

Summary Table: Efficacy Variables for the ITT Population and Treatment with
 FLONASE Aqueous Nasal Spray for the Non-Allergic Perennial
 Rhinitis Indication (STUDY FLN 350)

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

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.

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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, although slightly fewer AEs were seen at the FP 100 µg bid dose over the 200 µg bid dose. No serious adverse events or deaths occurred in any patients treated with FP Nasal Spray at either of the 2 doses. For all 3 treatment groups (including placebo), headache was the most common adverse event, followed by cough and throat irritation. No significant increase in oropharyngeal candidiasis or nasal septal ulcerations/perforations were seen in patients 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 failed to demonstrate consistent statistically significant efficacy for the majority of efficacy endpoints with the exception of the primary efficacy endpoint, though the numerical change in symptom scores were very similar to that seen in pivotal study FLTA 3010, supportive of clinical efficacy of FP 100 µg bid for the treatment of NAPR symptoms. Lack of statistical significance for these time points was most likely due to underpowering of the study.

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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APPENDIX I: STUDY FLN 350

Figure 1: Overall Time and Event Schedule

ACTIVITY	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
	Day -14 to 0	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	
Informed consent	X							
Medical history	X							
Physical examination	X					X		
Skin testing	X							
Sinus radiograph	X							
Total serum IgE	X							
Labs (chemistry, hematology, urinalysis, morning plasma cortisol, pregnancy)	X					X	(X)	
Nasal cytology		X				X		
Clinician-rated nasal symptom assessment	X	X	X	X	X	X	X	
Nasal/oropharyngeal exam	X	X	X	X	X	X	X	
Adverse event assessment		X	X	X	X	X	X	
Concomitant medications assessment		X	X	X	X	X	X	
Pharmacoeconomic questionnaires		X				X		
Overall patient evaluation				X			X ¹	
Overall clinical evaluation				X			X ¹	
Diary cards issued	X	X	X	X	X	X		
Study medication issued		X		X				
Period of study drug use		X—————X						

(X) Test to be repeated if abnormal at Visit 5.
 X¹ To be completed for all patients, including those who were withdrawn

PERENNIAL ALLERGIC RHINITIS (Bridging Trial):

- 8.4. Protocol No. FLN 310: A double-blind, randomized, parallel group, multi-center, placebo-controlled clinical trial to evaluate the efficacy and safety of once daily vs. twice daily intranasal administration of fluticasone propionate in patients with perennial allergic rhinitis (PAR).

Principal Investigator: None, multi-center study.

Participating Centers: 13 U.S. centers.

8.4.1 Objectives

The primary objective of this study was to investigate the safety and efficacy of a 24 week course of 2 different dosing regimens of fluticasone propionate (FP) nasal spray: FP 100 µg bid vs. FP 200 µg qd, and vs. placebo nasal spray for the treatment of symptoms of perennial allergic rhinitis (PAR). This study constituted 1 of 2 bridging studies for the PAR efficacy supplement for FLONASE Aqueous Nasal Spray whose objective (as also FLN 311) it was to demonstrate comparable clinical efficacy of the 200 µg qd regimen of FP Nasal Spray to the FP 100 µg bid regimen.

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

8.4.2. Study Design

The study was a phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group, with a 2 week placebo lead-in, safety and efficacy study of fluticasone propionate nasal spray (FP) 100 µg bid, vs. fluticasone propionate nasal spray (FP) 200 µg qd, and vs. placebo nasal spray bid given for a duration of 6 months (24 weeks) for the treatment of PAR in patients 12 years of age and older. The 24 week double-blind treatment period was followed by a 2 week post-treatment assessment (weeks 24-26) [NDA 20-121, S-009, 27:52-53]. The overall study design of FLN 310 (also FLN 311) was similar to that of studies FLN 350 and 351 with the exception that these former 2 trials were of longer duration (see below) and a number of additional parameters were assessed in FLN 310 (which were not evaluated in FLN 350 or 351, see below). While a number of amendments were made to the initial study protocol for FLN 310, the study design summary discussed in the medical officer review represents that of the final protocol for FLN 310 [NDA 20-121, S-009, 27:53-54].

FLN 310 consisted of a total of 16 patient visits: a screening visit (visit 0, day -29 to -22), visit 1 or 'the first day of the single-blind treatment period' (day -15), visit 2 (day -8), visit 3 (day -1), and visit 4 (day 1, week 0, the 1st day of the double-blind treatment period), visit 5 (day 8, week 1), visit 6 (day 15, week 2),

visit 7 (day 29, week 4), visit 8 (day 43, week 6), visit 9 (day 57, week 8), visit 10 (day 71, week 10), visit 11 (day 85, week 12), visit 12 (day 115, week 16), visit 13 (day 141, week 20), visit 14 (day 169, week 24), and the post-treatment visit: visit 15 (day 183, week 26) [NDA 20-121, S-009, 27:36, 443, 28:267]. Patients were evaluated in clinic from between 6:30 a.m.-9:30 a.m. for each study visit. The duration of the study for a given patient was approximately 26 weeks. A flow chart of FLN 310 is provided in Figure 1 of the sponsor's submission and is inserted in this review as Appendix I [NDA 20-121, S-009, 27:36, 443, 28:267-268].

