

Safety:

Overall, FP Nasal Spray was safe and well-tolerated given twice a day, at a dose of either 100 µg bid, or 200 µg bid. No serious adverse events or deaths occurred in patients treated with FP Nasal Spray at either of 2 doses. For all 3 treatment groups (including placebo), headache was the most common adverse event, followed by URI, and nasal irritation. No significant increase in oropharyngeal candidiasis or nasal septal ulcerations/perforations were seen in patient treated with FP Nasal Spray, compared with placebo. Four week treatment with FP Nasal Spray at either of the 2 doses did not show a large numerical difference in mean a.m. plasma cortisol measurements post-treatment or an increase in a.m. plasma cortisol outliers in the 2 active treatments, compared with placebo.

Summary:

Based on the results of this NAPR trial, FP Nasal Spray given at a dose of 100 µg bid and 200 µg bid failed to demonstrate adequate statistically significant efficacy for the primary efficacy endpoint and overall, demonstrated marginal evidence of efficacy at best (though the numerical trends were consistent with some clinical response) as compared with placebo, for the treatment of NAPR symptoms in adults and children 12 years of age and older. These conclusions, might in part be interpreted from the perspective of underpowering achieved in this study due to failure to enroll the target population that was pre-specified at the time of study design but other reasons for study failure could also have played a role.

From the safety perspective, the 2 doses were overall, well-tolerated with an unremarkable adverse event profile.

Hence, results of this study, which are primarily supportive, may used to recommend an appropriate dose of FP Nasal of 100 µg bid or 200 µg qd (once daily regimen) for the NAPR indication in adults and children 12 years of age and older based on the efficacy and safety data reviewed in this submission.

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ON ORIGINAL

STUDY FLN-351

4. Flowchart/Timetable

4

Protocol FLN-351

OVERALL TIME AND EVENT SCHEDULE

ACTIVITY	SCREENING	VISIT: 1 2 3 4 5 6					
		STUDY DAY: 1 8 15 22 29 36					
Run-In	X	-----X					
Period of Study Drug Use		X-----X					
Informed Consent	X						
Medical History	X						
Physical Exam	X					X	
Skin Testing	X						
Sinus Radiograph	X						
Total Serum IgE	X						
Labs (A.M. Serum Cortisol, Chemistry, Pregnancy, Hematology, Urinalysis)	X					X	(X)
Nasal Cytology			X			X	
Symptom Assessment	X		X	X	X	X	X
Nasal/Oropharyngeal Exam	X		X	X	X	X	X
Adverse Event Assessment			X	X	X	X	X
Quality of Life Assessment			X			X	
Diary Card Issued	X		X	X	X	X	
Study Medication Issued			X	X			
Summary Report/Treatment Evaluation				X			X ¹

(X) Test to be repeated if abnormal at Visit 5.
¹ To be completed for all patients in the trial, including those patients that are withdrawn.

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NON-ALLERGIC PERENNIAL RHINITIS (Supportive Trial):

- 8.3. Protocol No. FLN 350: A double-blind, randomized, placebo-controlled study of the efficacy and safety of 2 doses of fluticasone propionate aqueous nasal spray bid vs. placebo for 4 weeks in patients with perennial non-allergic rhinitis.

Principal Investigator: Suzanne Weakley, M.D.

Participating Centers: Kelsey-Seybold Clinic, PA
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8.3.1 Objectives

The primary objective of this study was to investigate the safety and efficacy of a 4 week course of 2 different doses of fluticasone propionate (FP) nasal spray (100 µg bid, and 200 µg bid) vs. placebo nasal spray for the treatment of symptoms of non-allergic perennial rhinitis (NAPR).

A secondary objective was to evaluate safety of the 2 doses of FP that could be expected to be used for treatment of NAPR, 100 µg bid and 200 µg bid.

8.3.2. Study Design

The study design of FLN 350 was essentially the same as that of study FLN 351. The study was a phase III, single-center, randomized, double-blind, placebo-controlled, parallel group, with a 4-14 day placebo lead-in, safety and efficacy study of fluticasone propionate nasal spray (FP) 100 µg bid, vs. fluticasone propionate nasal spray (FP) 200 µg bid, and vs. placebo nasal spray bid given for a duration of 28 days (4 weeks) for the treatment of NAPR in patients 18 years of age and older. The 4 week double-blind treatment period was followed by a post-treatment assessment at the day 36 visit [NDA 20-121, S-009, 25:16, 91].

The study consisted of a total of 7 patient visits: a screening visit (visit 1, day -14 to 0), visit 1 or 'the first day of the double-blind treatment period' (baseline visit, day 1), visit 2 (day 8), visit 3 (day 15), and visit 4 (day 22), visit 5 (day 29, the last day of the double-treatment period), and visit 6 (day 36, the post-treatment follow-up visit) [NDA 20-121, S-009, 25:44]. Patients were evaluated in clinic from between 7:30 a.m.-9:30 a.m. for each study visit. The duration of the study for a given patient was approximately 4 weeks. A flow chart of FLN 350 is provided in Appendix I (attached) [NDA 20-121, S-009, 25:44, 92].

8.3.3. Protocol

8.3.3.1.a. Population: Male or female patients, ≥ 18 years of age, with NAPR defined by the inclusion criteria listed below [NDA 20-121, S-009, 25:19, 96-97].

- (I) Inclusion Criteria [NDA 20-121, S-009, 25:19-20, 96-97]:
1. Diagnosis of NAPR as defined by the following criteria:
 - (a) appearance of the nasal mucosa consistent with a diagnosis of rhinitis (specific criteria for this diagnosis were not provided in the protocol) and history of NAPR for at least 1 year duration prior to study entry.
 - (b) evidence of a negative skin test performed within 3 months of the screening visit to the typical seasonal and perennial allergens in the study's geographic area. Skin testing was to be performed to a comprehensive panel of seasonal and perennial allergens via the method. Of note, in preparation for skin testing, patients were not to have used short-acting antihistamines for at least 72 hours.
 2. A morning (a.m.) plasma cortisol level of at least 7 $\mu\text{g/dL}$ on screening.
 3. The patient's self-rated severity of disease at baseline (visit 1, day 1) would need to meet the entry criteria of: a patient-rated total nasal symptom score (TNSS=nasal obstruction, rhinorrhea, postnasal drip) of ≥ 150 points out of a maximum total of 300 points, based on a visual analog rating scale for the daily TNSS for at least 4 out of 7 consecutive days immediately prior to receiving double-blind study medication. (This score was supposed to represent symptoms throughout the previous 24 hours, which were to be scored reflectively by patients in the p.m. prior to dosing with study medication). In addition, on those 4 days, severity of at least 2 of the 3 symptoms was to be at least 40 out of 100 possible points.

Reviewer's Notes: Criteria for a positive/negative skin test were not provided in the study protocol though in previous NAPR studies a positive response was defined as wheal diameter > 2 mm than the negative control) in order to fulfill the diagnosis of non-allergic perennial rhinitis (NAPR). Similar to the pivotal NAPR study FLTA 3010 and study FLN 351, specific criteria for the diagnosis of rhinitis were not provided in terms of nasal mucosal appearance, as was not provided information regarding the diluent used for the negative control in skin testing, nor the specific allergens tested.

