(II) Exclusion Criteria [NDA 20-121, S-009, 21:21-23, 134-135]:

1. Physical obstruction of the nares, as defined by septal deviation (≥ 50% obstruction by physical exam) or nasal polyps that could obstruct delivery of the nasal spray.
2. History of previous nasal or sinus surgery or nasal septal perforation.
3. History of reported abuse of cocaine at any time prior to the study.
4. Presence of any disease state which could place the patient at significant risk through study participation or could affect the analysis of response to therapy if the disease exacerbated during the study, as determined by the clinical investigator: i.e. corticosteroid-dependent asthma, immunologic compromise, perennial and active SAR, rhinitis medicamentosa or reported chronic use of nasal decongestants, malignancy, clinically significant cardiovascular, hepatic, neurologic, endocrine, (or other major systemic disease which would make interpretation of the protocol results difficult).
5. Clinical laboratory abnormalities that would confirm the diagnosis of the concurrent diseases listed above (in (3)).
6. History of hypersensitivity reactions to any intranasal, inhaled, or systemic corticosteroid therapy.
7. The use (regular or prn) of other prescription or OTC drugs that could affect the course of rhinitis for at least 72 hours prior to screening (visit 1) and throughout the double-blind treatment period. Specific criteria regarding restricted and concurrent medication use is summarized in Section (III) below.
8. Concurrent bacterial or viral infection (e.g. URI) that could confound analysis of efficacy. Patients with sinusitis would be excluded from the study based on sinus radiograph [redacted] results.
9. Use of any investigational new drug within 3 months prior to the screening visit.
10. Patients with intolerable symptoms that would make participation in the study unbearable.
11. Concurrent use of cigarettes, cigars, pipes, or marijuana.
12. History of previous enrollment in a NAPR study with fluticasone propionate aqueous nasal spray.
13. Females who are pregnant, lactating, or not using a medically acceptable form of birth control.

Reviewer's Note: The clinical criteria (e.g. specific radiographic findings, additional reliance on culture results) for defining 'sinusitis' were not discussed in the study report but were

discussed in the study protocol as: 'presence of mucosal thickening > 6 mm or an air fluid level or opacification' [NDA 20-121, S-009, 21:22, 135].

(III). Concurrent Medication Restrictions [NDA 20-121, S-009, 21:22-23, 134-135]:
The following medications were to be discontinued within the indicated time periods prior to visit 1, and were not allowed throughout the study duration:

	Medication	Time Discontinued Prior to Visit 1 (Screening visit)
1.	Antihistamines	≥ 72 hours
2.	Intranasal sodium cromolyn	≥ 2 weeks
3.	Intranasal, inhaled, or systemic corticosteroids	≥ 1 month
4.	Long term (i.e. ≥ 2 month) oral corticosteroid use (e.g. Prednisone, 20 mg po qd)	≥ 3 months

Patients were allowed to use β-agonists, theophylline, and medium potency topical corticosteroids during the study. As stated above patients requiring ≥ 20 mg prednisone daily (or equivalent doses of other corticosteroids) for ≥ 2 months must have discontinued use of the steroid at least 3 months before enrollment. Use of other prescription or OTC drugs that could affect the course of rhinitis, particularly antihistamines, anticholinergics (including tricyclic antidepressants), decongestants, sinus medications, cough/cold formulations, NSAIDs (except occasional use), high-dose birth control pills, β-blockers, and rauwolfia compounds would result in patient exclusion from participation in the trial.

Reviewer's Note: Again, similar to the pivotal study FLTA 3010, the medication exclusion criteria and concomitant wash-out periods were probably acceptable but not well-defined in terms of specific medication classes or products which comprise the different categories of restricted medications or the specific time periods that would be required for washout. For example, there is no mention of β-agonist (short or long-acting) restrictions, tricyclic antidepressant drugs, MAO inhibitors, depot (I.M. or I.V.) corticosteroids, etc. Furthermore, classes of drugs such as: decongestants, expectorants, sinus medications, cold/cough preparations, β-blockers, 'rauwolfia' compounds (e.g. reserpine)

along with their requisite washout-periods could have been classified in greater detail by the sponsor.

8.2.3.1.b. Procedure

(I) Screening Visit [NDA 20-121, S-009, 21:18-20, 143]:

A complete medical history and physical examination (to include ear and nasal exam, comprised of: an evaluation of the nasal septum, nasal polyps, the degree of enlargement of nasal turbinates, the appearance of the mucosa, and the quantity, consistency, and color of nasal secretions) [NDA 20-121, S-009, 21:17, 139-140] and an evaluation for oral or nasal candidiasis (with cultures obtained if there was clinical evidence of candidiasis in order to confirm the diagnosis) [NDA 20-121, S-009, 21:18, 139]) was performed at the screening visit. In addition, laboratory evaluation (to include a.m. plasma cortisol levels along with routine blood chemistry, hematology, total IgE, urinalysis and tests to rule out pregnancy), sinus radiography (using [redacted]), and confirmation of the patient's allergen hypersensitivity with skin prick testing was performed on all potential patients at the screening visit (at all study sites).

The purpose of the screening visit was to determine if prospective patients met the requisite inclusion/exclusion criteria to qualify for entry into the 0.5-2 week run-in period of the study, to be subsequently followed by the 4 week double-blind treatment period. Patients likewise underwent a self-rated nasal symptom assessment (TNSS) during screening which was used to determine if patients had NAPR symptoms sufficiently severe in order to qualify for study entry (see study inclusion criteria, section 8.2.3.1.a.(I)).

Diary cards for nasal symptom recording were issued to patients during the run-in period and patients were instructed as to their proper completion. Specifically, patients were to subjectively rate the following 4 nasal symptoms reflectively over the previous 24 hours on their diary cards prior to dosing with study medication: (1) rhinorrhea, (2) postnasal drip, (3) sneezing, and (4) nasal itch using the visual analog scale shown in Figure 1 below, which ranged from a score of 0 (=absent symptoms) to 100 (most severe symptoms) in the p.m. (at the end of each day but prior to dosing with study medication) [NDA 20-121, S-009, 21:18, 24-25, 140-141]. Patients additionally recorded the severity of nasal obstruction in the a.m.—upon awakening (and prior to taking the a.m. dose of study drug) [NDA 20-121, S-009, 21:18]. Thus, nasal obstruction was rated both in the a.m. and p.m. prior to dosing with study medication.

Figure 1: Subjective NAPR symptom rating scale:

NAPR Symptoms	Visual Analog Scale
Rhinorrhea	0 (Symptom Absent) —— 100 (Symptom most severe)
Nasal obstruction	0 (Symptom Absent) —— 100 (Symptom most severe)
Postnasal drip	0 (Symptom Absent) —— 100 (Symptom most severe)
Sneezing	0 (Symptom Absent) —— 100 (Symptom most severe)

The physician would then measure the distance (in millimeters) from the 0 score to the mark made by the patient and record the symptom severity number on the case report form (CRF). Beginning with visit 1, patients were instructed not to take any medications aside from study drug for treatment of rhinitis symptoms throughout the double-blind treatment period.

Reviewer's Note: The total nasal symptom score (TNSS) for the double-blind treatment period was calculated by summing the individual reflective symptom scores for nasal obstruction, rhinorrhea, and postnasal drip. Sneezing and nasal itch were excluded from the TNSS. Symptom severity was rated each day (once daily, in the p.m. immediately before dosing with study drug) during the double-blind treatment period for all 3 NAPR symptoms of rhinorrhea, postnasal drip, and nasal obstruction. As stated above, nasal obstruction was also scored in the morning, upon the patient's awakening; thus twice daily recordings of nasal obstruction were available (though not submitted as daily scores or line listings) for study FLN 351.

In addition to patient-rated symptoms (which were recorded once daily by all patients during the double-blind period in the p.m. immediately before dosing with study drug), physician-rated nasal symptoms were also obtained at each clinic visit and these were based on the nasal examination and physician's observation of the patient at the clinic visit (i.e. this was an instantaneous score based on the patient's presentation at the clinic visit and not based on the preceding 24 hours of symptoms). Again, these symptom scores (which were quantified for each individual symptom) were based on a visual analog scale of 0-100. The physician assessed rhinorrhea, nasal obstruction, and postnasal drip but not sneezing [NDA 20-121, S-009, 21:25, 148].

Nasal symptoms were evaluated individually and a TNSS was calculated by summing the individual scores for rhinorrhea, nasal obstruction, and postnasal drip. These evaluations were performed at each clinic visit during the

double-blind treatment period (Day 8, 15, 22, and Day 29) and at the post-treatment assessment visit (Day 36) [NDA 20-121, S-009, 21:25, 143-145].

In order to qualify for enrollment into the double-blind portion of the study, patients were to be sufficiently symptomatic for at least 4 of the 7 days immediately preceding the 1st day of double-blind treatment assignment (of the run-in period) as defined by a **daily total nasal symptom score** (TNSS=composite score of rhinorrhea, nasal obstruction, postnasal drip, of at least 150 out of a maximum score of 400 [NDA 20-121, S-009, 21:21, 142].

(II) Visit 1 (Day 1, 1st day of double-blind study medication) [NDA 20-121, S-009, 21:18, 143]:

After completion of the single-blind placebo lead-in portion of the study, patients underwent re-evaluation of NAPR symptomatology via review of the patient symptom diary and assessment of compliance with study medication for the lead-in period at study visit 1. Adverse events and concurrent medication assessments were reviewed by the investigator.

A repeat nasal/oropharyngeal and ear examination was performed (along with evaluation for oral or nasal candidiasis) and a physician-rated nasal symptom assessment was completed. Nasal cytology using collection of nasal mucosal cells via the [redacted] was performed at this visit in order to identify patients with non-allergic rhinitis eosinophilic syndrome (NARES) [NDA 20-121, S-009, 21:18, 140]. The relative numbers of eosinophils using this technique were assessed using the 5-point scale summarized in Figure 2 [NDA 20-121, S-009, 21:24, 140]:

Figure 2: Nasal Cytology Scale

0	=No eosinophils
1	=Few, scattered eosinophils
2	=Moderate #, small clumps of eosinophils
3	=Large clumps of eosinophils, not covering entire field
4	=Clumps of eosinophils covering the entire field

Reviewer's Note: As stated previously in the medical officer review of FLTA 3010, the nasal cytology scale employed a quasi-subjective rating system that was used by the investigating physician to broadly quantify the degree of eosinophilia in participating patients' nasal secretions.

