol:creatinine ratios) are generally believed to be superior to a.m. cortisols in identifying HPA suppressive effects of systemic steroids, representing decreased adrenal output due

16 **Narratives in study report found on pages 57-58, vol. 1.009**

17 **taken from table 25, page 143, vol. 1.009**

to lower ACTH levels. However, urinary cortisols do not provide any information on whether the adrenals can respond to stress (i.e., whether they could secrete increased cortisol in response to increased ACTH), which is a critical part of the response to stress/serious illness. The urinary ketosteroid are another indicator of low ACTH level, representing the output from the adrenals of the androgenic steroids that occurs in response to ACTH stimulation. The usefulness of the 17-ketosteroid in detecting adrenal insufficiency secondary to systemic steroids is not well established.

Urinary Cortisols:

	Placebo			FP100			FP200		
Measure	N	mean	SE	N	mean	SE	N	mean	SE
Cortisol (µg/day)									
Pretreatment	83	15.9	0.90	82	15.2	0.90	82	16.9	1.30
Day 29	72	17.3	1.10	80	14.5	0.90	75	14.3	1.10
Creatinine (g/day)									
Pretreatment	83	0.55	0.02	82	0.49	0.03	82	0.53	0.02
Day 29	72	0.59	0.03	80	0.48	0.02	75	0.59	0.05
Cortisol/creatinine									
Pretreatment	83	30.7	1.70	82	33.6	1.50	82	33.5	2.80
Day 29	72	30.7	1.70	80	33.3	2.40	75	27.0	1.70
17-ketosteroid (mg/day)									
Pretreatment	83	4	0	83	3	0	83	4	0
Day 29	71	4	0	78	3	0	73	4	0

Above is a tabulation of the 24 hour urinary cortisol results, which are represented both as a mean and as a ratio of creatinine (which is intended to correct for incomplete / over complete collections). Although not statistically different, it is apparent that the FP200 group trended towards some suppression of urinary cortisol after a 4 week treatment period, particularly when corrected for creatinine (statistical testing for this comparison shows a $p = 0.055$). This lack of statistical significance must be viewed with all the statistical caveats of this sort of analysis, where powering of the study was based on efficacy endpoints and that no adjustments were made for multiple comparisons. Also, it is not clear what the clinical significance of a 6.5 µg/mg drop in the urinary cortisol/creatinine ratio might be. The urinary ketosteroid levels were unchanged in all groups, although it is not clear whether the sensitivity of the assay was sufficient to detect more subtle changes, since the results

were reported in a single, whole integer. All that considered, there are indications from both the a.m. cortisol data and the 24-hour urinary cortisol data that some effect on the HPA axis is detectable with FP200 administered for 4 weeks in this population. The clinical significance of any such effect is uncertain, however.

8.2.4.3.5 Laboratory Abnormalities / Changes

There were no important signals detected in laboratory examinations (which were conducted only at screening and day 15). This includes examination of mean data as well as shift tables. Specifically, there is no signal of overt steroid effect in glucose, eosinophils or lymphocytes. There were no important liver-related chemistry changes. These data do not support any important systemic steroidal effects of either dosage group.

8.2.4.3.6 Vital Signs

Mean values for blood pressure, pulse rate, temperature, and respiratory rate were reported for study entry and endpoint and showed no definable treatment effect.

8.2.4.3.7 Physical Examination

There were no important findings relative to safety from serial physical examinations. In this study, wheezing was noted in 8 subjects, 3 in the placebo group, 1 in the FP100 group and 4 in the FP200 group.

8.2.5 Conclusions

8.2.5.1 Efficacy Conclusions

It appears by the measures of both physician and patient/surrogate symptom scoring that FP200 is effective in this age group for the treatment of SAR, although in the endpoint designated as primary by the sponsor, there was statistical significance on only two of the time periods. With the design of this study, it is only possible to say that efficacy was noted in some measures after 7 days of treatment.

Given the statistically significant results for FP200 and the general lack of such findings with the FP100 dose on many endpoints, this may be taken as evidence of a dose response, although pairwise comparisons of the two active doses do not often separate out statistically.

As with FLN-320, the individual symptom scoring with the most convincing results is nasal obstruction.

In this study, as opposed to the prior results, there was efficacy noted on the endpoint of rescue medication use. This efficacy was noted in both dosage groups at most time points. Since symptom scores may also

reflect the clinical benefit of rescue medications used, one could argue that a higher rescue use in the placebo group might lessen the ability to distinguish active treatment from placebo by symptom scores. Whether this could have played into the lack of convincing efficacy of the FP100 treatment in the symptom scoring is conjectural.