In addition, in this study sneezing was not included in the TNSS score for study entry (similar to FLTA 3010), making the maximum total score 300 [NDA 20-121, S-009, 25:20, 97]. In this respect study FLN 350 differed from study FLN 351 (where sneezing was included in the TNSS and the maximum score could be 400).

- (II) Exclusion Criteria [NDA 20-121, S-009, 25:20-21, 97-99]:
1. Physical obstruction of the nares, as defined by septal deviation ($\geq 50\%$ obstruction by physical exam) or nasal polyps that could obstruct delivery of the nasal spray.
 2. History of previous nasal septal surgery.
 3. 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).
 4. Clinical laboratory abnormalities that would confirm the diagnosis of the concurrent diseases listed above (in (3)).
 5. History of hypothyroidism, as evidenced by a T_4 value > 14 $\mu\text{g/dL}$ and a TSH value of ≥ 8 $\mu\text{IU/mL}$.
 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 treatment with study drug. 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, or clinical evidence sinusitis or a candidal infection of the nose or oropharynx.
 9. Use of any investigational new drug within 1 month prior to the screening visit.
 10. Patients with intolerable symptoms that would make participation in the study unbearable.
 11. Concurrent use of cigarettes, cigars, or pipes.
 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. ENT exam findings, specific radiographic findings, additional reliance on culture results) for defining 'sinusitis' were not discussed in the study report. Importantly, study FLN 350 did not employ radiographic screening to rule out sinusitis as did NAPR studies FLTA 3010 and FLN 351. Thus, the diagnosis of sinusitis, which appeared vague compared to the other NAPR studies, appeared to have been based solely on the physician's clinical decision.

(III). Concurrent Medication Restrictions [NDA 20-121, S-009, 25:20-21, 97-98]:

The only medications in which specific washout-periods were provided prior to visit 1 are listed as follows:

<u>Medication</u>	<u>Time Discontinued Prior to Visit 1 (Screening visit)</u>
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 studies FLTA 3010 and FLN 351, the medication exclusion criteria and concomitant wash-out periods are 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.

8.3.3.1.b. Procedure

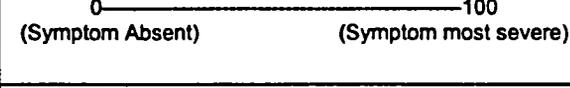
(I) Screening Visit [NDA 20-121, S-009, 25:16, 105]:

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, 25:23, 103] 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, 25:25-26, 103]) was performed at the screening visit. In addition, laboratory evaluation (to include a.m. plasma cortisol levels along with routine blood chemistry, hematology, urinalysis, and tests to rule out pregnancy), 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). Sinus X-rays to exclude radiographic findings consistent with sinusitis were not performed in this study (as they were in FLTA 3010 and FLN 351).

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 8.3.3.1.a.(I)).

Diary cards for nasal symptom recording were issued to patients during the run-in period and patients were instructed in their completion. Specifically, patients were to subjectively rate the following 4 nasal symptoms reflectively over the previous 24 hours in the p.m. (prior to dosing with the evening dose of study medication) on their diary cards: (1) rhinorrhea, (2) postnasal drip, (3) nasal obstruction, and (4) sneezing; 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. [NDA 20-121, S-009, 25:23]. In addition patients were asked to record 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, 25:23, 104].

Figure 1: Subjective NAPR symptom rating scale:

NAPR Symptoms	Visual Analog Scale
Rhinorrhea	
Nasal obstruction	
Postnasal drip	
Sneezing	

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 was 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 the 3 NAPR symptoms of rhinorrhea, postnasal drip and nasal obstruction, however, nasal obstruction was also rated by patients in the a.m. on awakening. Hence, nasal obstruction was rated in both the a.m. and p.m. prior to dosing with study medication. Thus, the method of scoring the TNSS for study 350 was the same as in 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 on that specific day (i.e. this was an 'instantaneous' assessment and was not an average score representing the period preceding the clinic visit) [NDA 20-121, S-009, 25:23, 103]. 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, postnasal drip and sneezing but sneezing was not included in the physician-rated TNSS [NDA 20-121, S-009, 25:23, 103].

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) along with at the post-treatment assessment visit (Day 36) [NDA 20-121, S-009, 25:23, 106-108].

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 300 [NDA 20-121, S-009, 25:17, 20, 97].

(II) Visit 1 (Day 1, 1st day of double-blind study medication) [NDA 20-121, S-009, 25:17, 106]:

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, 25:17,22, 104]. The relative numbers of eosinophils using this technique were assessed using the 5-point scale summarized in Figure 2 [NDA 20-121, S-009, 25:22, 104]:

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.

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, 25:22, 106]:

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 and study FLN 351, i.e. 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 studies FLTA 3010 and FLN 351.

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, 25:17, 107]:

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, 25:18, 107]:

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 and physician-rated total nasal symptoms, at visits 3 and 6 (or at the time of early patient discontinuation), the participating physicians subjectively rated their patients' 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, 25:24, 110]:

Figure 3: Physician Rated Overall Response to Therapy Evaluation Using an Ordinal Scale

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, 25:18, 107]:

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, 25:18, 108]

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.

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, 25:18-19, 108-109].

(VI) Collection of pollen counts:

Similar to studies FLTA 3010 and FLN 351, pollen counts were not collected on a daily basis by the sponsor, nor recorded in a log.

(VII) Safety evaluations [NDA 20-121, S-009, 25:24-26, 100-103]:

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 cortisol was performed prior to dosing with a.m. study medication at screening and day 29 of the study (between 7:30 a.m. and 9:30 a.m.).

An a.m. cortisol level of at least 7 µg/dL was required for study entry [NDA 20-121, S-009, 25:25] and considered in the normal range. Patients were instructed to fast overnight (~ 8 hours) for all clinical laboratory tests.

8.3.3.2. Clinical Endpoints:

Primary and secondary efficacy variables were not pre-specified in study FLN 350 (similar to study FLN 351). The following efficacy variables were assessed in this NAPR study [NDA 20-121, S-009, 25:23, 28, 111]:

- (1) Physician-rated overall evaluation of response to therapy for the double-blind treatment 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 350),
- (2) The change from baseline (defined as Visit 1) in the patient-rated average reflective daily TNSS (=sum of rhinorrhea, nasal obstruction, and (p.m.) postnasal drip) for each week of the double-blind period.
- (3) The change from baseline (defined as Visit 1) in the patient-rated average reflective daily individual nasal symptom scores: rhinorrhea, postnasal drip, sneezing, p.m. and a.m. nasal obstruction for each week of the double-blind period.
- (4) 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.
- (5) The change from baseline (defined as Visit 1) in the physician-rated average reflective daily individual nasal symptom scores: rhinorrhea, postnasal drip, and sneezing for each week of the double-blind period.

Reviewer's Note: Given a symptom score range of 0-100 for any individual NAPR symptom, patients could achieve a TNSS ranging from 0-300, 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 'physician-rated overall evaluation of response to therapy for the double-blind treatment period', this endpoint was taken to be the primary efficacy endpoint for FLN 350.