In addition, a pharmacoeconomic survey was completed by participating patients on visit 1 of the study, although results were not discussed in the sponsor's study report for FLN 351. [NDA 20-121, S-009, 21:18, 141].

Study enrollable patients were given new diary cards to record twice daily nasal symptoms and study medication usage (the latter, for assessment of compliance), and randomized to 1 of 3 study medication groups according to a computer generated code. Patients were then administered the 1st dose of study

medication in the clinic (hence the 1st dose of study medication was administered in the a.m.). The 3 treatment groups were as follows [NDA 20-121, S-009, 21:23, 143]:

Double Blind Treatment Groups:	
STUDY GROUPS	**DOSING**
(1) **Fluticasone propionate nasal spray 100 µg bid** (25 µg/actuation)	**2 sprays bid** (q a.m. and p.m.)
(2) **Fluticasone propionate nasal spray 200 µg bid** (50 µg/actuation)	**2 sprays bid** (q a.m. and p.m.)
(3) **Placebo**	**2 sprays bid** (q a.m. and p.m.)

Blinding of the 3 study medications were as per blinding in pivotal study FLTA 3010, such that bottles were identical in appearance (25 mL amber glass bottles of 200 sprays/bottle fitted with a white pump and dust cover) but differed in the concentration of FP in each bottle [NDA 20-121, S-009, 21:23; and Teleconference, 03/29/98, Mrs. Alison Bowers of Glaxo Wellcome, U.S. Regulatory Affairs and FAX, 04/02/98, Mrs. Alison Bowers of Glaxo Wellcome, U.S. Regulatory Affairs, p. 1-2 and FAX, 04/10/98, Mrs. Alison Bowers of Glaxo Wellcome, U.S. Regulatory Affairs, p. 3]. The concentrations of fluticasone propionate in the 100 µg bid and 200 µg bid doses (and respectively, the dose of FP/actuation) were the same as those utilized in FLTA 3010.

Patients in each group were instructed to take medication administered as the same number of sprays (2 sprays) in each nostril, morning and evening (approximately 12 hours apart. Patients were dispensed with a 2 week supply of study medication and instructed to return in 7 days to clinic, having withheld their a.m. dose of study medication prior to clinic evaluation.

(III) Visit 2 (Day 8) [NDA 20-121, S-009, 21:19, 143]:

During visit 2 of the study, NAPR symptoms were again assessed by the investigator (the physician-rated TNSS) and patient diaries were collected, with new diaries assigned. Again, AEs and concurrent medication use was assessed by the investigator. A follow-up nasal/oropharyngeal and ear examination was performed (along with evaluation for oral or nasal candidiasis but with no nasal cytology performed at this visit). Patients were given a new batch (1 week supply) of study medication with instructions to return to clinic for reassessment in 1 week.

(IV) Visit 3 (Day 15) [NDA 20-121, S-009, 21:19, 144]:

During visit 3 of the study, NAPR symptoms were again assessed by the investigator (the physician-rated TNSS) and patient diaries were collected, with new diaries assigned. Again, AEs and concurrent medication use was assessed by the investigator. A follow-up nasal/oropharyngeal and ear examination was performed (along with evaluation for oral or nasal candidiasis but with no nasal cytology performed at this visit). Patients were given a new

batch (1 week supply) of study medication with instructions to return to clinic for reassessment in 1 week.

In addition to patient-rated total nasal symptoms, at visits 3 and 6 (or at the time of early patient discontinuation), patients subjectively rated their overall response to treatment during the double-blind treatment period (visit 3) or after completion of the study and 1 week after discontinuation of study medication (visit 6) using the 7-point ordinal scale summarized in Figure 3 below [NDA 20-121, S-009, 21:25, 141]:

Figure 3: Patient-self Rated Overall Response to Therapy Evaluation Using An Ordinal Scale

Significant Improvement
Moderate improvement
Mild improvement
No change
Mildly worse
Moderately worse
Significantly worse

Physicians were likewise asked to rate patients' overall response to therapy using the same scale as the overall patient evaluation for visits 3 and 6 (or at the time of early patient discontinuation), albeit with the addition of a 'not evaluable' category to the ordinal scale (see Figure 4 below):

Figure 4: Physician Rating of Patients' Overall Response to Therapy Evaluation Using an Ordinal Scale [NDA 20-121, S-009, 21:25, 140]:

Significant Improvement
Moderate improvement
Mild improvement
No change
Mildly worse
Moderately worse
Significantly worse
Not evaluable

(V) Visit 4 (Day 22) [NDA 20-121, S-009, 21:19, 144]:

During visit 4 of the study, patients underwent repeat physical examination (including the nasal/oropharyngeal and ear examination, evaluation for oral or nasal candidiasis), along with a review of NAPR symptoms and concomitant medications by the investigator. Patient-rated and physician-rated overall evaluation of response to therapy was performed on this last visit of the double-blind treatment period.

(VI) Visit 5 (day 29, last day of the double-blind treatment period) [NDA 20-121, S-009, 21:19, 145]

During visit 5 of the study, patients underwent repeat physical examination (including the nasal/oropharyngeal and ear examination, evaluation for oral or nasal candidiasis, and nasal cytology), repeat laboratory testing (including a.m. plasma cortisol levels and serum IgE levels), along with a review of NAPR symptoms and concomitant medications by the investigator. Patient-rated and physician-rated overall evaluation of response to therapy was performed on this last visit of the double-blind treatment period. Another pharmacoeconomic survey was completed by patients.

(VII) Visit 6 (day 36, 7 days post-completion of treatment) constituted the final study visit. This visit was primarily comprised of follow-up physician symptom scoring, nasal examination, and AE assessment. Repeat laboratory tests were only performed (including a.m. cortisol levels) if Visit 5 lab tests were found to be abnormal [NDA 20-121, S-009, 21:20, 145].

(VIII) Collection of pollen counts:

For the purposes of this study, which was to assess the therapeutic response of non-allergic perennial rhinitis patients, pollen counts were not collected on a daily basis by the sponsor, nor recorded in a log.

(IX) Safety evaluations [NDA 20-121, S-009, 21:26-28, 137-139]:

In addition to the review of all adverse events (AEs) by the investigator, performance of routine laboratory tests, and physical examination performed at each clinic visit (with an emphasis in detecting potential adverse side effects associated with corticosteroid treatment), measurement of a.m. plasma cortisols was performed prior to dosing with a.m. study medication at screening and day 29 of the study (between 6:30 a.m. and 9:30 a.m.).

An a.m. cortisol level of at least 5 µg/dL was required for study entry [NDA 20-121, S-009, 21:27, 139] and an a.m. plasma cortisol level ranging from 5-18 µg/dL was considered in the normal range [NDA 20-121, S-009, 21:43]. Patients were instructed to fast overnight (~ 8 hours) for all clinical laboratory tests.

8.2.3.2. Clinical Endpoints:

Primary and secondary efficacy variables were not pre-specified in study FLN 351. The following efficacy variables were assessed in this NAPR study [NDA 20-121, S-009, 21:27, 30, 139, 147]:

(1) The change from baseline (defined as Visit 1) in the patient-rated average reflective daily TNSS (=sum of rhinorrhea, nasal obstruction, and postnasal drip) for **each week** of the double-blind period. **Because the powering of the study was based on this endpoint, this efficacy variable was taken to be the 'primary efficacy variable' for study FLN 351.**

(2) The change from baseline (defined as Visit 1) in the patient-rated average reflective daily individual nasal symptom scores: rhinorrhea, postnasal drip, sneezing, nasal itching, and a.m. nasal obstruction for **each** week of the double-blind period.
(3) The change from baseline (defined as Visit 1) in the physician-rated average reflective daily TNSS (=sum of rhinorrhea, nasal obstruction, and postnasal drip) for **each** week of the double-blind period.
(4) The change from baseline (defined as Visit 1) in the physician-rated average reflective daily individual nasal symptom scores: rhinorrhea, postnasal drip, sneezing, nasal itching, and a.m. nasal obstruction for **each** week of the double-blind period.
(5) Patient-rated overall evaluation of response to therapy at Visit 3 and 6.
(6) Physician-rated overall evaluation of response to therapy at Visit 3 and 6.

Reviewer's Note: Given a symptom score range of 0-100 for any individual NAPR symptom, patients could achieve a TNSS ranging from 0-400, based on the sponsor's definition of TNSS. The primary efficacy endpoint and primary comparison of interest (FP 100 μg bid vs. placebo) was not specified by the sponsor in either the study protocol or study report. Given that the study was powered on the 'mean change in patient-rated TNSS from baseline', this endpoint was taken to be the primary efficacy endpoint for FLN 351.

8.2.3.3. Statistical Analysis [NDA 20-121, S-009, 3:63, 21:29-30, 147-148]

The study was conducted with a target enrollment of 360 patients. A minimum sample size of 100 patients per treatment arm (or 300 patients total) was calculated in order to detect a treatment difference of at least 25 points in the **patient-rated TNSS symptom score**, between placebo and the 3 FP treatment groups, based on a 2-sided α=0.05, a power of 80%, and an estimated standard deviation of 70 points for the TNSS. This estimated sample size was based on results from NAPR study FLN-350 [NDA 20-121, S-009, 21:29, 148].
The patient-rated and physician-rated overall response to therapy was tabulated, and the Cochran-Mantel-Haenszel test was used to detect statistically significant differences between treatment groups [NDA 20-121, S-009, 3:63].

All efficacy variables were analyzed for intent-to-treat patients (patients who were exposed to double-blind medication with baseline and post-baseline symptom assessments) [NDA 20-121, S-009, 21:29]. An 'evaluable' efficacy population (i.e. all patients who had no major protocol violations as determined by the investigator(s)) was used to support results for the primary efficacy variable in the intent-to-treat population. Safety analyses were based on the intent-to-treat population who underwent evaluation for adverse event occurrence, clinical laboratory tests (including tests to assess adrenal function), vital signs, physical examination.

Same as in study FLTA 3010, missing symptom scores used to generate a total symptom score were handled by **not** replacing (or 'imputing') a particular missing score and with no last observation carried forward. In the case of missing diary card values, means were computed from the available data for that time period (i.e. week) [FAX, 04/02/98, Mrs. Alison Bowers, Glaxo Wellcome, U.S. Regulatory Affairs, p. 2].