8.4.3. Protocol

8.4.3.1.a. Population: Male or female patients, ≥ 12 years of age, with PAR defined by the inclusion criteria listed below [NDA 20-121, S-009, 27:55].

- (I) Inclusion Criteria [NDA 20-121, S-009, 27:55, 28:280-281]:
1. Diagnosis of PAR as defined by the following criteria:
 - (a) evidence of a positive skin test at screening to a relevant perennial allergen (e.g. dust mite, animal dander) that the patient was exposed to on a continuous basis (positive response defined as a $\geq 2+$ skin test reaction per physician reading) in order to fulfill the diagnosis of perennial allergic rhinitis (PAR).
 - (b) presence of nasal eosinophilia on nasal cytology exam.
 2. A morning (a.m.) plasma cortisol level of at least $7 \mu\text{g/dL}$ on screening and a normal response to Cortrosyn stimulation using the standard $250 \mu\text{g}$ dose or cosyntropin (this was defined a priori as an increase in plasma cortisol concentration $\geq 7 \mu\text{g/dL}$ from baseline to a level of at least $18 \mu\text{g/dL}$, 30' after I.V. administration of Cortrosyn or 60' after I.M. administration of Cortrosyn).
 3. The patient's self-rated severity of disease for at least 8 out of the 14 days immediately prior to receiving double-blind study medication (the single-blind run-in period) would need to meet the entry criteria of: a patient-rated total nasal symptom score (TNSS defined as being comprised of nasal obstruction and rhinorrhea for the run-in period) of ≥ 100 points out of a maximum total of 200 points, based on a visual analog rating scale for the daily TNSS. (Similar to the NAPR studies, this score was supposed to represent symptoms throughout the previous 24 hours, i.e. were to be scored reflectively by patients in the p.m. prior to dosing with study medication).

Reviewer's Notes: Similar to the pivotal NAPR study FLTA 3010, 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, the specific allergens tested, nor the definition of a $\geq 2+$ skin test reaction. In addition, the antihistamine washout times prior to skin testing were not delineated in the study protocol for FLN 310.

- (II) Exclusion Criteria [NDA 20-121, S-009, 27:56, 28:281-283]:
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. Diagnosis of rhinosinusitis, rhinitis medicamentosa, vasomotor rhinitis, or NARES.
 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: 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 hypersensitivity reactions to any intranasal, inhaled, or systemic corticosteroid therapy.
 6. Concurrent bacterial or viral infection (e.g. URI) that could confound analysis of efficacy.
 7. Use of any investigational new drug within 1 month prior to the screening visit.
 8. Patients with an elevated intraocular pressure (> 22 mm Hg)
 9. Patients with cataracts or lenticular .
 10. Patients starting immunotherapy who were not on stable doses of maintenance therapy.
 11. History of previous enrollment in a PAR study with fluticasone propionate aqueous nasal spray.
 12. 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 any capacity in the study report or study protocol.

(III). Concurrent Medication Restrictions [NDA 20-121, S-009, 27:56, 66, 28:293]:

The following medications were to be discontinued within the indicated time periods prior to visit 1, and were not allowed throughout the study duration:

<u>Medication</u>	<u>Time Discontinued Prior to Visit 1 (Screening visit)</u>
1. Intranasal sodium cromolyn	≥ 2 weeks
2. Intranasal, inhaled, or systemic corticosteroids	≥ 1 month
3. 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 and theophylline during the study for the treatment of asthma but use of these drugs were to be recorded on the case report forms (CRFs). 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 prescription or OTC drugs that could affect the course of rhinitis (e.g. decongestants, sinus medications, and including antihistamines with the exception of chlorpheniramine, which was allowed as a rescue medication during the run-in and double-blind treatment period) [NDA 20-121, S-009, 27:87] 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 whose use was prohibited, such as: decongestants, expectorants, sinus medications, cold/cough preparations, along with their requisite washout-periods could have been classified in greater detail by the sponsor.