8.3.3.1. Statistical Analysis [NDA 20-121, S-009, 25:27-28, 110-112, 174-176]:

The study was conducted with a target enrollment of 35-40 patients per treatment arm (i.e. 105-120 patients total). At the time that the study was designed, a minimum sample size of 35 patients per treatment arm (or 105 patients total) was calculated in order to detect a treatment difference of at least 0.87 points in the physician-rated overall clinical evaluation between placebo and the 2 FP treatment groups, based on a 2-sided $\alpha=0.05$, a power of 85%. This power calculation was based on a prior SAR study (FLN-202) involving 423 patients in which the difference between the FP groups (all doses) and placebo in mean overall physician-rated overall clinical evaluation was 0.87 [NDA 20-121, S-009, 25:27, 110]. An estimated standard deviation for the overall physician evaluation was not provided in the study protocol. For this study the **patient-rated TNSS symptom score**, was not used as the determining efficacy variable (as in FLTA 3010 or FLN 351) for powering of the study at the time of its design.

However, subsequent to completion of the double-blind treatment period, it was determined that the patient-rated TNSS symptom score, was a more appropriate primary efficacy endpoint [NDA 20-121, S-009, 25:27, 110]. The physician-rated overall evaluation was tabulated, and the Cochran-Mantel-Haenszel test was used to detect statistically significant differences between treatment groups [NDA 20-121, S-009, 25:28].

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, 25:27]. In the overall physician evaluation, patients who were 'unevaluable' (e.g. lost to follow-up) were excluded from efficacy analysis. 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, and physical examination.

Same as in study FLTA 3010, missing symptom scores used to generate a total symptom score were handled by not replacing ('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 other 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, 25:28, 111]. 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.

postnasal drip, rhinorrhea, and sneezing for the pre-treatment period; revealed small numerical differences between the treatment groups (e.g. range for TNSS: [redacted] for the 3 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, 25:64-66].

(E) Patient Validity

Patients' diary data were invalidated in study FLN 350 if patients failed to meet the minimal requirement for compliance (defined as $\geq 80\%$ 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, refer to Tables V-XVI of the medical officer review for FLN 350 below), 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 studies FLTA 3010 and FLN 351, the criteria for invalidation of patient data (insufficient number of diary recordings) in study FLN 350 was less stringent to those seen in rhinitis trials 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 3 treatment groups combined was 68/68 patients or 100% of enrolled patients [NDA 20-121, S-009, 25:71]. A total of 52 patients completed greater than 4 weeks of the study (including the 4 weeks of the double-blind treatment).

(G) Patient Compliance [NDA 20-121, S-009, 25:31, 50]

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, 25:50 (Table 4)]. Based on these data, at least 87% of patients (range 87-100%) in each treatment group (for the 3 groups) were $\geq 80\%$ compliant in taking study medication during each respective week of the study. The greatest degree of compliance was seen during week 1 of treatment during which 100% of patients in all 3 treatment groups reported being compliant with study medication dosing [NDA 20-121, S-009, 25:50].

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 Visit 5 (week 4) in a.m. plasma cortisol levels. ANOVA was utilized in order to determine significant differences between treatment groups.

The numbers of all adverse events were tabulated by treatment group and individual adverse event. Fisher's exact test was performed by the sponsor for each adverse event table in order to detect statistically significant treatment differences in the number of patients having any adverse event.

Reviewer's Note: Use of statistical significance in the interpretation of safety data when the study was not powered on safety analysis is not a meaningful comparison, hence all safety analyses evaluated by the medical reviewer for this study were evaluated in terms of tabulations of data and outlier results.

8.3.4. Results

8.3.4.1. Patient Demographics

(A) A total of 68 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 (significantly less than the target 105 patient enrollment) and comprised the intent-to-treat (ITT) population. Twenty-three (23) patients were randomized to placebo, 23 were assigned to FP 100 µg bid, and 22 were assigned to FP 200 µg bid [NDA 20-121, S-009, 25:30] and these patients comprised the intent-to-treat population (ITT). Sixty four patients (64, or 94% of all patients randomized into the double-blind portion of the study) completed the double-blind portion of the study and 4 patients withdrew from the study prior to study completion: 2 from the placebo group, 1 from the FP 100 µg bid, and 1 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, 25:48]

PATIENT DISPOSITION	DOUBLE-BLIND TREATMENT PERIOD			Total
	Placebo	FP 100 µg bid	FP 200 µg bid	
Enrolled Patients	23	23	22	68
Intent-to-Treat	23	23	22	68
Safety Evaluable (same as ITT)	23	23	22	68
Completed Study	21	22	21	64

(B) As discussed above, a total of 4 patients withdrew from the double-blind portion of the study prior to study completion, leaving 64 patients who completed the entire double-blind portion of the study. Of the 4 patients who discontinued treatment, 2 patients discontinued (patient # 3, placebo group and patient # 53, FP

100 µg bid group) due to poor compliance with study guidelines (1 patient (#3) took unauthorized drugs, the other patient (#53) missed study visits) while the other 2 patients discontinued treatment (patient # 1, placebo group and patient # 37, FP 200 µg bid group) due to adverse events (flu symptoms and development of candidal pharyngitis (FP 200 µg bid group patient), respectively) [NDA 20-121, S-009, 25:49]. While not significant because of the small patient numbers per treatment arm, the highest incidence (9%) of discontinuation was noted in the placebo group, [NDA 20-121, S-009, 25:48]. This data is summarized in Table III below [NDA 20-121, S-009, 25:48].

Table III. Number and Percentage (%) of Randomized Patients Who Discontinued the Study with Reasons for Discontinuation, ITT Population [NDA 20-121, S-009, 25:48]:

	DOUBLE-BLIND TREATMENT PERIOD			
	Placebo	FP 100 µg bid	FP 200 µg bid	Total
Number Enrolled	23	23	22	68
Number (%) Completed	21 (91%)	22 (96%)	21 (95%)	64 (94%)
Number (%) Withdrawn	2 (9%)	1 (4%)	1 (5%)	4 (6%)
Reason for Discontinuation				
Adverse event	1 (4%)	1 (4%)	0 (0%)	2 (3%)
Lack of Efficacy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Poor compliance	1 (4%)	0 (0%)	1 (5%)	2 (3%)
Patient failed to return	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Required medical intervention	0 (0%)	0 (0%)	0 (0%)	0 (0%)
*Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ALL REASONS	2 (9%)	1 (4%)	1 (5%)	4 (6%)

*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 6%, 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.