All efficacy variables were analyzed using 2-way analysis of variance (ANOVA), which used the F-test to assess statistically significant differences between treatment groups with regard to changes in mean weekly scores or mean scores per visit from baseline [NDA 20-121, S-009, 21:30, 148]. Both overall treatment comparisons and pairwise treatment comparisons were performed for the patient-rated and physician-rated nasal symptom scores. Subsequent pairwise comparisons were interpreted in the presence of all significant overall tests. Patient-rated symptom scores were averaged across each study week and summarized by treatment group. Physician-rated symptom scores were summarized at baseline and at all subsequent visits. Patients' and physicians' overall evaluation of response to therapy were tabulated, and the Cochran-Mantel-Haenszel test was used to detect statistically significant treatment differences. Subgroup analysis by age, gender, race, weight, severity of symptoms, or other demographic characteristics was not performed by the sponsor for either the primary or secondary efficacy variables.

The safety assessment of adrenal response was presented as a tabulation of the mean baseline and mean change from baseline in a.m. plasma cortisol levels. ANOVA was utilized in order to determine significant differences between treatment groups.

8.2.4. Results

8.2.4.1.a. Patient Demographics

(A) A total of 286 patients with a history of NAPR (and a negative skin test to all allergens relevant to the geographic area of each study site) were randomized into the study (less than the target 300 patient enrollment). Ninety-three (93) patients were randomized to placebo, 98 were assigned to FP 100 μg bid, and 95 were assigned to FP 200 μg bid [NDA 20-121, S-009, 21:31] and these patients comprised the intent-to-treat population (ITT). Two hundred and seventy four patients (274, or 96% of all patients randomized into the double-blind portion of the study) completed the double-blind portion of the study and 12 patients withdrew from the study prior to study completion: 5 from the placebo group, 4 from the FP 100 μg bid, and 3 from the FP 200 μg bid group.

A distribution of the patient population is summarized in Table II. below:

Table II. Patient Disposition [NDA 20-121, S-009, 21:31]

	DOUBLE-BLIND TREATMENT PERIOD			
PATIENT DISPOSITION	Placebo	FP 100 µg bid	FP 200 µg bid	Total
Enrolled Patients	93	98	95	286
Intent-to-Treat	**93**	**98**	**95**	**286**
Safety Evaluable (same as ITT)	93	98	95	286
Completed Study	88	94	92	274

(B) As discussed above, a total of 12 patients withdrew from the double-blind portion of the study prior to study completion, leaving 274 patients who completed the entire double-blind portion of the study. No overwhelming reason for early discontinuation was noted in the double-blind portion of the study, with adverse events (AE) being the most common reason for early withdrawal. The highest incidence (5%) of discontinuation was noted in the placebo group, [NDA 20-121, S-009, 21:3, 31, 56]. This data is summarized in Table III. [NDA 20-121, S-009, 21:3, 31, 56].

Table III. Number and Percentage (%) of Randomized Patients Who Discontinued the Study with Reasons for Discontinuation, ITT Population [NDA 20-121, S-009, 21:3, 31, 56]:

	DOUBLE-BLIND TREATMENT PERIOD			
	Placebo	FP 100 µg bid	FP 200 µg bid	Total
Number Enrolled	93	98	95	286
Number (%) Withdrawn	5 (5%)	4 (4%)	3 (3%)	12 (4%)
Reason for Discontinuation				
Adverse event	2 (2%)	3 (3%)	1 (1%)	6 (2%)
Lack of Efficacy	1 (1%)	0 (0%)	0 (0%)	1 (0.3%)
*Other	2 (2%)	1 (1%)	2 (2%)	5 (2%)
ALL REASONS	5 (5%)	4 (4%)	3 (3%)	12 (4%)

*Other: includes reasons, for e.g. withdrawal of consent, protocol violation, moving away.

Reviewer's Note: The total % of patient discontinuation was less than 10% of the total number of patients randomized into the study. The overall discontinuation rate for all 4 treatment arms was approximately 4%, which represents a reasonable rate of premature patient discontinuation for the double-blind period. Overall, the reasons for early patient discontinuation were deemed acceptable by the medical reviewer, although these reasons were not elaborated in as much detail as in study FLTA 3010 (e.g. failure to return to study).

(C) Pooled demographic data with regard to patient characteristics in the intent-to-treat population (ITT) for the double-blind treatment period are summarized in Table IV. below

Table IV. Patient Demographics for the ITT Population-Double Blind Treatment Period [NDA 20-121, S-009, 21:60-61]:

Variable	Placebo (n=93)	FP 100 µg bid (n=98)	FP 200 µg bid (n=95)	P-Value
Gender: (n, (%))				
Male	38 (41%)	50 (51%)	38 (40%)	0.234
Female	55 (59%)	48 (49%)	57 (60%)	
Race: (n, (%))				
Caucasian	89 (96%)	97 (99%)	91 (96%)	0.459
Black	1 (1%)	1 (1%)	3 (3%)	
Asian	0 (0%)	0 (0%)	0 (0%)	
Hispanic	2 (2%)	0 (0%)	0 (0%)	
Other	1 (1%)	0 ()%)	0 (0%)	
Age: (yrs)				
Mean ± SE	42.0 ± 1.6	39.7 ± 1.4	38.9 ± 1.6	0.283
Range	14-79	12-83	13-75	
Weight: (lbs.)				
Mean ± SE	160.8 ± 3.2	164.1 ± 3.2	160.4 ± 3.9	0.680
Range	114-233	105-291	97-290	
History of Non-allergic rhinitis:				
1-5 years	22 (24%)	17 (17%)	21 (22%)	0.819
6-10 years	16 (17%)	24 (24%)	23 (24%)	
11-20 years	29 (31%)	32 (33%)	28 (29%)	
> 20 years	26 (28%)	25 (26%)	23 (24%)	

P-value for gender, ethnic origin, and history of NAPR based on the Chi-square test.
P-value for age and weight based on the F-test.

Reviewer's Note: Overall, the 3 treatment groups were well-balanced in comparison to one another from a demographic standpoint. No statistically significant differences for any of the parameters evaluated were noted amongst the 3 treatment groups. The majority of study patients were Caucasian (≥ 96% of total). Only for the FP 100 µg bid group were patients down to the age of 12 included (the other 2 groups had patients down to age 14 and 13, although these are minor differences). A slightly greater number of female patients as male patients were enrolled in the study but surprisingly this numerical difference was not found to be statistically significant. While not presented in this table, the majority of patients (85-92%) in each treatment group had concurrent medical conditions at the time of randomization and a majority (59-74%) were using a concurrent medication (one that was allowed per study exclusion criteria) at the time of randomization. For all 3 treatment groups, the most commonly used classes of medications included: NSAIDs, analgesics (including: acetaminophen and aspirin), estrogens (female patients), oral contraceptive pills (female patients), and antibiotics [NDA 20-121, S-009, 21:62, 75-76].

(D) Patient distribution by disease severity at pre-treatment (Day -6 to Day 0) in the ITT population, as assessed by average patient self-rated total nasal symptom scores (TNSS) and the individual nasal symptoms of nasal obstruction, postnasal drip, rhinorrhea, sneezing, and nasal itching for the pre-treatment period; revealing small numerical differences between the treatment groups but

failed to reveal a statistically significant difference in TNSS and the respective individual nasal symptoms between the 3 treatment groups [NDA 20-121, S-009, 21:79-80].

(E) Patient Validity

Patients' diary data were invalidated in study FLN 351 if patients failed to meet the minimal requirement for compliance (defined as ≥ 80% use during the double-blind period). Patient line listings of invalidated visits were not provided by the sponsor, however based on the efficacy data (both the primary and secondary endpoints), few patients appeared to have had invalidated data in each of the 3 treatment groups.

Reviewer's Note: Similar to the medical reviewer's comments made for study FLTA 3010, the criteria for invalidation of patient data (insufficient number of diary recordings) in study FLN 351 was somewhat less stringent to those seen in rhinitis trials previously reviewed by the Division but overall deemed reasonable by the medical reviewer. Additionally, patients were altogether withdrawn from the study if they failed to return for clinic visits, failed to meet entrance criteria, withdrew consent, left for reasons of an adverse event. These criteria were comparable to that of other rhinitis studies. Hence, overall, the criteria for excluding patients from efficacy analysis were appropriate and consistent with other rhinitis trials.

(F) Duration of Study Medication Exposure

The extent of exposure to study medication of at least 2 weeks of double-blind treatment period for all 4 treatment groups combined was 282/286 patients or approximately 99% [NDA 20-121, S-009, 21:89]. A total of 4 patients completed 2 weeks or less of the double-blind treatment period.

(G) Patient Compliance [NDA 20-121, S-009, 21:59]

Assessment of patient compliance with double-blind medication was determined by diary card data in which patients recorded all doses of study medication taken and the time of dosing. The number of patients who reported that they took at least 80% of scheduled medication was tabulated by treatment group and study week [NDA 20-121, S-009, 21:59 (Table 4)]. Based on these data, at least 95% of patients (range 95-99%) in each treatment group (for the 3 groups) were ≥ 80% compliant in taking study medication during each respective week of the study.

8.2.4.1.b. Efficacy Endpoint Outcomes

(I) Primary Efficacy Variable:

All efficacy analyses in this review were based on the intent-to-treat (ITT) population (n=93 for the placebo group, n=98 for the FP 100 μg bid group, and n=95 for the FP 200 μg bid group). Based on the powering of study FLN 351, the

primary efficacy variable was defined as: (1) the change from baseline (defined as Visit 1) in the patient-rated average reflective daily TNSS (=sum of rhinorrhea, nasal obstruction, and postnasal drip) for each week of the double-blind period (4 weeks total) where the primary comparison of interest (though not explicitly specified in the study protocol) was the FP 100 μg bid treatment group (the proposed dose of FP for the NAPR indication) vs. placebo.

For the change from baseline in the patient-rated average daily reflective TNSS for each week of the double-blind treatment period, the 100 μg bid dose of FP nasal spray failed to demonstrate statistically significantly greater efficacy in decreasing total nasal symptoms from baseline at all time points, compared to placebo treatment (Table V). Numerically, this difference in change in weekly TNSS ranged from [redacted] points between the FP 100 μg bid treatment group and placebo. When compared to the magnitude of effect in decreasing weekly TNSS seen in study FLTA 3010, the results of study FLN 351 were somewhat lower (refer to the integrated summary of efficacy section) with an effect size difference ranging from [redacted] points lower for the FP 100 μg bid treatment group for the 4 weekly measurements in study FLN 351, compared to study FLTA 3010.