8.2.5.2 Overall Safety Conclusions

Flonase administered intranasally in a total daily dose of 100 and 200 µg to 4 - 11 year olds is well tolerated for 28 days duration, with little evidence of important adverse events, either local or generalized. There again seems to be an excess of GI adverse events noted with active treatment, as well as an excess of asthma-related events. Considered together with FLN-320, these classes of adverse events both appear to be truly related to active treatment. Finally, there is a hint from this study that the FP200 group did experience some systemic response to the topical fluticasone administration, as evidenced by the lower mean urinary cortisol/creatinine ratio and the increased numbers of abnormally low serum a.m. cortisols. The clinical significance of these findings over a 4 week period is doubtful. However, these data do raise some concern for the long-term administration of the FP200 dose to this age group. This will need to be examined in the ISS and in the FLD-220 safety study.

8.3 STUDY FLNT52"

"A double-blind comparison of fluticasone propionate aqueous nasal spray 100 µg given once daily, fluticasone propionate aqueous nasal spray 200 µg given once daily and placebo aqueous nasal spray given twice daily in the treatment of seasonal allergic rhinitis in children aged 4 - 11 years." [sponsor title]

8.3.1 **Objectives/Rational**

To compare the efficacy and tolerability of FP 100 µg QD and 200 µg QD versus placebo in the treatment of seasonal allergic rhinitis in children ages 4 - 11 over a 4 week treatment period.

8.3.2 **Design**

Eighteen centers in Europe, randomized, double-blind, placebo-controlled, parallel group study of 4 weeks duration (no run-in period), with a 2 week follow-up period.

8.3.3 Summary of the Study Protocol (as amended)

8.3.3.1 Population

Inclusions: Male or female patients, 4 - 11 (targeted for ≥1/3 between the ages of 4 - 8) years who have symptoms of seasonal allergic rhinitis with the following symptom requirements:

skin prick positivity to one or more sensitizing plant allergens relevant to season and geography; symptoms of seasonal rhinitis (nasal blockage, sneezing, itching of the nose, rhinorrhea, eye watering /irritation) of at least moderate severity for one previous season.

Exclusions: Patients with concurrent PAR, lack of symptoms on study entry; physical nasal obstruction; serious or unstable concomitant diseases; no infections of the respiratory/sinus/nasal tract; contraindication to or history of adverse reactions to corticosteroids; inability to withdraw from treatment of nasal symptoms at the start of the study; nasal surgery in the previous six weeks; systemic or inhaled corticosteroids for the previous month before the start of the study and intranasal steroids in the previous two weeks; exposure to inhaled cromolyn or nedocromil within the previous 1 month prior to the study; oral astemizole in the previous 6 weeks; immunotherapy in the prior 12 months.

8.3.3.2 Treatment Arms

Fluticasone 100 µg/day -	**1 spray of 50 µg/spray FP in each nostril QAM**
Fluticasone 200 µg/day -	**1 spray of 100 µg/spray FP in each nostril QAM**
Placebo -	**1 spray of 0 µg/spray FP in each nostril QAM**

Comment: ***This study also allowed use of rescue antihistamine. In this case, that rescue medication was determined by the country in which the study was conducted. Cromolyn sodium was also allowed intraocularly for rescue of eye symptoms. Note also that the 200 mcg dose of fluticasone was administered as a formulation that is not approved in the US, being 100 mcg per actuation rather than the approved 50 mcg (0.05%) formulation. This will impact on the interpretability of the FP200 dosing.***

8.3.3.3 Assignment to Treatment

Randomized within each center in a 1:1:1 ratio. There was no reported stratification of the randomization.

8.3.3.4 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.

8.3.3.5 Dosing

The study drug was administered QD as above. The times specified were not exact, but rather "morning only."

8.3.3.6 Study sequence

Following the randomization visit (once eligibility is established), subjects were to return at 14 days and 28 days (±3 days for each) for treatment evaluations. A final evaluation was also performed at 42 days.

8.3.3.7 Assessments

Assessments were conducted by daily diaries for patient symptom scores on nasal blockage on awakening and separately for throughout the day, sneezing, nasal itching, rhinorrhea and eye watering/irritation. All of this was done on a 4 point scale (0 - 3, 0 = none, 3 = severe). Investigators also rated the symptoms at study visits. Routine laboratories and physicals were also performed, the latter including checks for oral candidiasis. Note that this study did not include routine measures of cortisol production or response.

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

8.3.3.9 Endpoints

Two populations were defined by the sponsor. The intent-to-treat population (ITT) consisted of all patients randomized to treatment. The efficacy population was defined as those who adhered closely to the protocol.

Efficacy parameters:

Efficacy variables included the assessment of patient's rated symptom scores (presumably surrogate in many cases), investigator rated nasal symptoms, and diary recorded rescue antihistamine use. The primary analysis was prespecified as the analysis of patient rated % of symptom-free days for sneezing and on rhinorrhea. Secondary analyses include assessments of all other nasal component scores, for investigator ratings, as well as rescue antihistamine use.