(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:

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Table IV. Patient Demographics for the ITT Population-Double Blind Treatment Period [NDA 20-121, S-009, 25:51-52]:

Variable	Placebo (n=93)	FP 100 µg bid (n=98)	FP 200 µg bid (n=95)	P-Value
Gender: (n, (%))				
Male	10 (43%)	14 (61%)	12 (55%)	0.494
Female	13 (57%)	9 (39%)	10 (45%)	
Race: (n, (%))				
Caucasian	19 (83%)	19 (83%)	21 (95%)	0.544
Black	1 (4%)	2 (9%)	0 (0%)	
Asian	3 (13%)	2 (9%)	1 (5%)	
Hispanic	0 (0%)	0 (0%)	0 (0%)	
American Indian	0 (0%)	0 (0%)	0 (0%)	
Other	0 (0%)	0 (0%)	0 (0%)	
Age: (yrs)				
Mean ± SE	46.6 ± 2.2	45.7 ± 2.4	47.5 ± 2.4	0.869
Range	25-64	27-66	29-70	
Weight: (lbs.)				
Mean ± SE	173.1 ± 7.8	174.5 ± 5.1	176.5 ± 7.7	0.943
Range	128-254	130-235	124-291	
Smoking Status:				
Never Smoked	16 (70%)	17 (74%)	10 (45%)	0.108
Previous Smoker	7 (30%)	6 (26%)	12 (55%)	
History of Non-allergic rhinitis:				
1-5 years	6 (26%)	10 (43%)	6 (27%)	0.024
6-10 years	1 (4%)	6 (26%)	1 (5%)	
> 10 years	16 (70%)	7 (30%)	15 (68%)	

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 except for the duration of NAPR in which the majority of patients in the FP 100 µg bid group had a history of NAPR of > 10 years, in contrast to a longer duration (> 10 years) for the placebo and FP 200 µg bid group. The majority of study patients were Caucasian (83-95% of total) and were ≥ 25 years of age. Except for the FP 200 µg bid group, the majority of patients had never smoked. While not presented in this table, all patients (100%) in each treatment group had concurrent medical conditions at the time of randomization and anywhere from 30-57% of all patients 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 thyroid preparations [NDA 20-121, S-009, 25:53, 63].

(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,

8.3.4.2. Efficacy Endpoint Outcomes

(I) Primary Efficacy Variable:

All efficacy analyses in this review were based on the intent-to-treat (ITT) population (n=23 for the placebo group, n=23 for the FP 100 µg bid group, and n=22 for the FP 200 µg bid group). As this study was significantly underpowered due to failure to enroll the target patient number per treatment arm, conclusions about efficacy in this trial are at best supportive.

Based on the powering of study FLN 350, the primary efficacy variable was defined as: the physician-rated overall clinical evaluation which compared placebo to the 2 FP treatment groups for the double-blind treatment period, although 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 would have been a more appropriate primary efficacy variable.

Nonetheless, results for the sponsor's pre-defined primary efficacy variable of overall physician evaluation (shown in Table V) indicates that only the FP 100 µg bid treatment group demonstrated statistically significant efficacy compared with placebo (p=0.004), although approximately twice as many patients in the FP 200 µg bid treatment group had a relatively greater numerical decrease in NAPR symptoms compared with placebo treatment for this endpoint as well [NDA 20-121, S-009, 25:70]. As will be seen for the rest of the secondary efficacy endpoints, the FP 100 µg bid treatment group tended numerically to show a greater decrease in NAPR symptoms than did the FP 200 µg bid treatment group, although for the majority of endpoints these differences in the FP 100 µg bid treatment group were not statistically significant compared with placebo.

Reviewer's Note: In comparing the magnitude of difference in total nasal symptom scores for study FLN 350 and the pivotal NAPR study FLTA 3010, overall the magnitude of difference in scores was minimal and in fact, the mean weekly symptom scores recorded by patients were very similar. This finding suggests that FP Nasal Spray did show efficacy in decreasing NAPR symptoms when compared to placebo, but due to inadequate patient enrollment, statistical significance was not demonstrated.

(II) Secondary Efficacy Variables:

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 demonstrated statistically significantly greater efficacy in decreasing total nasal symptoms from baseline at weeks 1-3 of the double-blind treatment period, compared to placebo treatment (Table VI) but failed to do so for week 4 and the week that followed discontinuation of treatment (Day 29-35 post-treatment) [NDA 20-121, S-009, 25:65]. The FP 200 µg bid group failed to show statistically significant efficacy at any of the time points for the patient-rated TNSS [NDA 20-121, S-009, 25:65]. With discontinuation of treatment with FP

nasal spray in the 2 groups receiving this study medication, the TNSS increased more than that of the respective placebo group, thus indicative of a real treatment effect.

For the individual NAPR symptom scores, the 3 symptom scores of rhinorrhea, nasal obstruction, and postnasal drip contributed approximately equally to the determination of the TNSS. The sneezing score (which was not included in the TNSS), was approximately half of the other NAPR scores, consistent with results seen in the other 2 NAPR trials: FLTA 3010 and FLN 351.

The FP 100 μ g bid and FP 200 μ g bid treatments both failed to demonstrate statistically significant efficacy in decreasing the individual NAPR symptoms of rhinorrhea (Table VII), postnasal drip (Table VIII), or sneezing (Table XI); although a numerical decrease in symptom scores by the 2 active treatments which were in excess of the numerical decrease in symptom scores due to placebo treatment was evident at all 4 weeks of the double-blind treatment period for the 2 active treatments with the exception of the post-treatment week) [NDA 20-121, S-009, 25:65-66]. Importantly, the numerical decrease in these endpoints in study FLN 350 was similar to the numerical decrease in study FLN 3010, hence lack of statistical significance for most efficacy endpoints in study FLN 350 may have primarily been due to inadequate powering and not lack of a response in the FP treated patients with respect to a decrement in nasal symptom scores.

Furthermore, this decrement was progressive with each subsequent week of the study (i.e. increasing from week 1 to week 2, etc.), suggestive of clinical efficacy even though (due to underpowering) the study was not able to demonstrate a statistically significant change in symptom scores.

Greater efficacy was seen for the nasal obstruction score (both a.m. and p.m.) in which the FP 100 μ g bid treatment group again demonstrated a greater numerical decrease in nasal obstruction than did the FP 200 μ g bid treatment group or placebo group, and this difference (between FP 100 μ g bid and placebo) was statistically significant at weeks 1-2 for the a.m. nasal obstruction score (Table X) and weeks 1-3 for the p.m. nasal obstruction score (Table IX) [NDA 20-121, S-009, 25:65-66].

Evaluation of the physician-rated NAPR symptom scores for the double-blind treatment period overall supported the findings seen in the patient-rated NAPR symptom scores, namely, a generally greater numerical decrease in symptom scores in the FP 100 μ g bid treatment group over the FP 200 μ g and placebo treatment groups (exception: rhinorrhea score at most time points) [NDA 20-121, S-009, 25:68-69]. A summary of these data are presented in Tables XII-XVI of the medical officer review. The conclusion regarding efficacy based on the physician-rated symptom scores for the 3 treatment groups is that while statistically significant efficacy was only seen in several efficacy endpoints: (1) Day 15 for the physician-rated TNSS both the FP 100 μ g bid and 200 μ g bid treatment groups (Table XII) [NDA 20-121, S-009, 25:68], (2) Day 29 for the physician-rated postnasal drip score for the FP 100 μ g bid treatment group (Table XIV) [NDA 20-121, S-009, 25:68], and (3) Day 8 and 15 for the physician-rated

nasal obstruction score for the FP 100 µg bid treatment group (Table XV) [NDA 20-121, S-009, 25:68], the greater progressive decrease in NAPR symptom scores for the 2 FP treatment groups relative to placebo treatment again represented a trend that was supportive of clinical efficacy for the 2 active treatments.