For the FP 200 μg bid dose, statistically significantly greater efficacy compared to placebo treatment was demonstrated for weeks 2-4 of treatment (but not week 1 or post-treatment) ($p \leq 0.02$) [NDA 20-121, S-009, 21:79 (Table V)]. Furthermore, all 3 treatment groups were reasonably balanced with respect to overall NAPR symptom scores (the TNSS) at baseline (i.e. pre-treatment visit; range in TNSS scores: [redacted] [NDA 20-121, S-009, 21:79], with a slightly higher baseline score for the FP 200 μg bid group.

Numerically, the FP 200 μg bid treatment group showed the greatest degree of change in patient self-rated TNSS with a mean maximum decrease in TNSS of -80.2 points by week 4 of treatment, as compared with placebo (mean -60.5 point decrease) [NDA 20-121, S-009, 21:79], although this difference was not statistically significantly different from the FP 100 μg bid treatment group. As noted above, efficacy was not seen at any time point during the double-blind period for the FP 100 μg bid treatment group but was seen by week 2 for the FP 200 μg bid treatment group. Overall, the TNSS scores demonstrated a progressive numerical decrease with FP Nasal Spray treatment from week 1-4 of treatment relative to placebo treatment with some reversal of this decrease evident on discontinuation of active drug by the post-treatment visit.

The postnasal drip, nasal obstruction, and rhinorrhea scores contributed relatively equally to the TNSS but the sneezing and nasal itch scores which were not calculated into the TNSS did not (these were half the numerical value of the latter 3 NAPR scores).

A subgroup analysis of the primary efficacy variable was not performed in this study.

Reviewer's Note: Realizing that the study was inadequately powered due to failure to achieve the target number of patients on enrollment, the primary

efficacy data nonetheless were supportive of efficacy of the FP 200 μg bid at some of the study time points (weeks 2-4). The numerical trends in symptom score decrement were supportive of some degree of efficacy for both the FP 100 μg bid and FP 200 μg bid doses of FLONASE Nasal Spray. Thus, based on these data for the primary efficacy variable, a reasonable starting dose of fluticasone propionate nasal spray for NAPR symptoms would be 100 μg bid (or conversely 200 μg qd).

(II) Secondary Efficacy Variables:

None of the individual patient self-rated daily nasal symptom scores showed statistically significant change in efficacy in FP Nasal Spray treated patients, compared to placebo treatment, with the exception of the following endpoints: (1) rhinorrhea in the FP 200 μg bid treatment group at week 3, and (2) a.m. nasal obstruction score in the FP 100 μg bid treatment group at week 2 and 4 and in the FP 200 μg bid treatment group for weeks 1-4 and post-treatment [NDA 20-121, S-009, 21:79-81, Tables VI-XI]. Similar to results seen with the primary efficacy variable, the FP 200 μg bid treatment group tended to demonstrate a numerically greater decrease in the individual NAPR symptoms than did the FP 100 μg bid treatment group (with the exception of the sneezing and nasal itch scores), but these differences were not statistically significant between the FP 100 and FP 200 μg bid treatment groups. Furthermore, both doses of FP Nasal Spray demonstrated a progressive numerical decrement in the individual patient self-rated nasal symptoms over the 4 week double-blind period compared to placebo treatment which became less evident on discontinuation of the active drug.

For the physician-rated NAPR symptom scores (total and individual symptom scores), likewise no clear dose response was demonstrable for the 2 FP Nasal Spray doses, and statistically significant changes in efficacy were not consistent across endpoints or time points for either dose. Results of the physician-rated TNSS showed statistically significant efficacy for the FP 100 μg bid group only at Day 29 (week 4) and for the FP 200 μg bid group at Day 8, 15, and 29 [NDA 20-121, S-009, 21:83, Table XII].

For the individual physician-rated NAPR symptoms, statistically significant decreases in symptom scores relative to placebo treatment were only seen for: (1) the nasal obstruction score at Day 15 with FP 100 μg bid treatment and at Days 8 and 15 with FP 200 μg bid treatment, and (2) the nasal itch score at Day 15 for the FP 100 μg bid treatment [NDA 20-121, S-009, 21:83-84, Tables XV and XVII]. All other individual NAPR symptoms failed to demonstrate statistically significant differences in efficacy compared with placebo for both the FP 100 and FP 200 μg bid treatment groups. Furthermore, no consistent difference in response was seen for the FP 100 μg bid treatment group compared to the FP 200 μg bid treatment group, hence no conclusion could be made with regard to dose response for the 2 FP doses for the individual NAPR symptoms.

Review of the patient's overall response to treatment (Table XVIII), showed that patients in the FP 100 μg bid treatment group had a statistically significant

improvement in symptoms by both Visits 3 and 6 (i.e. Day 15 and Day 36, respectively), whereas the FP 200 μg bid treatment group had a statistically significant improvement in symptoms by Visit 6 of treatment only [NDA 20-121, S-009, 21:85-86, Table XVIII]. Similar results were seen for the physician-rating of patients' overall response to treatment (Table XIX) in which both the FP 100 μg bid and FP 200 μg bid treatment groups demonstrated statistically significant improvement in NAPR symptoms at both Visits 3 and 6, compared with placebo treatment [NDA 20-121, S-009, 21:86-87, Table XIX].

Reviewer's Note: Again, review of the secondary efficacy endpoints was overall only able to provide supportive evidence of clinical efficacy of the 2 FP doses based on several statistically significant endpoints and a general trend to decrease the numerical values of the respective symptom scores over the 4-week double-blind period with treatment by the active drug. Based on review of efficacy for the secondary efficacy variables, the proposed dose of FP Nasal Spray for the treatment of NAPR symptoms would be the same as the proposed dose FP Nasal spray that had been based on the primary efficacy variable—that is FP 100 μg bid (or FP 200 100 μg qd).

Table V.
Efficacy of Flonase Nasal Spray vs. Placebo:
Patient-Rated Daily Total Nasal Symptom Score; Primary Efficacy Variable
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:79]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total Nasal Symptom Score (TNSS): Composite of Rhinorrhea + Nasal Obstruction + Postnasal Drip						
# of Pts at Screening	93	98	95			
Pre-Treatment (day -6 to 0) (n, mean score ± [2]SE)	92 181.4 ± 4.6	98 181.7 ± 3.9	95 185.1 ± 4.0	0.935	0.492	0.538
Week 1 (day 1- 7) (n, Δ in score ± SE)	93 -30.8 ± 5.8	98 -35.1 ± 5.2	94 -44.1 ± 5.2	0.561	0.084	0.243
Week 2 (day 8-14) (n, Δ in score ± SE)	93 -45.3 ± 5.5	98 -58.7 ± 6.0	94 -64.9 ± 6.1	0.089	0.017	0.468
Week 3 (day 15-21) (n, Δ in score ± SE)	90 -51.8 ± 6.4	97 -63.0 ± 6.8	94 -75.0 ± 5.8	0.163	0.009	0.202
Week 4 (day 22-28) (n, Δ in score ± SE)	89 -60.5 ± 6.7	95 -70.8 ± 6.8	92 -80.2 ± 6.3	0.220	0.036	0.365
Post-treatment (day 29-35) (n, Δ in score ± SE)	89 -57.6 ± 6.2	94 -65.1 ± 5.7	92 -68.9 ± 6.4	0.318	0.188	0.742

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Days -6 to 0) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table VI.
Efficacy of Flonase Nasal Spray vs. Placebo:
Patient-Rated Daily Rhinorrhea Symptom Score
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:80]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (day -6 to 0) (n, mean score ± [2]SE)	92 61.7 ± 2.0	98 57.3 ± 2.2	95 58.2 ± 2.5	0.162	0.245	0.817
Week 1 (day 1- 7) (n, Δ in score ± SE)	93 -12.3 ± 2.1	98 -12.7 ± 2.2	94 -15.1 ± 2.0	0.929	0.381	0.424
Week 2 (day 8-14) (n, Δ in score ± SE)	93 -17.4 ± 2.0	98 -20.9 ± 2.4	94 -22.5 ± 2.3	0.256	0.100	0.597
Week 3 (day 15-21) (n, Δ in score ± SE)	90 -19.6 ± 2.3	97 -22.9 ± 2.6	94 -25.9 ± 2.2	0.272	0.053	0.388
Week 4 (day 22-28) (n, Δ in score ± SE)	89 -22.3 ± 2.3	95 -24.4 ± 2.6	92 -26.9 ± 2.4	0.496	0.182	0.502
Post-treatment (day 29-35) (n, Δ in score ± SE)	89 -21.7 ± 2.3	94 -23.6 ± 2.3	92 -22.3 ± 2.6	0.538	0.837	0.680

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Days -6 to 0) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table VII.
Efficacy of Flonase Nasal Spray vs. Placebo:
Patient-Rated Daily Postnasal Drip Score
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:79]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (day -6 to 0) (n, mean score ± [2]SE)	92 61.3 ± 2.5	98 61.7 ± 2.6	95 67.1 ± 2.2	0.897	0.073	0.091
Week 1 (day 1- 7) (n, Δ in score ± SE)	93 -9.5 ± 2.3	98 -7.8 ± 2.0	94 -13.1 ± 2.2	0.568	0.249	0.083
Week 2 (day 8-14) (n, Δ in score ± SE)	93 -15.1 ± 2.3	98 -16.1 ± 2.6	94 -20.9 ± 2.8	0.738	0.109	0.197
Week 3 (day 15-21) (n, Δ in score ± SE)	90 -17.5 ± 2.6	97 -17.8 ± 2.9	94 -24.6 ± 2.6	0.852	0.062	0.087
Week 4 (day 22-28) (n, Δ in score ± SE)	89 -21.4 ± 2.7	95 -21.1 ± 3.0	92 -27.1 ± 2.7	0.998	0.150	0.145
Post-treatment (day 29-35) (n, Δ in score ± SE)	89 -20.2 ± 2.6	94 -20.6 ± 2.6	92 -24.4 ± 2.6	0.843	0.256	0.341