Safety Endpoint Parameters:

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

8.3.3.12 Statistical Analysis

The power calculations are 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 35% and therefore planned the sample size of the study to achieve an 80% power to detect a difference of 15% in the mean percent of symptom-free days, with an α of 0.05. The target

er rollment was for sufficient size to achieve 280 evaluable patients.

Comment *Although prior experience helped the sponsor identify what they felt to be an appropriate standard deviation, the effect size which they would like to achieve is based more on this than any clear argument of clinical meaning for that effect size.*

1. Efficacy Analysis

   The analysis of percent symptom free days was to be based on Wilcoxan rank-sum testing. Adjustment for centers was to be done by the van Elteren method. Study centers with low enrollment were to be combined. The primary comparison of interest was of the active groups to placebo, with a secondary interest in the comparison between FP groups. Analysis of mean data was to be performed through a proportional odds model for ordinal data.

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

8.3.3.13 Amendments to the protocol

None reported.

8.3.4 **Results**

8.3.4.1 Study population characteristics

The study was initiated on April 17, 1990 and completed in August 30, 1990. A total of 143 subjects were into the study: 47 were randomized to FP100, 46 to FP200, and 50 to placebo. The intent-to-treat population was further refined for the record card analysis to eliminate those with less than 10 days' data or no available data. This led to an elimination of 7 subjects (the study report incorrectly states that 8 were eliminated)[19], roughly evenly distributed across groups. The efficacy population was 126 (considerably short of the target of 280). The most common reason by far for exclusion from the efficacy population was failure to record diary data, as well as use of proscribed medications.

Demographics revealed reasonably good balance between dosage groups for the reported characteristics, including age, gender, and ethnic characteristics.[20] It should be noted, however, that there were essentially no non-whites in the study (1 each of "other" category in FP100 and placebo). Also, although gender make-up was almost identical across groups, males outnumbered females overall in the study (73:27). Although mean ages were similar, the age distribution was not, with the placebo group being somewhat concenctrated in the 9-11 year old range

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19 **vol. 1.014, page 49, table 1**

20 **table 11 of vol. 1.014, page 59**

compared with the FP groups.

Baseline clinical characteristics related to atopy and allergy history were comparable. Most of the seasonal allergens were grass (this was a late spring-summer study). A few positive tests to birch and assorted other allergens were also recorded. In terms of distribution of the history of previous rhinitis symptoms, if appears that the FP100 group had a somewhat more severe pattern in the past than the other two treatment arms.

8.3.4.1.1 Concurrent Medication use

The use of concomitant medications was similar between groups.

8.3.4.2 Efficacy Analysis

8.3.4.2.1 *Data set analyzed*

Data analysis was performed on the intent-to-treat population and efficacy populations as defined above. Testing for interactions by treatment, by center and by allergic classification were conducted as well. This reviewer's discussion will focus on the ITT analysis.

8.3.4.2.2 Percentage of Patient Rated Symptom-free days

The percentage of symptom free days is reported for each component of the subject's ratings of their nasal scores, although the primary comparisons were designated *a priori* only as the percent of symptom free days for sneezing and rhinorrhea. These two primary comparisons are presented below for the entire treatment period in a tabular summary:

Symptom # subjects in analysis n =	FP 100 44	FP 200 44	Placebo 48
Rhinorrhea			
median % symp. free days	71.4	60.0	33.9
lower quartile	33.4	32.1	3.7
upper quartile	90.8	85.2	74.5
adjusted p value (vs. Placebo)	.005	.017	*FP vs. FP, p = .462*
Sneezing			
median % symp. free days	54.7	46.5	25.5
lower quartile	21.5	22.6	25.5
upper quartile	78.6	76.2	56.0
adjusted p value (vs. Placebo)	.005	.004	*FP vs. FP, p = .749*

On these primary endpoints, as well as on the other components of the nasal symptom scoring, the FP100 dose was statistically superior to

placebo on days 1-28 for all comparisons except nasal itching (p=0.148) and eye symptoms (p=0.175). This is despite the small sample size and the observation that by history, the FP100 group had a higher past severity than did the other treatment groups. The FP200 group was marginally less effective, though statistically significant on both primary endpoints. Although the FP200 group failed to meet statistical significance on the nasal blockage on awakening endpoint (p=0.052), it did meet it on nasal itching (p=0.004) which FP100 did not. When looked at by a proportional odds analysis of the median NS scores, FP100 was significant on all components of the NSS except for the eye symptoms. FP200 was significant for all except rhinorrhea and eye symptoms.[21]

Findings from the analyses conducted on the efficacy population were largely similar and add nothing to the conclusions.

8.3.4.2.3 Diary Recorded Use of Rescue Medications

The use of rescue antihistamine and of cromolyn eye drops were tracked in the subject daily diaries. Such use was limited, with a median of only 4.5 times in the placebo group. Even so, FP100, with a median of 0.0 was statistically superior to placebo for antihistamine use, while FP200 was not. Neither treatment achieved significance for eye drop use.