Reviewer's Note: Because of study underpowering and choice of the primary efficacy variable, the clinical efficacy data of study FLN 350 are problematic when assessing clinical efficacy from the aspect of presence or absence of statistically significant differences in symptoms scores for the FP treatment group, compared to placebo treatment. Nonetheless, the overall trend of numerical data, similarity of the symptom score data to those in pivotal NAPR study FLTA 3010, and the fact that despite underpowering some efficacy endpoints (including results for the primary efficacy endpoint for the FP 100 µg bid treatment group) were shown to have statistically significant improvements with FP treatment, more than simply suggests that FP Nasal Spray was effective in decreasing NAPR symptoms during the 4 week double-blind treatment period. In addition, the greater relative increase in NAPR symptom scores post-discontinuation of FP Nasal Spray at both the FP 100 µg bid and 200 µg bid dose, compared to placebo treatment, further supports efficacy of the 2 active treatments in decreasing NAPR symptoms.

Thus, based on these data for the primary efficacy variable and the supportive secondary efficacy data, a reasonable dose of fluticasone propionate nasal spray for the treatment of NAPR symptoms would be 100 µg bid (or conversely 200 µg qd).

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Table V.
 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, 25:70]

	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	23	23	22			
Total # of Evaluable Pts:	23	23	21			
Patient Response to Treatment:				0.004	0.150	0.106
Significant Improvement	3 (13%)	10 (43%)	5 (24%)	NA	NA	NA
Moderate Improvement	6 (26%)	7 (30%)	6 (29%)	NA	NA	NA
Mild Improvement	4 (17%)	4 (17%)	6 (29%)	NA	NA	NA
No change	9 (39%)	2 (9%)	4 (19%)	NA	NA	NA
Mildly Worse	1 (4%)	0 (0%)	0 (0%)	NA	NA	NA
Moderately Worse	0 (0%)	0 (0%)	0 (0%)	NA	NA	NA
Significantly Worse	0 (0%)	0 (0%)	0 (0%)	NA	NA	NA

¹FP=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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Table VI.
 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, 25:65]

	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	23	23	22			
Pre-Treatment (day -6 to 0) (n, mean score ± ² SE)	23 205.4 ± 7.8	23 204.6 ± 8.5	22 205.5 ± 7.8	0.938	0.997	0.935
Week 1 (day 1-7) (n, Δ in score ± SE)	23 -23.1 ± 7.8	23 -56.3 ± 12.9	22 -38.7 ± 11.5	0.034	0.317	0.261
Week 2 (day 8-14) (n, Δ in score ± SE)	23 -39.9 ± 12.4	23 -86.6 ± 17.2	22 -71.6 ± 13.8	0.026	0.131	0.474
Week 3 (day 15-21) (n, Δ in score ± SE)	22 -57.3 ± 16.2	23 -109 ± 17.2	22 -74.0 ± 17.3	0.033	0.491	0.142
Week 4 (day 22-28) (n, Δ in score ± SE)	22 -69.5 ± 18.6	23 -108 ± 16.8	21 -81.0 ± 16.8	0.121	0.648	0.280
Post-treatment (day 29-35) (n, Δ in score ± SE)	21 -61.1 ± 17.0	22 -88.7 ± 17.4	21 -70.9 ± 15.1	0.242	0.681	0.448

¹FP=Fluticasone propionate. ²SE=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 Rhinorrhea Symptom Score

Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 25:66]

	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	23	23	22			
Pre-Treatment (day -6 to 0) (n, mean score ± ² SE)	23 59.7 ± 5.8	23 57.5 ± 6.6	22 61.3 ± 6.7	0.805	0.856	0.671
Week 1 (day 1- 7) (n, Δ in score ± SE)	23 -9.8 ± 4.1	23 -18.1 ± 5.8	22 -13.9 ± 4.7	0.235	0.562	0.549
Week 2 (day 8-14) (n, Δ in score ± SE)	23 -13.4 ± 5.1	23 -28.4 ± 7.6	22 -26.5 ± 5.3	0.086	0.134	0.836
Week 3 (day 15-21) (n, Δ in score ± SE)	22 -18.9 ± 6.1	23 -34.8 ± 7.1	22 -28.4 ± 6.8	0.097	0.326	0.498
Week 4 (day 22-28) (n, Δ in score ± SE)	22 -18.6 ± 8.3	23 -33.7 ± 6.9	21 -28.3 ± 7.9	0.156	0.298	0.723
Post-treatment (day 29-35) (n, Δ in score ± SE)	21 -21.3 ± 5.6	22 -23.7 ± 6.7	21 -28.3 ± 7.9	0.801	0.470	0.631

¹FP=Fluticasone propionate. ²SE=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 Postnasal Drip Score
 Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 25:65]

	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	23	23	22			
Pre-Treatment (day -6 to 0) (n, mean score ± ² SE)	23 61.3 ± 2.5	23 61.7 ± 2.6	22 67.1 ± 2.2	0.701	0.946	0.655
Week 1 (day 1-7) (n, Δ in score ± SE)	23 -9.5 ± 2.3	23 -7.8 ± 2.0	22 -13.1 ± 2.2	0.276	0.322	0.931
Week 2 (day 8-14) (n, Δ in score ± SE)	23 -15.1 ± 2.3	23 -16.1 ± 2.6	22 -20.9 ± 2.8	0.092	0.253	0.593
Week 3 (day 15-21) (n, Δ in score ± SE)	22 -17.5 ± 2.6	23 -17.8 ± 2.9	22 -24.6 ± 2.6	0.057	0.738	0.115
Week 4 (day 22-28) (n, Δ in score ± SE)	22 -21.4 ± 2.7	23 -21.1 ± 3.0	21 -27.1 ± 2.7	0.289	0.695	0.150
Post-treatment (day 29-35) (n, Δ in score ± SE)	21 -20.2 ± 2.6	22 -20.6 ± 2.6	21 -24.4 ± 2.6	0.133	0.985	0.138

¹FP=Fluticasone propionate. ²SE=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 Nasal Obstruction Score

Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 25:65]

	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	23	23	22			
Pre-Treatment (day -6 to 0) (n, mean score ± SE)	23 68.1 ± 4.5	23 61.7 ± 2.6	22 66.9 ± 3.5	0.867	0.843	0.974
Week 1 (day 1-7) (n, Δ in score ± SE)	23 -5.8 ± 2.5	23 -24.1 ± 5.8	22 -11.3 ± 3.9	0.003	0.372	0.039
Week 2 (day 8-14) (n, Δ in score ± SE)	23 -13.0 ± 3.8	23 -30.7 ± 6.5	22 -22.0 ± 5.3	0.021	0.237	0.254
Week 3 (day 15-21) (n, Δ in score ± SE)	22 -18.9 ± 5.2	23 -36.7 ± 6.5	22 -23.0 ± 6.1	0.039	0.640	0.108
Week 4 (day 22-28) (n, Δ in score ± SE)	22 -23.9 ± 6.0	23 -36.5 ± 6.0	21 -28.1 ± 6.0	0.137	0.626	0.325
Post-treatment (day 29-35) (n, Δ in score ± SE)	21 -18.7 ± 6.0	22 -29.3 ± 7.0	21 -21.2 ± 4.8	0.220	0.772	0.349

¹FP=Fluticasone propionate. ²SE=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 A.M. Nasal Obstruction Score

Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 25:66]