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Days -6 to 0) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table VIII.
Efficacy of Flonase Nasal Spray vs. Placebo:
Patient-Rated Daily Nasal Obstruction Score
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:79]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (day -6 to 0) (n, mean score ± [2]SE)	92 58.4 ± 2.2	98 61.7 ± 2.6	95 67.1 ± 2.2	0.897	0.073	0.091
Week 1 (day 1- 7) (n, Δ in score ± SE)	93 -8.9 ± 2.1	98 -7.8 ± 2.0	94 -13.1 ± 2.2	0.568	0.249	0.083
Week 2 (day 8-14) (n, Δ in score ± SE)	93 -12.7 ± 2.0	98 -16.1 ± 2.6	94 -20.9 ± 2.8	0.783	0.109	0.197
Week 3 (day 15-21) (n, Δ in score ± SE)	90 -14.6 ± 2.4	97 -17.8 ± 2.9	94 -24.6 ± 2.6	0.852	0.062	0.087
Week 4 (day 22-28) (n, Δ in score ± SE)	89 -16.7 ± 2.4	95 -21.1 ± 3.0	92 -27.1 ± 2.7	0.998	0.150	0.145
Post-treatment (day 29-35) (n, Δ in score ± SE)	89 -15.6 ± 2.3	94 -20.6 ± 2.6	92 -24.4 ± 2.6	0.843	0.256	0.341

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Days -6 to 0) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table IX.
Efficacy of Flonase Nasal Spray vs. Placebo:
Patient-Rated Daily A.M. Nasal Obstruction Score
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:81]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (day -6 to 0) (n, mean score ± [2]SE)	92 62.6 ± 2.1	98 64.4 ± 2.2	95 65.3 ± 2.1	0.516	0.356	0.777
Week 1 (day 1- 7) (n, Δ in score ± SE)	93 -6.0 ± 2.1	98 -10.1 ± 1.7	94 -14.0 ± 1.8	0.112	0.004	0.171
Week 2 (day 8-14) (n, Δ in score ± SE)	93 -10.4 ± 2.2	98 -18.3 ± 2.2	94 -20.8 ± 2.4	0.008	< 0.001	0.484
Week 3 (day 15-21) (n, Δ in score ± SE)	90 -13.2 ± 2.3	97 -18.6 ± 2.4	94 -25.6 ± 2.4	0.082	< 0.001	0.050
Week 4 (day 22-28) (n, Δ in score ± SE)	89 -14.8 ± 2.5	95 -22.2 ± 2.5	92 -27.2 ± 2.6	0.032	< 0.001	0.210
Post-treatment (day 29-35) (n, Δ in score ± SE)	89 -15.0 ± 2.3	94 -19.2 ± 2.3	92 -23.7 ± 2.8	0.199	0.017	0.255

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Days -6 to 0) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table X.
Efficacy of Flonase Nasal Spray vs. Placebo: **Patient-Rated Daily Sneezing Score** Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:80]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (day -6 to 0) (n, mean score ± [2]SE)	92 36.3 ± 2.3	98 38.1 ± 2.6	95 31.2 ± 2.5	0.569	0.121	0.032
Week 1 (day 1- 7) (n, Δ in score ± SE)	93 -9.7 ± 1.7	98 -9.5 ± 2.0	94 -9.6 ± 2.1	0.963	0.918	0.954
Week 2 (day 8-14) (n, Δ in score ± SE)	93 -11.6 ± 2.0	98 -14.5 ± 2.4	94 -12.1 ± 2.4	0.337	0.904	0.401
Week 3 (day 15-21) (n, Δ in score ± SE)	90 -14.4 ± 2.1	97 -13.6 ± 2.5	94 -14.7 ± 2.3	0.898	0.927	0.823
Week 4 (day 22-28) (n, Δ in score ± SE)	89 -14.4 ± 2.0	95 -18.0 ± 2.6	92 -15.7 ± 2.5	0.272	0.750	0.433
Post-treatment (day 29-35) (n, Δ in score ± SE)	89 -13.7 ± 1.9	94 -16.2 ± 2.4	92 -13.6 ± 2.7	0.440	0.887	0.357

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Days -6 to 0) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table XI.
Efficacy of Flonase Nasal Spray vs. Placebo:
Patient-Rated Daily Nasal Itching Score
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:80]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (day -6 to 0) (n, mean score ± [2]SE)	92 29.8 ± 2.5	98 31.7 ± 2.7	95 30.8 ± 2.8	0.510	0.835	0.650
Week 1 (day 1- 7) (n, Δ in score ± SE)	93 -6.6 ± 1.7	98 -8.0 ± 1.9	94 -6.8 ± 2.0	0.596	1.000	0.595
Week 2 (day 8-14) (n, Δ in score ± SE)	93 -10.0 ± 2.0	98 -15.2 ± 2.3	94 -11.3 ± 2.2	0.071	0.720	0.146
Week 3 (day 15-21) (n, Δ in score ± SE)	90 -12.4± 2.0	97 -14.6 ± 2.2	94 -12.1 ± 2.3	0.395	0.918	0.334
Week 4 (day 22-28) (n, Δ in score ± SE)	89 -13.7± 2.0	95 -15.8 ± 2.4	92 -14.2 ± 2.4	0.426	0.938	0.470
Post-treatment (day 29-35) (n, Δ in score ± SE)	89 -13.5 ± 1.9	94 -14.6 ± 2.4	92 -12.9 ± 2.3	0.667	0.766	0.471

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Days -6 to 0) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observe

Table XII.
Efficacy of Flonase Nasal Spray vs. Placebo:
Physician-Rated Daily Total Nasal Symptom Score
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:83]

	TREATMENT GROUPS					
	Placebo	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total Nasal Symptom Score (TNSS): Composite of Rhinorrhea + Nasal Obstruction + Postnasal Drip						
# of Pts at Screening	93	98	95			
Pre-Treatment (Day1) (n, mean score ± [2]SE)	93 189.0 ± 5.4	98 193.6 ± 4.8	95 192.6 ± 5.1	0.464	0.607	0.830
Day 8 (n, Δ in score ± SE)	93 -50.8 ± 6.7	97 -60.1 ± 5.1	94 -70.3 ± 7.2	0.253	0.035	0.321
Day 15 (n, Δ in score ± SE)	93 -55.3 ± 7.5	95 -68.0 ± 6.9	93 -76.1 ± 7.3	0.176	0.049	0.529
Day 22 (n, Δ in score ± SE)	89 -63.2 ± 7.0	95 -78.0 ± 6.5	91 -76.3 ± 7.5	0.107	0.204	0.739
Day 29 (n, Δ in score ± SE)	93 -65.3 ± 7.4	98 -84.3 ± 6.6	94 -85.6 ± 7.4	0.044	0.049	0.976
Post-treatment (Day 36) (n, Δ in score ± SE)	88 -49.8 ± 7.0	93 -61.3 ± 6.0	92 -59.7 ± 6.6	0.189	0.316	0.755

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Day 1) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table XIII.
Efficacy of Flonase Nasal Spray vs. Placebo:
Physician-Rated Daily Rhinorrhea Symptom Score
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:84]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (Day 1) (n, mean score ± [2]SE)	93 61.9 ± 3.1	98 59.9 ± 3.0	95 59.7 ± 3.1	0.648	0.509	0.833
Day 8 (n, Δ in score ± SE)	93 -19.2 ± 3.0	98 -25.1 ± 3.0	94 -24.2 ± 3.0	0.127	0.251	0.711
Day 15 (n, Δ in score ± SE)	90 -21.4 ± 3.5	95 -22.3 ± 3.6	93 -26.4 ± 3.2	0.767	0.320	0.478
Day 22 (n, Δ in score ± SE)	89 -23.8 ± 3.2	95 -27.3 ± 3.2	91 -24.8 ± 3.2	0.368	0.835	0.489
Day 29 (n, Δ in score ± SE)	93 -24.0 ± 3.3	98 -30.4 ± 3.2	94 -29.9 ± 3.2	0.132	0.216	0.796
Post-treatment (Day 36) (n, Δ in score ± SE)	88 -18.7 ± 3.3	93 -20.1 ± 3.1	92 -18.0 ± 3.3	0.695	0.870	0.575

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Day 1) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table XIV.
Efficacy of Flonase Nasal Spray vs. Placebo:
Physician-Rated Daily Postnasal Drip Score
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:83]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (Day 1) (n, mean score ± [2]SE)	93 64.9 ± 2.8	98 70.2 ± 2.6	95 70.4 ± 2.6	0.151	0.124	0.909
Day 8 (n, Δ in score ± SE)	93 -17.7 ± 3.2	97 -18.2 ±3.0	94 -24.0 ± 3.3	0.874	0.177	0.229
Day 15 (n, Δ in score ± SE)	90 -18.7 ± 3.2	95 -22.5 ± 3.1	93 -24.0 ± 3.3	0.385	0.270	0.809
Day 22 (n, Δ in score ± SE)	89 -19.7 ± 3.3	95 -26.2 ± 3.3	91 -25.1 ± 3.2	0.140	0.250	0.754
Day 29 (n, Δ in score ± SE)	93 -22.1 ± 3.3	98 -28.4 ± 3.3	94 -30.4 ± 3.0	0.129	0.070	0.751
Post-treatment (Day 36) (n, Δ in score ± SE)	88 -17.9 ± 3.3	93 -25.0 ± 3.0	92 -22.9 ± 2.9	0.100	0.275	0.578

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Day 1) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

Table XV.
Efficacy of Flonase Nasal Spray vs. Placebo:
Physician-Rated Daily Nasal Obstruction Score
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:83]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (Day 1) (n, mean score ± [2]SE)	93 62.1 ± 2.2	98 63.5 ± 2.5	95 62.5 ± 2.3	0.682	0.917	0.758
Day 8 (n, Δ in score ± SE)	93 -13.8 ± 2.8	97 -16.7 ± 2.4	94 -22.1 ± 2.8	0.389	0.027	0.171
Day 15 (n, Δ in score ± SE)	90 -15.2 ± 3.0	95 -23.2 ± 2.7	93 -25.7 ± 2.9	0.034	0.010	0.632
Day 22 (n, Δ in score ± SE)	89 -19.6 ± 2.6	95 -24.4 ± 3.0	91 -26.3 ± 3.1	0.203	0.120	0.760
Day 29 (n, Δ in score ± SE)	93 -19.2 ± 3.0	98 -25.4 ± 3.0	94 -25.2 ± 3.0	0.117	0.155	0.894
Post-treatment (Day 36) (n, Δ in score ± SE)	88 -13.3 ± 3.0	93 -16.1 ± 2.7	92 -18.8 ± 2.8	0.426	0.188	0.595