8.3.4.2.4 Investigator's Rating of Nasal Symptoms

This analysis largely confirms the patient rated symptom scores, particularly at visit 2 (i.e., the 2 week visit). There is less clear cut separation of active from placebo by week 4, with significance only found for FP200 on rhinorrhea of the primary comparisons of sneezing and rhinorrhea. FP100 only achieved statistical separation from placebo on nasal blockage at visit 3.

8.3.4.2.5 Investigator's Findings on Nasal Examination

The results of the investigator examinations of the nasal passages revealed data supportive of efficacy, though only modestly so. The sponsor appropriately did not do a statistical analysis of these data. There were also no safety signals found in these tabulations, including no evidence that epistaxis occurred in a clear relationship to active treatment.

8.3.4.3 Safety Analysis

The safety analysis included all patients who received any study drug, a total of 143 subjects. These 143 were broken down into 47 in the FP 100 group, 46 in the FP 200 group and 50 in the placebo group. Almost all subjects were exposed to a full course of treatment (i.e., 4 weeks ± a few days). Of those who did not complete the study, there were only 2

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21 **table 33 of vol. 1.014, page 83-85**

subjects (one in FP100 and one placebo) who were reported to have discontinued due to adverse events. Only 2 subjects withdrew due to lack of effect - both placebo subjects.

8.3.4.3.1 Adverse Event Occurrence Rate

Overall, the adverse event profile of the active treatment groups was largely comparable. Although the sponsor characterized AE's both during treatment and those during the 2 week follow-up, this discussion will focus on the "on treatment" events with only brief mention of AE's during the follow-up period. An abbreviated summary of the overall adverse events is found below (based on those categories where AE's were reported in 3% or more patients in any treatment group OR categories of potentially expected topical / corticosteroidal effects)[22]:

Adverse Event		FP100 N (%)	FP200 N (%)	Placebo N (%)
Total Pt. Numbers		47	46	50
Number of Subjects with events		20 (43)	13 (28)	23 (46)
Total Events reported		103	90	88
ENT	URTI/viral RI	6 (13)	1 (2)	3 (6)
	Rhinitis	0	0	3 (6)
	Sore throat	1 (2)	3 (7)	2 (4)
	Epistaxis	1 (2)	0	2 (4)
Respiratory	Asthma events	5 (11)	1 (2)	7 (14)
	Cough	2 (6)	3 (7)	3 (6)
GI	Gastroenteritis	2 (4)	0	0

This adverse event profile is quite dissimilar to that seen in other studies. The number of asthma events is not clearly treatment-associated in this study, unlike what was observed in the two US SAR trials. This argues somewhat against a true treatment effect, but this issue can be resolved in the ISS review. In many circumstances, including overall occurrences, it appears that the FP100 dosage and placebo were less well tolerated than the FP200 dosage. Again, the meaning of this observation in relation to the sNDA is unclear since the FP200 dose was a different formulation than available in the US. It does lead to speculation, however, that this may be a concentration effect, since this formulation has 0.10% substance compared to 0.05% in the US product and the FP100 arm in this trial.

22 **taken from table 54, page 128, vol. 1.014**

8.3.4.3.2 Adverse Event Severity

There were no deaths reported in this trial. Only one serious adverse event was reported during the trial, which was a case of trauma. This was a fall in an 8 year old boy on FP100. He was admitted to the hospital for two days but continued on study drug. There was no plausible connection to study treatment. There were 2 subjects withdrawn for adverse events, 1 in the FP100 group and 1 in the placebo group.[23] These two cases, with narrative on page 44 of volume 1.014, show no apparent relation to study drug. In particular, the FP100 case was a 10 year old male who became jaundiced 4 days into therapy, but had elevated LFTs on randomization.

8.3.4.3.3 HPA Axis Effects of FP

HPA axis assessment was apparently not conducted by any means in this study. That is unfortunate, given that the four week duration of this trial makes it one of the longer trials in the sNDA.

8.3.4.3.5 Laboratory Abnormalities / Changes

A review of these shift tables provided no evidence of any important treatment effect. Specifically, there were no changes in eosinophils, glucose, lymphocytes or other parameters that would suggest a systemic response to fluticasone administration.

8.3.4.3.6 Vital Signs

No important signals were noted for vital signs.

8.3.5 Conclusions

8.3.5.1 Efficacy Conclusions

This study, taken together with the two US SAR trials, supports the efficacy of both doses of FP in the treatment of allergic rhinitis in 4 - 11 year olds. Given the failure of this study to achieve its target enrollment, these are convincing data. Two important caveats must be borne in mind about these conclusions, however. First is that the 100 mcg dose appeared equally to more effective than the 200 mcg dose. There are no data coming from this or any other source so far in the sNDA to support a dose titration scheme for effectiveness considerations. Secondly, as previously discussed, since the FP200 is a different formulation than the US formulation, these data for 200 mcg/day must be considered supportive and not definitive.