	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	23	23	22			
Pre-Treatment (day -6 to 0) (n, mean score ± ² SE)	23 70.3 ± 5.1	23 66.6 ± 4.1	22 71.6 ± 3.5	0.546	0.836	0.422
Week 1 (day 1- 7) (n, Δ in score ± SE)	23 -3.4 ± 4.5	23 -17.3 ± 4.2	22 -13.6 ± 4.4	0.027 ¹	0.107	0.551
Week 2 (day 8-14) (n, Δ in score ± SE)	23 -11.8 ± 5.0	23 -28.0 ± 5.9	22 -24.3 ± 5.8	0.043 ¹	0.119	0.643
Week 3 (day 15-21) (n, Δ in score ± SE)	22 -16.9 ± 6.0	23 -31.1 ± 6.5	22 -27.2 ± 6.3	0.114	0.252	0.667
Week 4 (day 22-28) (n, Δ in score ± SE)	22 -23.5 ± 6.3	23 -32.4 ± 5.9	21 -32.0 ± 6.3	0.311	0.344	0.963
Post-treatment (day 29-35) (n, Δ in score ± SE)	21 -20.4 ± 6.6	22 -28.3 ± 6.2	21 -25.8 ± 6.6	0.385	0.558	0.781

¹FP=Fluticasone propionate. ²SE=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 Sneezing Score**
 Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 25:66]

	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	23	23	22			
Pre-Treatment (day -6 to 0) (n, mean score ± ² SE)	23 35.7 ± 5.1	23 27.5 ± 5.8	22 35.9 ± 6.5	0.317	0.984	0.313
Week 1 (day 1- 7) (n, Δ in score ± SE)	23 -7.0 ± 4.0	23 -8.6 ± 3.9	22 -11.9 ± 3.5	0.763	0.377	0.557
Week 2 (day 8-14) (n, Δ in score ± SE)	23 -6.7 ± 3.9	23 -14.2 ± 6.4	22 -18.0 ± 5.9	0.337	0.153	0.628
Week 3 (day 15-21) (n, Δ in score ± SE)	22 -12.3 ± 4.9	23 -16.8 ± 5.9	22 -23.0 ± 5.6	0.563	0.176	0.425
Week 4 (day 22-28) (n, Δ in score ± SE)	22 -15.2 ± 4.3	23 -15.2 ± 6.0	21 -17.4 ± 5.3	0.995	0.778	0.771
Post-treatment (day 29-35) (n, Δ in score ± SE)	21 -12.7 ± 5.2	22 -13.3 ± 5.7	21 -17.6 ± 5.2	0.935	0.524	0.573

¹FP=Fluticasone propionate. ²SE=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 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, 25:68]

	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	23	23	22			
Pre-Treatment (Day 1) (n, mean score ± ² SE)	23 205.5 ± 6.5	23 188.9 ± 5.9	22 204.0 ± 8.0	0.088	0.880	0.123
Day 8 (n, Δ in score ± SE)	23 -54.0 ± 12.9	23 -66.1 ± 13.9	22 -60.7 ± 11.9	0.506	0.715	0.769
Day 15 (n, Δ in score ± SE)	21 -41.6 ± 12.8	22 -79.4 ± 13.8	21 -81.8 ± 13.3	0.049	0.039	0.899
Day 22 (n, Δ in score ± SE)	20 -56.5 ± 14.7	22 -80.7 ± 12.2	21 -56.9 ± 13.9	0.211	0.981	0.214
Day 29 (n, Δ in score ± SE)	23 -52.7 ± 12.2	23 -80.2 ± 14.2	22 -67.2 ± 13.2	0.142	0.442	0.489
Post-treatment (Day 36) (n, Δ in score ± SE)	23 -29.3 ± 12.2	22 -21.6 ± 9.1	22 -27.9 ± 14.1	0.653	0.933	0.718

¹FP=Fluticasone propionate. ²SE=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, 25:69]

	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	23	23	22			
Pre-Treatment (Day 1) (n, mean score ± SE)	23 56.6 ± 4.7	23 41.0 ± 4.6	22 54.9 ± 6.4	0.039	0.820	0.067
Day 8 (n, Δ in score ± SE)	23 -16.0 ± 5.6	23 -13.0 ± 6.9	22 -20.6 ± 5.5	0.726	0.593	0.379
Day 15 (n, Δ in score ± SE)	21 -10.4 ± 7.8	22 -15.6 ± 5.2	21 -27.5 ± 6.6	0.575	0.071	0.201
Day 22 (n, Δ in score ± SE)	20 -18.7 ± 7.3	22 -20.3 ± 6.3	21 -20.2 ± 7.9	0.870	0.881	0.990
Day 29 (n, Δ in score ± SE)	23 -15.4 ± 6.3	23 -14.7 ± 7.6	22 -25.0 ± 6.7	0.939	0.333	0.297
Post-treatment (Day 36) (n, Δ in score ± SE)	23 -9.4 ± 5.6	22 0.4 ± 4.9	22 -4.1 ± 7.0	0.240	0.525	0.590

¹FP=Fluticasone propionate. ²SE=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, 25:68]

	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	23	23	22			
Pre-Treatment (Day 1) (n, mean score ± ² SE)	23 77.2 ± 3.4	23 76.1 ± 4.0	22 75.9 ± 3.6	0.835	0.803	0.966
Day 8 (n, Δ in score ± SE)	23 -21.3 ± 6.2	23 -23.2 ± 6.5	22 -17.8 ± 4.8	0.819	0.683	0.526
Day 15 (n, Δ in score ± SE)	21 -17.3 ± 4.3	22 -32.7 ± 6.7	21 -29.4 ± 6.1	0.064	0.150	0.685
Day 22 (n, Δ in score ± SE)	20 -19.3 ± 5.9	22 -33.3 ± 5.2	21 -16.3 ± 7.0	0.106	0.737	0.049
Day 29 (n, Δ in score ± SE)	23 -16.3 ± 4.9	23 -33.3 ± 6.6	22 -17.9 ± 5.6	0.040	0.849	0.064
Post-treatment (Day 36) (n, Δ in score ± SE)	23 -9.9 ± 5.9	22 -11.5 ± 5.4	22 -8.9 ± 5.3	0.836	0.898	0.740

¹FP=Fluticasone propionate. ²SE=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 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, 25:68]

	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	23	23	22			
Pre-Treatment (Day 1) (n, mean score ± ² SE)	23 71.7 ± 3.0	23 71.7 ± 3.2	22 73.3 ± 3.5	1.000	0.737	0.737
Day 8 (n, Δ in score ± SE)	23 -16.7 ± 4.7	23 -30.0 ± 4.4	22 -22.3 ± 5.0	0.049	0.409	0.253
Day 15 (n, Δ in score ± SE)	21 -14.0 ± 4.5	22 -31.1 ± 4.7	21 -24.9 ± 4.9	0.013	0.110	0.358
Day 22 (n, Δ in score ± SE)	20 -18.6 ± 4.7	22 -27.1 ± 4.4	21 -20.4 ± 4.6	0.192	0.782	0.297
Day 29 (n, Δ in score ± SE)	23 -21.0 ± 4.2	23 -32.3 ± 5.4	23 -24.3 ± 5.0	0.107	0.633	0.261
Post-treatment (Day 36) (n, Δ in score ± SE)	23 -10.0 ± 4.9	22 -10.5 ± 4.4	22 -14.8 ± 5.1	0.937	0.478	0.533

¹FP=Fluticasone propionate. ²SE=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, 25:69]