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Day 1) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table XVI.
Efficacy of Flonase Nasal Spray vs. Placebo: **Physician-Rated Daily Sneezing Score** Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:84]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (Day 1) (n, mean score ± [2]SE)	93 30.4 ± 2.7	98 31.5 ± 3.1	95 25.8 ± 2.7	0.699	0.233	0.111
Day 8 (n, Δ in score ± SE)	93 -11.2 ± 2.5	97 -11.5 ± 3.3	94 -12.6 ± 2.8	0.934	0.745	0.807
Day 15 (n, Δ in score ± SE)	90 -12.0 ± 3.0	95 -13.3 ± 3.3	93 -11.0 ± 2.9	0.720	0.777	0.517
Day 22 (n, Δ in score ± SE)	89 -12.4 ± 2.9	95 -11.3 ± 3.3	91 -10.7 ± 3.2	0.836	0.621	0.768
Day 29 (n, Δ in score ± SE)	93 -12.4 ± 3.5	98 -15.4 ± 3.2	94 -14.3 ± 2.8	0.481	0.678	0.774
Post-treatment (Day 36) (n, Δ in score ± SE)	88 -9.3 ± 2.7	93 -11.5 ± 3.1	92 -6.0 ± 3.0	0.580	0.422	0.170

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Day 1) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

Table XVII.
Efficacy of Flonase Nasal Spray vs. Placebo:
Physician-Rated Daily Nasal Itching Score
Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:84]

	TREATMENT GROUPS					
	Placebo	**FP 100 µg bid**	**FP 200 µg bid**	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
# of Pts at Screening	93	98	95			
Pre-Treatment (Day 1) (n, mean score ± [2]SE)	93 27.7 ± 2.9	98 30.1 ± 3.0	95 29.4 ± 3.2	0.436	0.685	0.710
Day 8 (n, Δ in score ± SE)	93 -8.9 ± 2.9	97 -13.9 ± 2.6	94 -10.9 ± 3.0	0.186	0.645	0.389
Day 15 (n, Δ in score ± SE)	90 -9.9 ± 3.2	95 -17.9 ± 2.7	93 -13.7 ± 2.9	0.038	0.403	0.209
Day 22 (n, Δ in score ± SE)	89 -14.4 ± 2.8	95 -16.2 ± 3.0	91 -13.1 ± 3.0	0.590	0.642	0.311
Day 29 (n, Δ in score ± SE)	93 -15.6 ± 2.7	98 -15.6 ± 2.9	94 -14.2 ± 2.9	0.904	0.710	0.619
Post-treatment (Day 36) (n, Δ in score ± SE)	88 -11.8 ± 2.8	93 -13.7 ± 2.5	92 -9.4 ± 3.0	0.592	0.477	0.208

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Day 1) were based on mean scores at baseline, and at subsequent visits. P-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observe

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Table XVIII.
Efficacy of Flonase Nasal Spray vs. Placebo: **Overall Patient Evaluation**
Primary Efficacy Variable: Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:85-86]

	TREATMENT GROUPS			P-value:		
	Placebo	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. at Baseline	93	98	95			
Total # of Evaluable Pts:						
Visit 3	90	96	93			
Visit 6	93	98	94			
Patient Response to Treatment:						
Visit 3				<0.007	0.113	0.319
Visit 6				<0.001	<0.001	0.570
Significant Improvement						
Visit 3	11 (12%)	19 (19%)	18 (19%)	NA	NA	NA
Visit 6	7 (8%)	29 (30%)	28 (30%)			
Moderate Improvement						
Visit 3	15 (16%)	29 (30%)	24 (26%)	NA	NA	NA
Visit 6	20 (22%)	19 (19%)	27 (29%)			
Mild Improvement						
Visit 3	39 (42%)	31 (32%)	27 (29%)	NA	NA	NA
Visit 6	35 (38%)	28 (29%)	18 (19%)			
No change				NA	NA	NA
Visit 3	18 (19%)	15 (15%)	21 (22%)			
Visit 6	23 (25%)	18 (18%)	29 (20%)			
Mildly Worse				NA	NA	NA
Visit 3	4 (4%)	2 (2%)	3 (3%)			
Visit 6	5 (5%)	3 (3%)	1 (1%)			
Moderately Worse						
Visit 3	1 (1%)	0 (0%)	0 (0%)	NA	NA	NA
Visit 6	0 (0%)	0 (0%)	1 (1%)			
Significantly Worse						
Visit 3	2 (2%)	0 (0%)	0 (0%)	NA	NA	NA
Visit 6	3 (3%)	1 (1%)	0 (0%)			

[1]FP=Fluticasone propionate. P-values based on the Cochran-Mantel-Haenszel test controlling for investigator. Percentages are based on the number of evaluable patients. NA=Not available (i.e. analysis not performed).

Table XIX.
Efficacy of Flonase Nasal Spray vs. Placebo: **Overall Physician Evaluation**
Primary Efficacy Variable: Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 21:87-88]

	TREATMENT GROUPS			P-value:		
	Placebo	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. at Baseline	93	98	95			
Total # of Evaluable Pts:						
Visit 3	90	96	92			
Visit 6	93	97	94			
Patient Response to Treatment:						
Visit 3				<0.001	0.002	0.971
Visit 6				0.003	<0.001	0.423
Significant Improvement						
Visit 3	4 (4%)	11 (11%)	14 (15%)	NA	NA	NA
Visit 6	5 (5%)	18 (24%)	32 (34%)			
Moderate Improvement						
Visit 3	16 (17%)	32 (33%)	27 (29%)	NA	NA	NA
Visit 6	18 (19%)	23 (24%)	32 (34%)			
Mild Improvement						
Visit 3	39 (42%)	38 (39%)	30 (32%)	NA	NA	NA
Visit 6	38 (41%)	33 (34%)	26 (28%)			
No change				NA	NA	NA
Visit 3	24 (26%)	14 (14%)	20 (21%)			
Visit 6	26 (28%)	20 (21%)	19 (20%)			
Mildly Worse				NA	NA	NA
Visit 3	3 (3%)	1 (1%)	1 (1%)			
Visit 6	3 (3%)	2 (2%)	0 (0%)			
Moderately Worse						
Visit 3	4 (4%)	0 (0%)	0 (0%)	NA	NA	NA
Visit 6	1 (1%)	1 (1%)	0 (0%)			
Significantly Worse						
Visit 3	0 (0%)	0 (0%)	0 (0%)	NA	NA	NA
Visit 6	2 (2%)	0 (0%)	0 (0%)			

[1]FP=Fluticasone propionate. P-values based on the Cochran-Mantel-Haenszel test controlling for investigator. Percentages are based on the number of evaluable patients. NA=Not available (i.e. analysis not performed).

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Analysis of Duration of Effect:

Analysis of the end-of-dosing interval efficacy (or duration of drug effect) was not readily evaluable as reflective and not instantaneous nasal symptom scores were quantified by patients. Since data presented for the physician's 'instantaneous' clinic visit assessments were not performed on a daily basis, these scores were likewise not useful for the purpose of assessing duration of drug effect.

Analysis of Onset of Efficacy:

Formal analysis of the onset of efficacy of the 2 FP doses vs. placebo was not performed by the sponsor in FLN 351.

8.2.4.2. Nasal Cytology Studies

Nasal cytology studies were conducted in order to assess the proportion of patients enrolled in FLN 351 that might have NARES (non-allergic rhinitis with eosinophilia), a disorder different in etiology from perennial non-allergic rhinitis. Prevalence of eosinophils in nasal secretions was assessed at Day 1 (baseline of the double-blind treatment period) and Day 29 (last day of the double-blind treatment period). Based on these [redacted] studies; at baseline, the majority of patients enrolled into the 3 treatment groups did not have evidence of nasal eosinophilia (69% of placebo group patients, 70% of FP 100 μg bid patients, and 68% of FP 200 μg bid patients) [NDA 20-121, S-009, 21:70], which would be consistent with lack of a supporting clinical finding for NARES for most patients enrolled in the study. No significant pairwise differences were observed in the distribution of eosinophils between placebo and the FP 100 μg bid group ($p=0.007$) and between placebo and the FP 200 μg bid group ($p=0.001$), with overall higher percentages in the 2 FP groups showing no eosinophils [NDA 20-121, S-009, 21:33].

Furthermore, the percentage of nasal smears with no eosinophils increased in each of the 2 active treatment groups by Day 29 but did not change in the placebo group (70% of placebo group patients, 87% of FP 100 μg bid patients, and 93% of FP 200 μg bid patients) [NDA 20-121, S-009, 21:70]. Of note, similar results for distribution of nasal eosinophilia were seen in study FLTA 3010.

Regarding the distribution of other cell types, namely neutrophils, it appeared that treatment with FP Nasal Spray decreased the percentage of neutrophils in nasal secretions (compared to placebo) by Day 29 of treatment. This finding was also associated with an increase in the number of bacteria seen in the same respective nasal secretions at Day 29 of treatment in the FP Nasal Spray treatment groups. The number of patients with bacteria in each response category for bacteria differed significantly between the placebo group and each FP group at Day 29 ($p=0.007$), with fewer FP patients having scores of zero and more FP patients having scores of 3 or 4 (i.e. 3=large clumps or 4=clumps covering the entire field) [NDA 20-121, S-009, 21:33,72]. Despite these statistically significant findings, the actual percentage difference for the 3 treatment groups from Day 1 to Day 29 was not large (i.e. $\leq 5\%$) [NDA 20-121, S-009, 21:33,72].

8.2.4.3. Safety Analysis

Safety analysis for study FLN 351 consisted of an evaluation of adverse events, standard laboratory tests (along with special safety studies such as a.m. plasma cortisols but no Cortrosyn stimulation testing pre- and post-treatment with study drug), vital signs, and changes in physical examination (especially with regard to oropharyngeal and nasal exams) pre-and post-treatment in patients randomized into the study and 'exposed' to study medication (the intent-to-treat population) [NDA 20-121, S-009, 21:26-28, 137-139]. In this trial, the safety evaluable population was the same as the ITT population. All 286 patients who received study medication were included in the safety database and comprised the intent-to-treat population (n=93 for the placebo group, n=98 for the FP 100 μg bid group, and n=95 for the FP 200 μg bid group) [NDA 20-121, S-009, 21:40].

8.2.4.3.1. Demographics of the Exposed Population

There were no statistically significant differences among the treatment groups with regard to the demographic variables of age, gender, race, weight, or history of NAPR (Table V. of sponsor's submission) [NDA 20-121, S-009, 21:60-61]).

8.2.4.3.2. Duration of Patient Exposure/Patient Disposition

The extent of exposure to study medication of at least 2 weeks of double-blind treatment period for all 4 treatment groups combined was 282/286 patients or approximately 99% [NDA 20-121, S-009, 21:89]. A total of 4 patients completed 2 weeks or less of the double-blind treatment period.