8.3.5.2 Overall Safety Conclusions

It appears that in this age range (4 - 11 year olds) for a 4 week treatment period, Flonase is well tolerated. Regarding particularly the more relevant FP100 dose, it appears that the local toxicity profile is quite acceptable.

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23 **Information taken from table 53 on page 127 in vol. 1.014 and appendix 9**

Some of the concerns raised by the review of the two US SAR trials are not borne out in this trial, particularly the apparent relationship to wheezing/asthma and active treatment. The occurrence of epistaxis and pharyngitis appears not to be related to active treatment in this trial. As for systemic safety, there are no clear indications of a substantial effect, although again, we have no definitive tests of systemic activity (other than the rather crude looks at differential WBC counts and glucose).

8.4 STUDY FLNT60[24]

"A double-blind comparison of fluticasone propionate aqueous nasal spray 100 µg given once daily, fluticasone propionate aqueous nasal spray 200 µg given once daily and placebo nasal spray given twice daily in the treatment of perennial rhinitis in paediatric patients (aged 4 - 11 years) " [sponsor title]

8.4.1 Objectives/Rational

To compare the efficacy and safety FP 100 µg QD and 200 µg QD versus placebo in the treatment of perennial allergic rhinitis in children ages 4 - 11 over a 4 week treatment period.

8.4.2 Design

Thirty eight centers in nine countries (Denmark, Finland, Greece, Iceland, Israel, Italy, South Africa, Spain and the UK), randomized, double-blind, placebo-controlled, parallel group study of 4 weeks duration, with a 2 week follow-up period.

8.4.3 Summary of the Study Protocol (as amended)

8.4.3.1 Population

Inclusions: Male or female patients, 4 - 11 (targeted for ≥1/3 between the ages of 4 - 7) years who have moderate to severe perennial rhinitis with the following symptom requirements:

> two or more symptoms (nasal blockage, rhinorrhea, sneezing, nasal itching or post-nasal drip) regarded as severe on study entry

Exclusions: Lack of symptoms on study entry; physical nasal obstruction; serious or unstable concomitant diseases; infections of the respiratory/sinus/nasal tract; contraindication to or history of adverse reactions to corticosteroids; inability to withdraw from treatment of nasal symptoms at the start of the study; nasal surgery in the previous six weeks; systemic or inhaled corticosteroids for the previous month before

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the start of the study and intranasal steroids in the previous two weeks; exposure to inhaled cromolyn or nedocromil within the previous 2 weeks prior to the study; oral astemizole in the previous 6 weeks; immunotherapy in the prior 12 months.

8.4.3.2 Treatment Arms

Fluticasone 100 µg/day -	**1 spray of 50 µg/spray FP in each nostril QAM**
Fluticasone 200 µg/day -	**1 spray of 100 µg/spray FP in each nostril QAM**
Placebo -	**1 spray of 0 µg/spray FP in each nostril QAM**

Comment: *This study also allowed use of rescue antihistamine. In this case, that rescue medication was determined by the country in which the study was conducted, but generally represented 4 mg of chlorpheniramine tablets or syrup. Note also that the 200 mcg dose of fluticasone was administered as a formulation that is not approved in the US, being 100 mcg per actuation rather than the approved 50 mcg (0.05%) formulation. This will impact on the interpretability of the FP200 dosing.*

8.4.3.3 Assignment to Treatment

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

8.4.3.4 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.

8.4.3.5 Dosing

The study drug was administered QD as above. The times specified were not exact, but rather "morning only."

8.4.3.6 Study sequence

There are 4 visits, a screening visit, 2 treatment visits at weeks 2 and 4 and a follow-up visit at week 6.

8.4.3.7 Assessments

Standard assessments similar to the previously detailed studies were performed. It should be noted that skin prick testing was done at entry for the following antigens: house dust, house dust mites, animal dander (dog, cat) and molds. 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), and daily rescue medication use. A.M. cortisols were the only assay used for HPA axis assessment.

8.4.3.8 Concurrent Medications Exclusions: All medications which might affect nasal function will be excluded for the entire study period, except for the

rescue antihistamine provided.

8.4.3.9 Endpoints

Two populations were defined by the sponsor. The intent-to-treat population consisted of all patients randomized to treatment. This population was subgrouped by allergic status on skin prick. The efficacy population was defined as those who adhered closely to the protocol, except for the inclusion of some subjects out of the age range (high and low).

Efficacy parameters:

Efficacy variables included the assessment of patient's rated symptom scores (presumably surrogate in many cases), investigator rated nasal symptoms, and diary recorded 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 placebo. This was to be supplemented by an analysis of all days where scores of 1 or less (i.e., < 2) were recorded. Secondary analyses include assessments of all other nasal component scores, and patients overall assessment, as well as rescue antihistamine use.