	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	23	23	22			
Pre-Treatment (Day 1) (n, mean score ± SE)	93 30.4 ± 2.7	23 31.5 ± 3.1	22 25.8 ± 2.7	0.364	0.842	0.484
Day 8 (n, Δ in score ± SE)	23 -11.2 ± 2.5	23 -11.5 ± 3.3	22 -12.6 ± 2.8	0.190	0.073	0.609
Day 15 (n, Δ in score ± SE)	21 -12.0 ± 3.0	22 -13.3 ± 3.3	21 -11.0 ± 2.9	0.063	0.108	0.811
Day 22 (n, Δ in score ± SE)	20 -12.4 ± 2.9	22 -11.3 ± 3.3	21 -10.7 ± 3.2	0.240	0.987	0.241
Day 29 (n, Δ in score ± SE)	23 -12.4 ± 3.5	23 -15.4 ± 3.2	22 -14.3 ± 2.8	0.932	0.767	0.833
Post-treatment (Day 36) (n, Δ in score ± SE)	23 -9.3 ± 2.7	22 -11.5 ± 3.1	22 -6.0 ± 3.0	0.821	0.710	0.555

¹FP=Fluticasone propionate. ²SE=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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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.

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 350.

8.3.4.2. Nasal Cytology Studies

Nasal cytology studies were conducted in order to assess the proportion of patients enrolled in FLN 350 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 (96% of placebo group patients, 96% of FP 100 µg bid patients, and 95% of FP 200 µg bid patients) [NDA 20-121, S-009, 25:61], 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 ($p=1.000$) and between placebo and the FP 200 µg bid group ($p=0.975$) [NDA 20-121, S-009, 25:61].

Furthermore, the percentage of nasal smears with no eosinophils remained approximately unchanged in each of the 2 active treatment groups by Day 29 but increased slightly in the placebo group (87% of placebo group patients, 96% of FP 100 µg bid patients, and 91% of FP 200 µg bid patients) [NDA 20-121, S-009, 25:61-62].

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8.3.4.3. Safety Analysis

Safety analysis for study FLN 350 consisted of an evaluation of adverse events, standard laboratory tests (along with special safety studies such as a.m. plasma cortisol) 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, 25:27]. In this trial, the safety evaluable population was the same as the ITT population. All 68 patients who received study medication were included in the safety analysis and comprised the intent-to-treat population (n=23 for the placebo group, n=23 for the FP 100 µg bid group, and n=22 for the FP 200 µg bid group) [NDA 20-121, S-009, 25:30,37].

8.3.4.3.1. Demographics of the Exposed Population

With the minor exception of differences in duration of NAPR between the 3 treatment groups, 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, 25:51-52]). Importantly, the ages of patients studied in FLN 350 were older than other respective NAPR studies (age ≥ 25 years for all 3 treatment groups) and thus this study does not represent a well-balanced study with respect to the pediatric or adolescent population.

8.3.4.3.2. 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 3 treatment groups combined was 68/68 patients or 100% of enrolled patients [NDA 20-121, S-009, 25:71]. A total of 52 patients completed greater than 4 weeks of the study (including the 4 weeks of the double-blind treatment).

8.3.4.4. Adverse Events (AE's)

The overall incidence of adverse events (AEs) was generally similar for all 3 treatment groups (39-55% range, highest in the FP 200 µg bid group). Of note, these overall AE ranges were similar to that of NAPR studies FLTA 3010 and FLN 351. 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, rhinorrhea, throat irritation, cough, viral respiratory infections, and pain in the 2 FP 200 µg bid treatment group compared to placebo and FP 100 µg bid treatment groups) [NDA 20-121, S-009, 25:38].

The most common AE for the 3 FP treatment groups was headache and migraines (incidence ≥ 22% for the 2 FP groups), followed by cough (incidence ≥ 4% for the 2 FP groups), and throat irritation (incidence ≥ 4% for the 2 FP groups) (see Table XVII). A slight dose response for the 2 active treatment groups was

noted for the adverse event of 'pain' (0 % incidence in the placebo group, a 4% incidence in the FP 100 µg bid group, and a 9% incidence in the FP 200 µg bid group) [NDA 20-121, S-009, 25:38, 73]. Importantly, no significant increase in the incidence of viral respiratory infections (incidence=4% for the placebo group, vs. 0% for the FP 100 µg bid group, and 9% for the FP 200 µg bid group) or URI (incidence= 9% for the placebo group, vs. 4% for the FP 100 µg bid group, and 0% for the FP 200 µg bid group) [NDA 20-121, S-009, 25:72] was seen across treatment groups except as noted previously, for a minor increase in viral respiratory infections in the FP 200 µg bid group. However, it appears that for this study, a slight increase (1 case in 22 patients or 5%) in oral candidiasis was noted in the FP 200 µg bid group [NDA 20-121, S-009, 25:74, 86]. Again, this data is difficult to interpret based on the small number of patients in the safety database for each treatment arm. No significant increase in the incidence of nasal sinus disorders (not specified in tabulation) was noted in either of the 3 treatment groups with treatment (incidence=0% for the placebo group, vs. 4% for the FP 100 µg bid group, and 0% for the FP 200 µg bid group) [NDA 20-121, S-009, 25:72].

In summary, the safety profile for the double-blind period for FP nasal in study FLN 350 was similar to that seen in the other NAPR studies (FLTA 3010 and FLN 351), 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, unusual infections that would be indicative of immunosuppression (such as recurrent herpes or zoster), oral or nasal candidiasis in the sponsor's AE database.

A summary of the most common reported adverse events for the 3 treatment groups (including placebo) presented in Table XVII. below.

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**Table XVII. Adverse Event (AE) Frequency:
Most Common AE's ($\geq 5\%$ incidence) in Any Fluticasone Treatment Group
(FLONASE Aqueous Nasal Spray), by Organ System and Preferred Term; ITT
Population [NDA 20-121, S-009, 25:72-73]**

BODY SYSTEM	Preferred Term	Placebo	FP 100 μ g	FP 200 μ g
		(n=23)	bid (n=23)	bid (n=22)
		n (%)	n (%)	n (%)
All Systems	Any AE	11 (48%)	9 (39%)	12 (55%)
ENT	Rhinorrhea	1 (4%)	0 (0%)	3 (14%)
	Throat Irritation	1 (4%)	1 (4%)	2 (9%)
	URI	2 (9%)	1 (4%)	0 (0%)
	Upper respiratory inflammation	2 (9%)	0 (0%)	1 (5%)
Neurology	Headaches	6 (26%)	5 (22%)	8 (36%)
	Migraines	6 (26%)	5 (22%)	8 (36%)
Gastrointestinal	Nausea and vomiting	2 (2%)	2 (2%)	5 (5%)
Lower Respiratory	Cough	1 (4%)	1 (4%)	3 (14%)
	Viral respiratory infections	1 (4%)	0 (0%)	2 (9%)
Non-site specific	Pain	0 (0%)	1 (4%)	2 (9%)
Reproduction	Menstruation symptoms	0 (0%)	1 (11%)	0 (0%)

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

8.3.4.5. 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.