8.2.4.4. Adverse Events (AE's)

The overall incidence of adverse events (AEs) were generally similar for all 3 treatment groups (43-58% range, highest in the FP 200 μg bid group). Of note, these overall AE ranges were similar to that of pivotal NAPR study FLTA 3010. With regard to individual/specific AEs, the incidence of AEs were also similar across all 3 treatment groups, with the exception of a slight increase in the incidence of headaches and throat irritation in the 2 FP treatment groups over placebo.

The most common AE for the 3 FP treatment groups was headache (incidence ≤ 20% for the 2 FP groups) followed by upper respiratory infection/URI (incidence ≤ 14% for the 2 FP groups), and throat irritation (incidence ≤ 8% for the 2 FP groups) (see Table XXIII). A slight dose response for the 2 active treatment groups was noted for headache (12 % incidence in the placebo group, a 16% incidence in the FP 100 μg bid group, and a 20% incidence in the FP 200 μg bid group) and throat irritation (3% incidence in the placebo group, a 7% incidence in the FP 100 μg bid group, and an 8% incidence in the FP 200 μg bid group) [NDA 20-121, S-009, 21:40]. Importantly, no significant increase in the incidence of viral respiratory infections (incidence=2% for the placebo group, vs. 1% for the FP 100 μg bid group, and 4% for the FP 200 μg bid group), or sinusitis (incidence= 0 for the placebo group, vs. 1% for the FP 100 μg bid group, and 0%

for the FP 200 μg bid group) [NDA 20-121, S-009, 21:90, 92] was seen with active drug treatment. It appears that for this study, cutaneous or oropharyngeal fungal disorders were not tabulated. No significant increase in the incidence of nasal septal disorders was noted in either of the 3 treatment groups with treatment (incidence=0% for the placebo group, vs. 1% for the FP 100 μg bid group, and 0% for the FP 200 μg bid group) [NDA 20-121, S-009, 21:90].
In summary, the safety profile for period for FP nasal in study FLN 351 was unremarkable, with no evidence of a significant increase in the incidence of AEs known to be associated with use of intranasal steroids, such as nasal septal ulcerations, oral or nasal candidiasis, glaucoma, and cataracts in the sponsor's AE database.

A summary of the more common reported adverse events for the 3 treatment groups (including placebo), is presented in Table XXIII below. A cutoff in AE frequency of ≥ 3% was arbitrarily chosen by the medical officer as representing the frequency of the more common AEs.

Table XXIII. Adverse Event (AE) Frequency:
More Common AE's (Incidence ≥ 3%) in Any Fluticasone Treatment Group (FLONASE Aqueous Nasal Spray), by Organ System and Preferred Term; ITT Population [NDA 20-121, S-009, 21:40, 90-95]

BODY SYSTEM	Preferred Term	Placebo (n=93) n (%)	FP 100 μg bid (n=98) n (%)	FP 200 μg bid (n=95) n (%)
All Systems	Any AE	40 (43%)	47 (48%)	55 (58%)
ENT	Epistaxis	3 (3%)	**5 (5%)**	**5 (5%)**
	Throat irritation	3 (3%)	**5 (5%)**	**5 (5%)**
	URI	**6 (6%)**	**5 (5%)**	**13 (14%)**
	Nasal irritation	**6 (6%)**	**8 (8%)**	4 (4%)
	Blood in nasal mucosa	3 (3%)	3 (3%)	4 (4%)
	Dryness of nose	3 (3%)	3 (3%)	2 (2%)
	Upper respiratory inflammation	0 (0%)	2 (2%)	3 (3%)
Neurology	Headaches	**11 (12%)**	**16 (16%)**	**19 (20%)**
Gastrointestinal	Nausea and vomiting	2 (2%)	2 (2%)	**5 (5%)**
	Diarrhea	1 (1%)	1 (1%)	4 (4%)
Lower Respiratory	Cough	1 (1%)	2 (2%)	4 (4%)
	Viral respiratory infections	2 (2%)	1 (1%)	4 (4%)
Non-site specific	Temperature regulation disturbances	0 (0%)	3 (3%)	0 (0%)
Musculoskeletal	Musculoskeletal pain	4 (4%)	1 (1%)	0 (0%)
Blood and Lymphatic	Hemorrhage	3 (3%)	1 (1%)	1 (1%)

NOTE: All AE's ≥ 5% in frequency are denoted in 'bold-face' type.

8.1.4.5. Adverse Event Stratification by Duration of Treatment

Adverse event stratification by duration of treatment was not performed by the sponsor, nor is it particularly relevant for a clinical trial such as this one which is only 4 weeks total in duration.

8.1.4.6. Adverse Event Stratification by Demographics (Age, Gender, Race)

Adverse event stratification by demographics was not performed in this study.

8.1.4.7. Patient Discontinuation due to Adverse Events

A total of 6 patients discontinued treatment prematurely during the 4 week double-blind treatment period due to adverse events (2 in the placebo group, 3 in the FP 100 μg bid group, and 1 in the FP 200 μg bid group) [NDA 20-121, S-009, 21:41]. No particular AE was responsible for the majority of patient discontinuations, although 3 cases were related to sinus problems (2 placebo group patients #033 and #073 discontinued treatment due to sinus headache and one FP 100 μg bid group patient (# 191) discontinued treatment due to sinusitis/exacerbation of cough [NDA 20-121, S-009, 21:41]. Only 2 patients were deemed by the principal investigators to have had AEs that could have been attributed to drug treatment. This included the 1 placebo patient who reported sinus headache (patient # 073) and the 1 FP 100 μg bid group patient who reported stinging at the study drug application site, epistaxis, and ulceration of nasal mucosa (patient # 103).

8.1.4.8. Serious Adverse Events and Death

[2]Serious AEs were reported for 3 patients in study FLN 351 (2 FP 100 μg bid group patients and 1 FP 200 μg bid group patient). None of the serious AEs were considered to be related to study medication: 1 FP 100 μg bid patient (patient # 077) who developed prostatitis, renal insufficiency, and gout with related symptoms, 1 FP 100 μg bid patient (patient # 276) who developed worsening of prostatic cancer which required orchiectomy, and 1 FP 200 μg bid patient (patient # 252) who developed an ovarian cyst that required surgical removal [NDA 20-121, S-009, 21:41, 98-99]. No deaths were reported in this study.

8.1.4.9. Laboratory Test Results

Laboratory tests performed during pre-treatment (screening visit), visit 4 (completion of double-blind treatment), and visit 5 of the study (completion of the 4 week trial, 1 week post-discontinuation of study drug treatment) and which consisted of a complete blood count with differential count, blood chemistries, liver function tests (SGOT, SGPT, alkaline phosphatase, total protein, albumin, and total bilirubin), urinalysis, and serum pregnancy test (for all women) did not reveal any unexpected abnormalities in FP treated patients, as compared with placebo treated patients. The effects of the 3 treatments on laboratory parameters were analyzed (with the exception of serum pregnancy tests) using the change from baseline for the study visit, shift tables, and a tabulation of outlier values for individual patients [NDA 20-121, S-009, 21:105-121]. The sponsor's criteria for

[2] Serious Adverse Event-defined as any of the following AEs: (1) death due to an adverse event, (2) death due to any cause, (3) immediate risk of death, (4) an adverse event which resulted in, or prolonged in-patient hospitalization, (5) an adverse event which resulted in permanent disability, (6) congenital abnormality, (7) cancer, or (8) overdose.

an abnormal laboratory value was a value outside the limits of normal for that parameter, based on Glaxo Wellcome definitions of clinically significant abnormal values [NDA 20-121, S-009, 21:103-104]. Summary tables for each laboratory value were computed using the designation of abnormally 'low' and 'high' values, based on the definitions of each respective lab value, as determined by Glaxo Wellcome [NDA 20-121, S-009, 3:107-108]. Statistical comparisons were not attempted by the sponsor with regard to analysis of laboratory abnormalities.

Summary tables for each laboratory value computed using the designation of abnormally 'low' and 'high' values, based on the definitions of each respective laboratory value, as determined by Glaxo Wellcome did not reveal any significant changes post-randomization during the double-blind treatment period (see Table 26 in the NAPR submission, NDA 20-121, S-009, 21:107-108].
Analysis of laboratory tests by shift tables (comparison between screening and visit 5) failed to reveal any significant differences between the 3 treatment groups during the double-blind treatment period [NDA 20-121, S-009, 21:42, 105-106]. The majority of patients had laboratory tests within normal range at screening and remained within the normal range throughout the double-blind treatment period. In general, shifts in laboratory test results were minor and showed no trends or dose response relationships.

An evaluation of individual laboratory value outliers (defined as marked abnormalities in laboratory parameters, based on a lower/higher cutoff limit for normal values for the given laboratory parameter, as determined by the sponsor) for each laboratory test showed no obvious difference in the number of patients with outliers between the 3 treatment groups and overall, the number of patients with clinically significant abnormal laboratory test results was very low ≤1% [NDA 20-121, S-009, 21:42]. These data are summarized in Table 27 of the study report for FLN 351 [NDA 20-121, S-009, 21:109-112]. No pattern of clinical laboratory abnormalities in the active treatment groups was seen, as compared to placebo treatment. One patient with an increase in serum bilirubin (from a normal screening level) was reported in both the placebo and FP 200 μg bid group, and a one patient with a decrease in WBC (from a normal screening count) was reported in both a placebo and FP 100 μg bid group [NDA 20-121, S-009, 21:109, 110, 112]. Again, the change (increase) in serum bilirubin was generally less than 1.5 mg/dL in the 2 patients who were detected to have bilirubinemia, and in both cases (# 085 and 066) was noted to occur predominantly in patients with a baseline elevated serum bilirubin level [NDA 20-121, S-009, 21:109, 112]. No cases of hyperglycemia were seen in the 2 FP treatments, though one case of hyperglycemia was seen in a placebo patient at the day 28 visit which had not been detected at screening [NDA 20-121, S-009, 21:109].

No patients were withdrawn from the study because of abnormal laboratory values.

8.2.4.9.1. A.M. Plasma Cortisol Studies

Adrenal function was evaluated in FLN 351 by measurement of only 1 adrenal response parameter: (1) a.m. plasma cortisol levels at screening (visit 1) and post-4 weeks (visit 5) of treatment with study drug (or at early patient discontinuation.

A.M. plasma cortisol measurements (pre- and post-treatment) for the double-blind were presented in the FLN 351 submission as the mean cortisol levels pre-treatment and post-4 weeks of treatment (see Table XXV below, as individual patient line listings and as a list of patient outlier values [NDA 20-121, S-009, 21: 113-121]. For purposes of this study, a normal a.m. plasma cortisol level was defined as: a cortisol level between 5-18 μg/dL [NDA 20-121, S-009, 21:43].