Safety Endpoint Parameters:

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

8.4.3.12 Statistical Analysis

The power calculations are 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 35% and therefore planned the sample size of the study to achieve an 80% power to detect a difference of 14% in the mean percent of symptom-free days, with an α of 0.05. The target enrollment ($\geq$386 subjects) was for sufficient size to achieve 300 evaluable patients, 100 in each treatment arm.

Comment ***Although prior experience helped the sponsor identify what they felt to be an appropriate standard deviation, the effect size which they would like to achieve is based more on this than any clear argument of clinical meaning for that effect size.***

1. Efficacy Analysis

   The analysis of percent symptom free days and of days with a score less than 2 was to be based on Wilcoxan rank-sum testing. Adjustment for centers was to be done by the van Elteren method. Study centers with low enrollment were to be combined. The

primary comparison of interest was of the active groups to placebo, with a secondary interest in the comparison between FP groups.

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

8.4.3.13 Amendments to the protocol

Minor changes which are reflected in the protocol summary above.

8.4.4 **Results**

8.4.4.1 Study population characteristics

The study was conducted from October of 1991 to March of 1992. A total of 415 subjects were recruited (the target of 386 being exceeded) into the study: 138 were randomized to FP100, 136 to FP200, and 141 to placebo. The intent-to-treat population was further refined for the record card analysis to eliminate those with less than 10 days' data or no available data , or inability to characterize disease status (PAR vs. PNAR). This led to an elimination of 15 subjects, roughly evenly distributed across groups. The efficacy population was 339 (target of 300). The most common reason by far for exclusion from the efficacy population was failure to meet eligibility criteria (inclusion and exclusion) accounting for 51 out of the 76 subjects excluded. Disallowed drugs only accounted for 5 total exclusions from this population - 1 in each active treatment and 3 in placebo.

Demographics revealed reasonably good balance between dosage groups for the reported characteristics, including age, gender, and ethnic characteristics.[25] It should be noted, however, that there was a substantial paucity of blacks in the study (3 subjects in all) which certainly under represents this group compared to the US population. Also, although gender make-up was almost identical across groups, males outnumbered females overall in the study (62%).

Baseline clinical characteristics related to atopy and allergy history were comparable, including the balance of PAR to PNAR (65% to 32% overall, with 2 not recorded). The majority of subjects who were allergic reacted to skin prick testing for house dust mites, followed numerically by cat and house dust.

8.4.4.1.1 Concurrent Medication use

The use of concomitant medications was similar between groups.

8.4.4.2 Efficacy Analysis

8.4.4.2.1 *Data set analyzed*

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25 **table 11 of vol. 1.015, page 62**

Data analysis was performed on the intent-to-treat population and efficacy populations as defined above. Testing for interactions by treatment, by center and by allergic classification were conducted as well.

8.4.4.2.2 Percentage of Patient Rated Symptom-free days

The percentage of symptom free days is reported for each component of the subject's ratings of their nasal scores, although the primary comparisons were designated *a priori* only as the percent of symptom free days for nasal blockage on awakening, during the day and rhinorrhea. These three primary comparisons are presented below for the entire treatment period in a tabular summary:

Symptom # subjects in analysis n =	FP 100 132	FP 200 131	Placebo 136
Nasal Blockage on awakening			
mean % symp. free days	26	25	20
median % symp. free days	11	11	7
lower quartile	0	0	0
upper quartile	43	43	31
adjusted p value (vs. Placebo)	.484	.108	*FP vs. FP p = .621*
Day time Nasal Blockage			
mean % symp. free days	36	35	30
median % symp. free days	26	25	16
lower quartile	0	0	0
upper quartile	64	62	57
adjusted p value (vs. Placebo)	.220	.124	*FP vs. FP p = .685*
Rhinorrhea			
mean % symp. free days	47	46	35
median % symp. free days	45	46	27
lower quartile	11	11	4
upper quartile	78	79	58
adjusted p value (vs. Placebo)	**.014**	**.005**	*FP vs. FP p = .894*

Statistically, there is only a separation of the active treatments from placebo on the percent of rhinorrhea symptom free days, out of the three "primary" efficacy variables. It is notable that other than for rhinorrhea, the p values aren't even very close to 0.05, indicative that there is not even much of a trend towards an effect, especially for the more relevant dose. This despite the study achieving a sample size in excess of the planned enrollment. The sponsor makes no mention of how they planned to regard a situation where only one of there 3 primary comparisons showed significance. However, if they had planned on declaring a win for any of the three coming out as a winner, they would have needed to correct for multiple comparisons. It appears, therefore, that they had not planned to declare a "win" based solely on one or two of these comparisons being positive.

A consideration of the % of symptom free days for the non-primary component scores adds some information to the above. There appears to be meaningful treatment differences in the mean percent of sneezing

free days for both FP doses compared to placebo, but not to each other (p= 0.05 for FP100; 0.03 for FP200 and 0.830 for FP vs. FP). On nasal itching/rubbing there is no difference between any of the treatments. When considered overall, it appears that the FP200 dose is superior to placebo (p=0.024) but not the FP100 dose (p=0.112). These doses again do not separate from each other, however.