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

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

8.3.4.7. Patient Discontinuation due to Adverse Events

A total of 2 patients discontinued treatment prematurely during the 4 week double-blind treatment period due to adverse events (1 in the placebo group: patient #1, and 1 in the FP 200 μ g bid group: patient #37) [NDA 20-121, S-009, 25:75-76]. The reasons for discontinuation for 2 patients consisted of the following: (1) patient # 1 in the placebo withdrew from the study due to an AE consisting of frontal headache, pain in the mouth, sore throat, and influenza symptoms) [NDA 20-121, S-009, 25:75] and (2) patient #37 in the FP 200 μ g bid group withdrew from the study due to sore throat, earache, oral candidiasis, throat infection, and otitis [NDA 20-121, S-009, 25:76, 86, 26:73].

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8.3.4.8. Serious Adverse Events and Death

No ³serious AEs nor any deaths were reported in this study at any time point for any patients in either of the 3 treatment groups [NDA 20-121, S-009, 25:38].

8.3.4.9. 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) 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. Same as in all other NAPR studies, 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, 25:78-84]. The sponsor's criteria for 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, 25:77]. 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, 3:80-81]. With the exception of the a.m. plasma cortisol levels, 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 with the exception of 1 patient in the FP 200 µg bid group (patient # 11) that developed an increase in SGPT outside of the 'normal' range to 131 U/L at day 37 of the study from a screening value of 19 U/L (see Table 24 in the NAPR submission, NDA 20-121, S-009, 25:40, 80-81, 82).

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, 25:78-79]. 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.

³ 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 evaluation of individual 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 $\leq 1\%$ [NDA 20-121, S-009, 25:82]. These data are summarized in Table 25 of the study report for FLN 351 [NDA 20-121, S-009, 25:82]. No pattern of clinical laboratory abnormalities in the active treatment groups was seen, as compared to placebo treatment. Only 1 patient (patient # 11, FP 200 μg bid group, discussed previously above) was recorded with an increase in SGPT (from a normal screening level) to 95 U/L on Day 29 of the study which continued to increase to 131 U/L one week post-discontinuation of the drug and finally reverted to a normal value of 30 U/L approximately 1 month later (day 71 of the study) [NDA 20-121, S-009, 25:82].

As compared with study FLTA 3010 and FLN 351, no cases of either hyperbilirubinemia or hyperglycemia were detected in study FLN 350. No patients were withdrawn from the study because of abnormal laboratory values.

8.3.4.9.1. A.M. Plasma Cortisol Studies

Similar to study FLN 351, adrenal function was evaluated in FLN 350 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 treatment period were presented in the FLN 350 submission as the mean cortisol levels pre-treatment and post-4 weeks of treatment (see Table XVIII below, as individual patient line listings and as a list of patient outliers [NDA 20-121, S-009, 25:83-84, 26:206-211]. For purposes of this study, a normal a.m. plasma cortisol level was defined as: a cortisol level between 5-18 $\mu\text{g}/\text{dL}$ [NDA 20-121, S-009, 25:40].

Based on mean a.m. cortisol measurements pre- and post-treatment with study drug, no statistically significant pairwise differences were seen between either of the 2 FP treatments and placebo. For the post-treatment a.m. cortisol levels, a statistically significant difference was noted between the FP 100 μg bid and FP 200 μg bid treatment groups, although numerically these differences were very small [NDA 20-121, S-009, 25:83].

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 any of the 3 treatments, no patients had a.m. plasma cortisol levels post-treatment that were lower than the pre-treatment value. Hence, a.m. cortisol outlier data primarily comprised a.m. plasma cortisol values at post-treatment that were approximately the same as or higher than the pre-treatment values and

therefore not indicative of any trend toward adrenal suppression [NDA 20-121, S-009, 25:84, 26:206-211].

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) and the study was only carried out to 4 weeks duration (i.e. short-term study), the data presented above are thus somewhat limited with respect to the applicability in cortisol suppression (the extent or lack thereof) with long-term FP Nasal Spray use. Again, 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 diagnostic methods employed in this study.

Table XVIII. 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, 25:83]

A.M. PLASMA CORTISOL (µg/dL)	Placebo Pre-Rx, n=23 Post-week 4, n=23 (mean ± SE)	FP 100 µg bid Pre-Rx, n=23 Post-week 4, n=23 (mean ± SE)	FP 200 µg bid Pre-Rx, n=22 Post-week 4, n=22 (mean ± SE)	P-Values		
				P vs. FP 100	P vs. FP 200	FP 100 vs. FP 200
Pre-Rx (Screening)	13.1 ± 0.73	14.4 ± 1.23	14.1 ± 1.40	0.436	0.558	0.853
Post-week 4 (Visit 5)	12.7 ± 1.11	12.0 ± 0.94	14.8 ± 2.01	0.178	0.455	0.040

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.

8.3.4.10. Physical Examination (including ENT exam)

Evaluation of change in the physical examination of patients during the 4 week double-blind period revealed no significant trends in physical findings and only minor changes on exam in select patients. In this study, no particular treatment group was noted to have more changes on physical examination (including ENT changes), compared with the other groups [NDA 20-121, S-009, 25:85].

With regard to the ENT exam, no significant change in nasal obstruction by nasal polyps (by those patients who had them) or in the appearance of the nasal septum was seen in the FP treated patients, compared to placebo at the 2 different doses of FP Nasal Spray [NDA 20-121, S-009, 25:54-55].

With respect to infections, in particular, sinusitis, for the active treatment patients, no patients in either of the 2 active treatment groups were noted to have developed sinusitis. In summary, based on the AE database in Table 19 and the

somewhat limited physician report in Table 28 in the sponsor's submission, no notable increase in the incidence of viral, bacterial, or fungal infections was seen in FP Nasal Spray treated patients [NDA 20-121, S-009, 25:72-73, 85, 26:53-56].

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, 25:25-26, 40-41, 26:57-75] and results of these examinations revealed that only 1 patient in the FP 200 µg bid treatment group developed oral candidiasis during study visit 2 which was confirmed with [REDACTED] requiring treatment with Mycostatin torches after discontinuation of FP nasal spray and with recurrence of oral candidiasis 4 days later nonetheless [NDA 20-121, S-009, 25:40-41, 26:73]. Clinical evaluation to detect nasal septal ulcers or perforations revealed no cases of either in any patients in study FLN 350. Cataracts and glaucoma were not specifically evaluated in this study as safety endpoints.

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8.3.5. 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, only patients age 25 years and older were specifically evaluated in this study.
- (2) A summary table (see below) of all efficacy parameters, studied in patients age 25 years and older is presented below and shows that for the majority of all efficacy endpoints 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 and continuing throughout the 4 week double-blind treatment period. Importantly, the study did show statistically significant improvement in the physician-rated overall evaluation (the primary efficacy endpoint for FLN 350) for the FP 100 µg bid treatment group. Since the study was not adequately powered to detect statistical significance, interpretability of other secondary efficacy data in this study is unfortunately limited, although the numerical trends in symptom scores would support efficacy in the 2 active treatments which is beyond that seen with placebo treatment. Furthermore, cross-study comparison with pivotal study FLTA 3010 demonstrated that the mean change in weekly TNSS were very similar between these 2 studies for the FP 100 µg bid dose, supporting the clinical efficacy of FP 100 µg bid in the treatment of NAPR symptoms, despite inadequate patient enrollment to detect a statistical difference in symptom scores. Also 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).

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.

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