Review of patient outlier data for a.m. plasma cortisol levels revealed that for the a.m. plasma cortisol measurements post-4 weeks of double-blind treatment with FP 200 μg bid, only 1 patient (# 157) had an a.m. plasma cortisol level below the sponsor's pre-specified normal range (the pre-treatment a.m. cortisol level=13.0 μg/dL and post-4 week treatment with FP 200 μg bid, the a.m. cortisol level=4.0 μg/dL) [NDA 20-121, S-009, 21:120]. Again, no dose response was noted for the different doses of FP with respect to suppression of a.m. plasma cortisol levels during this 4 week study. Hence, overall, the likelihood of adrenal suppression, while very small, was not likely to be significant for most patients receiving FP Nasal Spray compared to placebo treatment post-4 weeks of therapy with study drug based on this diagnostic method.

Reviewer's Note: Realizing that a.m. plasma cortisol measurements are not as sensitive in detecting adrenal suppression as other laboratory parameters (e.g. 24 hour urinary free cortisol, 24 hour plasma cortisol AUC), the data presented above are thus somewhat limited with respect to determination of potential cortisol suppression (the extent or lack thereof) with FP Nasal Spray use. Only 1 patient receiving FP 200 μg bid (out of ~300 patients total) was found to have a plasma cortisol abnormality after receiving 4 weeks of treatment with intranasal fluticasone. While these data are reassuring in terms of the likelihood of significant adrenal suppression and the FP 100 μg bid dose, blunting of the adrenal response could occur in patients on active FP treatment and not be detected via the methods employed in this study.

Table XXV. A.M. Plasma Cortisol Levels Pre- and Post-4 Weeks of Treatment with Study Drug (FLONASE Aqueous Nasal Spray); ITT Population [NDA 20-121, S-009, 21:113]

A.M. PLASMA CORTISOL (µg/dL)	Placebo	FP 100 µg bid	FP 200 µg bid	P-Values		
	Pre-Rx, n=93 Post-week 4, n=91 (mean ± SE)	Pre-Rx, n=98 Post-week 4, n=96 (mean ± SE)	Pre-Rx, n=94 Post-week 4, n=93 (mean ± SE)	P vs. FP 100	P vs. FP 200	FP 100 vs. FP 200
Pre-Rx (Screening)	17.4 ± 1.01	16.1 ± 0.85	16.6 ± 0.94	0.334	0.542	0.725
Post-week 4 (Visit 5)	16.8 ± 1.12	15.9 ± 0.85	17.0 ± 0.94	0.622	0.290	0.564

Pre-Rx=Pre-treatment. P=Placebo, FP=Fluticasone Propionate Nasal Spray.
P-values are based on mean scores for pre-treatment and on differences from pre-treatment for Visit 5 using the F-test.
P-values are not adjusted for multiple comparisons.

8.2.4.10. Physical Examination (including ENT exam)

Evaluation of change in the physical examination of patients during the 4week double-blind period revealed no significant trends in physical findings and only minor changes on exam. For FLN 351 only 9 patients had minor changes in physical exam (Tables 30 and 31 of the sponsor's submission) [NDA 20-121, S-009, 21:122-123]. Overall, patients receiving FP 200 µg bid experienced a slightly greater increase in change in physical examination, compared with either the FP 100 µg bid or placebo. This is somewhat in contrast to results found in study FLTA 3010 where both the FP 100 µg bid and FP 200 µg bid groups experienced a slight increase in physical exam changes, compared with placebo treated patients. A slightly greater incidence of ENT changes (not classified in table) was noted in the FP 200 µg bid group (6 % of patients), as compared to placebo treatment (1 % of patients), and the FP 100 µg bid group (0 % of patients) [NDA 20-121, S-009, 21:122].

With regard to the ENT exam, no significant change in nasal obstruction by nasal polyps (by those patients who had them) was seen in the FP treated patients, compared to placebo at the 2 different doses of FP Nasal Spray [NDA 20-121, S-009, 22:154-222].

With respect to infections, in particular, sinusitis, for the active treatment patients, 1 patient with a normal ENT at screening, subsequently treated with FP 100 µg bid was diagnosed with sinusitis at visit 3 of the study by physical examination which was not further elaborated upon in the sponsor's submission (patient # 191) [NDA 20-121, S-009, 22:191]. Aside from these reports, no notable increase in the incidence of viral, bacterial, or fungal infections was seen in FP Nasal Spray treated patients at either of the 2 doses.

Evaluation of the ear, nose, and throat (ENT exam) to rule out nasal or oral candidiasis or nasal septal ulcerations and/or perforations was performed at every clinic visit [NDA 20-121, S-009, 21:52] and results of these examinations revealed that no patients in either of the 3 treatments group developed oral or nasal candidiasis during treatment with study drug (including placebo) at any of

the study visits [NDA 20-121, S-009, 22:319-373]. Clinical evaluation for presence of nasal septal ulcers or perforations revealed a case of a 3 mm nasal septal excoriation after 28 days of treatment with FP 100 μg bid (patient # 126) [NDA 20-121, S-009, 22:186] and a case of ulceration of the nasal mucosa, again in a patient treated with FP 100 μg bid (patient # 103, occurred at day 23 of treatment) [NDA 20-121, S-009, 22:310]. In study FLN 351, ear exams to assess perforations and serous effusions were not performed (as had been for study FLTA 3010).

8.2.5. Reviewer's Conclusion of Study Results (Efficacy and Safety):

(1) The results of this study support the safety of FLONASE Aqueous Nasal Spray for the treatment of symptoms of NAPR (nasal obstruction, rhinorrhea, and postnasal drip) in adults and adolescents 12 years of age and older.

(2) A summary table of all efficacy parameters (below) studied in patients age 12 years and older is presented below and shows that for the majority of all efficacy endpoints (primary and secondary) FLONASE Aqueous Nasal Spray 100 μg bid and 200 μg bid did not demonstrate statistically significant efficacy compared to placebo treatment, although a greater numerical decrease for the 2 active treatments was seen for all efficacy parameters, beginning with week 1 of treatment. When compared to NAPR study FLTA 3010, however, the magnitude of the effect size for the primary efficacy variable in study study FLN 351 was significantly lower (~17-20 points lower) than the change in patient self-rated mean daily reflective TNSS in FLTA 3010. When compared to placebo, this mean change in TNSS for the FP 100 μg bid group was in a range of 5-14 points, which though small, indicated a consistent trend in decreasing TNSS. A dose response from the 100 μg bid dose of FP Nasal Spray to the 200 μg bid dose was not seen in this study for any efficacy endpoint. Similar to pivotal study FLTA 3010, FLONASE Aqueous Nasal Spray (both doses) demonstrated greatest efficacy in decreasing the NAPR symptoms of nasal obstruction over that of rhinorrhea, postnasal drip, or sneezing (or nasal itch, which was evaluated in FLN 351).

Summary Table: Efficacy Variables for the ITT Population and Treatment with FLONASE Aqueous Nasal Spray for the Non-Allergic Perennial Rhinitis Indication (**STUDY FLN 351**)

EFFICACY VARIABLE	**Statistically Significant Response** (as compared with placebo) **Yes/No**
Primary Efficacy Variable	
1. Δ from baseline in patient-rated average daily reflective TNSS:	**Yes:** FP 200 µg bid: Week 3 **No:** FP 100 µg bid: Week 1-4, post-Rx FP 200 µg bid: Week 1, 2, 4, post-Rx
Secondary Efficacy Variables	
1. Δ from baseline in patient-rated average daily nasal obstruction score	**No:** FP 100 and 200 µg bid: Week 1-4, Post-Rx
2. Δ from baseline in patient-rated average a.m. nasal obstruction score	**Yes:** FP 100 µg bid: Week 1-4, FP 200 µg bid: Week 2, 4. **No:** FP 200 µg bid: Week 1, 3, post-Rx
3. Δ from baseline in patient-rated average daily postnasal drip score	**No:** FP 100 and 200 µg bid: Week 1-4, Post-Rx.
4. Δ from baseline in patient-rated average daily rhinorrhea score	**Yes:** FP 200 µg bid: Week 3 **No:** FP 100 µg bid: Week 1-4, post-Rx FP 200 µg bid: Week 1, 2, 4, post-Rx
5. Δ from baseline in patient-rated average daily sneezing score	**No:** FP 100 and 200 µg bid: Day 8, 15, 22, 29, Post-Rx.
6. Δ from baseline in patient-rated average daily nasal itch score	**No:** FP 100 and 200 µg bid: Day 8, 15, 22, 29, Post-Rx.
	Yes: FP 100 µg bid: Day 29. FP 200 µg bid: Day 8, 15, and 29. **No:** FP 100 µg bid: Day 8, 15, 22, Post-Rx. FP 200 µg bid: Day 22, Post-Rx.
8. Δ from baseline in Physician-rated nasal obstruction score	**Yes:** FP 100 µg bid: Day 15 FP 200 µg bid: Day 8, 15. **No:** FP 100 µg bid: Day 8, 22, 29, Post-Rx FP 200 µg bid: Day 22, 29, Post-Rx.
9. Δ from baseline in Physician-rated postnasal drip score	**No:** FP 100 and 200 µg bid: Day 8, 15, 22, 29, Post-Rx.
10. Δ from baseline in Physician-rated rhinorrhea score	**No:** FP 100 and 200 µg bid: Day 8, 15, 22, 29, Post-Rx.
11. Δ from baseline in Physician-rated sneezing score	**No:** FP 100 and 200 µg bid: Day 8, 15, 22, 29, Post-Rx.
12. Δ from baseline in Physician-rated nasal itch score	**Yes:** FP 100 µg bid: Day 15 **No:** FP 100 µg bid: Day 8, 22, 29, Post-Rx FP 200 µg bid: Day 8, 15, 22, 29, Post-Rx.
11. Overall Patient Evaluation	**Yes:** FP 100 µg bid: Visit 3 and 6. FP 200 µg bid: Visit 6. **No:** FP 200 µg bid: Visit 3.
12. Overall Physician Evaluation	**Yes:** FP 100 and 200 µg bid: Visit 3 and 6.

Important efficacy variables for the approval of FLONASE AQ Nasal Spray for NAPR are represented in bold italics.
Δ=Change, Sx=Symptom, Post-Rx=Post-treatment.