8.4.4.2.3 Percentage of Days with Scores less than 2

This analysis adds little to the consideration of efficacy, but does demonstrate some intriguing disparities. Only the FP100 dose separates from placebo on any of the component scores, and then only for sneezing and rhinorrhea. These results must be looked at as somewhat questionable, however, as this analysis may not be a very sensitive way to approach the symptom scoring.

8.4.4.2.4 Diary Recorded Use of Rescue Antihistamine

The use of rescue antihistamine was tracked in the subject daily diaries. It should be noted that few subjects appeared to be using rescue medication during the trial, even for placebo (averaging 82% of subjects not using rescue on any given day in placebo, with a median of 100% when the total duration of the trial is considered). It is unlikely that even a dramatic treatment effect on this endpoint could have been shown statistically given how little rescue was used in the placebo arm. This was born out in the statistical analysis where the comparisons for percent of rescue free days showed p values of 0.246 for FP100, 0.424 for FP200 and 0.607 for FP vs. FP.

8.4.4.2.5 Investigator's Rating of Nasal Symptoms

This analysis actually appears to offer more support of efficacy than the subject ratings do. A presentation of these data is offered by the sponsor for each symptom component score at each clinic visit (i.e., visit 1 is week 0, visit 2 is week 2 and visit 3 is week 4). An analysis based on proportional odds was performed. No adjustment for multiple comparisons was apparently made. In this assessment, it appears that there is a trend favoring active treatment in virtually all comparisons. However, it only reaches a level of <0.05 for the following scores (times):

Treatment(s)	visit #	symptom/sign	relative odds	p value
FP100	2	post-nasal drip	0.5	0.007
FP100	2	nasal itching	0.59	0.028
FP100; FP200	2	rhinorrhea	0.54; 0.52	0.008; 0.006
FP200	3	nasal itching	0.49	0.006
FP200	3	rhinorrhea	0.55	0.012

8.4.4.2.6 Investigator's Rating of Nasal Examinations

The results of the investigator examinations of the nasal passages revealed no striking supportive data, since improvement was seen in all subjects regardless of treatment assignment. However, for some categories such as secretions, there was a not too impressive trend that favored active treatment.

8.4.4.2.7 Subgrouping by Skin Test Results[26]

A presentation of the efficacy parameters for subjects grouped into PAR versus PNAR by skin prick test results does not add much to the above results. The apparent trends favoring active treatment were observed in many parameters for both subgroups and for the most part do not appear any more striking for the allergic population than the non-allergic group. Although no statistics were given (or appropriate) on these groups, it appears that there were some noticeable differences in the efficacy results for sneezing and daytime nasal blockage in the two subgroups, with a more discernable trend towards a treatment effect on these parameters in the PAR group.

8.4.4.3 Safety Analysis

The safety analysis included all patients who received any study drug, a total of 415 subjects. These 415 were broken down into 130 in the FP 100 group, 130 in the FP 200 group and 139 in the placebo group. There were only a few exceptions to a full exposure time, with 8 in FP100, 8 in FP200 and 3 in placebo being treated for three weeks or less (see below for details).

8.4.4.3.1 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% or more patients in any treatment group OR categories of potentially expected topical / corticosteroidal effects)[27]:

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26 tables 45-51 of vol. 1.015, page 117-133

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

Adverse Event		Placebo N (%)	FP100 N (%)	FP200 N (%)
Total Pt. Numbers		139	130	130
Number of Subjects with events		57 (40)	64 (46)	57 (42)
Total Events reported		88	103	90
ENT	All	28 (20)	36 (26)	24 (18)
	URTI/viral RI	16 (12)	17 (13)	14 (11)
	Sore throat	4 (3)	3 (2)	5 (4)
	Epistaxis	2 (1)	9 (7)	2 (1)
	Ear problems (NOS)*	3 (2)	8 (6)	3 (2)
Neuro	Headache	6 (4)	6 (4)	7 (5)
Respiratory	All	23 (16)	21 (15)	17 (13)
	Asthma events	14 (10)	8 (6)	7 (5)
	Cough	6 (4)	10 (7)	6 (4)
	Respiratory Infection	4 (3)	2 (1)	4 (3)
General	Influenza	2 (1)	5(4)	4 (3)

** includes tympanitis, otitis media, otitis, ear infections, ear pain and secretory otitis media*

This adverse event profile is not too dissimilar to that seen in other studies. It is interesting to note that for asthma events, the highest occurrence was in the placebo group, which argues somewhat against the conclusion stemming from the results of the SAR trials. Although there were more AE's reported and more subjects with AE's in active treatment than for placebo, there appear to be no events which clearly occurred in a dose dependant manner. In many circumstances, including the overall occurrences, it appears that the FP100 dosage was less well tolerated than the FP200 dosage. Again, the meaning of this observation in relation to the sNDA is unclear since the FP200 dose was a different formulation than available in the US. However, like FLNT 52, these data support a concentration effect (that is that the 0.1% formulation may be better tolerated locally than that marketed in the US).

8.4.4.3.2 Adverse Event Severity

There were no deaths reported in this trial. Only two serious adverse events were reported, both were the sequelae of trauma. There was no plausible connection to study treatment / assignment. There were 6 subjects withdrawn for adverse events, 2 in the FP100 group, 2 in the FP200 group and 2 in the placebo group.[28] A review of the sponsor's accounting for withdrawals after randomization reveals that in addition to

28 **Information taken from table 6 on page 57 and appendix 10, page 244-45 in vol. 1.015**

these 6 subjects, there were 18 subjects who withdrew either for a desire not to continue or a failure to return. These events were less balanced than the withdrawals for adverse events with 9 in the FP100 group, 6 in the FP200 group and 3 in the placebo group. It is possible that these withdrawals represent unreported AE's leading to withdrawal although that cannot be ascertained with certainty. The two events leading to withdrawal in the FP100 group were a 7 year old subject withdrawn for influenza, cough and vomiting on day 9, and a 9 year old subject withdrawn on day 10 for treatment of an asthma exacerbation. The two cases in the FP200 group were an 8 year old subject withdrawn for an acute viral infection on day 7 of treatment, characterized by fever, cough, general malaise and chest pain, along with an 11 year old subject withdrawn for an acute URI with fever on day 20 of treatment. The placebo subjects withdrawn include a 10 year old subject withdrawn for asthma on day 20 following a URI episode 11 days earlier. There was also an 8 year old withdrawn for a URI, with fever and acute tonsillitis.

8.4.4.3.3 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. Three subjects occurred in the FP100 group, and 7 each in the FP200 and placebo groups.

Comment - ***Given the high occurrence of such shifts in the placebo group, nothing definitive can be concluded from these studies about the systemic safety of FP in these doses. However, given all the caveats about the problems with a.m. cortisol assessments, these data do not raise any alarms about undo suppression.***

8.4.4.3.5 Laboratory Abnormalities / Changes

There were a few interesting findings in the shift tables that may relate to systemic effects of FP. There were 7 and 8 patients respectively in the FP100 and 200 groups that experienced a fall from high or normal eosinophils to low, with only one such subject in the placebo group. Conversely, there were 14 subjects in the placebo group who went from low or normal to high for eosinophil counts, as opposed to 2 and 8 in the FP100 and 200 groups. This is at least compatible with a systemic action of FP. However, no such shifts in relation to active treatment were noted in the lymphocyte counts. As for other routine values, there were some disparities for serum calciums and ASTs in the FP100 groups versus placebo, but these were not accompanied by any such abnormalities in the FP200 group which argues for these findings being spurious rather than active treatment related.

8.4.4.3.6 Vital Signs

No important signals were noted for vital signs.

8.4.4.3.7 Physical Examination

Physical examinations were noted above in the efficacy discussion for nasal findings. General examinations did not reveal any worrisome trends. Particularly, wheezing was no more commonly noted with active treatment than in placebo. Most noted findings were for ear, throat or common adenopathy related to URTI.

8.4.5 Conclusions

8.4.5.1 Efficacy Conclusions

As opposed to FLIT-61, a review of which follows, this is a placebo controlled trial of adequate duration and enrollment to examine the efficacy of FP in this population of PAR and PNAR afflicted children. Unfortunately, the efficacy results are less than striking, with only occasional findings of statistical significance for the active treatments versus placebo. When examined for trends, it does not appear that the efficacy results strongly support any dose response, although on almost all measures it appears that overall active treatment is numerically better than placebo, albeit rarely significantly so.

Since Flonase has been approved for PAR in adults and since these doses have been shown to have some efficacy in SAR in the pediatric age range, it may be reasonable to infer efficacy for PAR in the pediatric population based primarily on the finding in adults with PAR along with the findings for SAR in children and to consider this inference as balanced by all the existing safety data. This issue will be further discussed in the ISE.

8.4.5.2 Overall Safety Conclusions

It appears that in this age range (4 - 11 year olds) for a 4 week treatment period, Flonase is well tolerated. Regarding particularly the more relevant FP100 dose, it appears that the local toxicity profile is acceptable. This study, along with FLNT52, again refutes the apparent association raised by the review of the US SAR trials between wheezing/asthma and active treatment. In this trial, the highest number of asthma events occurred in the placebo arm. The occurrence of epistaxis and pharyngitis appears not to be related to active treatment in this trial. As for systemic safety, there are no clear indications of a substantial effect. However, the relative fall in eosinophil counts in active treatment compared to placebo at least raises the possibility that the FP was systemically absorbed and active at these doses in this population.