8.4.3.1.b. Procedure

As stated above, the overall design of PAR study FLN 310 was similar to that of studies FLTA 3010, FLN 350 and 351, with the exception of a number or caveats: a longer duration for study FLN 310 (6 months total), allowance for the use of rescue medication during the run-in and double-blind treatment periods of the study (chlorpheniramine 4 mg tablets q 6 h pm, up to a maximum allowed dose of 6 tablets qd for 'intolerable' symptoms), the inclusion of safety monitoring for glaucoma and cataracts (study visits 1, 11, and 14=weeks 0, 12, and 24), the performance of 12-lead ECGs (study visits 1, 4, 7, and 14=weeks 0, 4, 12, and 24), and the performance of PFTs during FLN 310 (study visits 1, 7, 11, and 14=weeks -2, 4, 12, and 24) [NDA 20-121, S-009, 27:62-63, 65, 87]. A summary of the study design for FLN 310 is provided below and delineated in Appendix I of this review) [NDA 20-121, S-009, 27:36].

During the screening visit, a complete medical history and physical examination (to include ear and nasal exam which was 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, along with an evaluation for oral or nasal candidiasis (with cultures obtained if there was clinical evidence of candidiasis in order to confirm the diagnosis), and nasal cytology studies (using the same scoring system as reviewed in NAPR studies FLTA 3010, FLN 350 and 35) was performed [NDA 20-121, S-009, 27:62-63]. In addition, laboratory evaluation (to include a.m. plasma cortisol levels and pre-/post-Cortrosyn stimulation testing 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).

Again, the purpose of the screening visit was to determine if prospective patients met the requisite inclusion/exclusion criteria to qualify for entry into the 2 week run-in period of the study, to be subsequently followed by the 24 week double-blind treatment period. Patients likewise underwent a self-rated nasal symptom assessment of rhinorrhea, nasal obstruction, sneezing, and nasal itch during screening which was used to compute a TNSS (total nasal symptom score consisting of a composite of rhinorrhea and nasal obstruction) that would determine if patients had PAR symptoms sufficiently severe in order to qualify for study entry (see study inclusion criteria, section 8.2.3.1.a.(I)) [NDA 20-121, S-009, 27:7-8].

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) nasal obstruction, (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, 27:52, 58]. Patients additionally recorded the severity of nasal obstruction in the a.m.—upon awakening (i.e., as an ‘instantaneous’ assessment and prior to taking the a.m. dose of study drug) [NDA 20-121, S-009, 27:58]. Thus, nasal obstruction was rated both in the a.m. and p.m. prior to dosing with study medication.

Figure 1: Subjective PAR symptom rating scale:

PAR Symptoms	Visual Analog Scale
Rhinorrhea	0 ————— 100 (Symptom Absent) (Symptom most severe)
Nasal obstruction	0 ————— 100 (Symptom Absent) (Symptom most severe)
Nasal itching	0 ————— 100 (Symptom Absent) (Symptom most severe)
Sneezing	0 ————— 100 (Symptom Absent) (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 and rescue medication (only if absolutely necessary) throughout the double-blind treatment period.

Reviewer’s Note: In this study, postnasal drip was not rated by patients, making study FLN 310 somewhat different with respect to the nasal symptoms evaluated, compared with studies FLN 350 and 351. 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, sneezing, and nasal itch, allowing a maximum TNSS of 400. 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 4 PAR symptoms of rhinorrhea, sneezing, nasal itch, 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 310.

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, sneezing, and nasal itching but not postnasal drip [NDA 20-121, S-009, 27:58].

Nasal symptoms were evaluated individually and a TNSS was calculated by summing the individual scores for rhinorrhea, nasal obstruction, sneezing, and nasal itching (postnasal drip not quantified). In addition, the physician was to assess composite eye symptoms: tearing, irritation, and ocular itching, but unfortunately the eye symptoms were later not felt, per the sponsor, to have adequately differentiated between allergic conjunctivitis and periorbital swelling secondary to venous obstruction associated with rhinitis and these were treated as secondary efficacy endpoints [NDA 20-121, S-009, 27:58]. These evaluations were performed at each clinic visit during the double-blind treatment period (Visits 4-14, weeks 0-24) along with at the post-treatment assessment visit (Visit 15, week 26) [NDA 20-121, S-009, 27:36, 58].

In order to qualify for enrollment into the double-blind portion of the study, patients were to be sufficiently symptomatic for at least 8 out of the 14 days immediately prior to receiving double-blind study medication (the single-blind run-in period) by meeting the entry criteria of: a patient-rated total nasal symptom score (TNSS=nasal obstruction and rhinorrhea) of ≥ 100 points out of a maximum total of 200 points, based on a visual analog rating scale for the **daily** TNSS. [NDA 20-121, S-009, 27:59].

After completion of the single-blind placebo lead-in portion of the study, patients underwent re-evaluation of PAR symptomatology via review of the patient symptom diary, an ophthalmologic exam using exam to rule out subcapsular cataracts/lenticular opacities, re-evaluation for presence of oral or nasal candidiasis, and assessment of compliance with study medication for the lead-in period at study visit 1. At visit 1, patients underwent their 1st set of PFT measurements (FEV₁, FVC, FEF_{25-75%} recorded). Adverse events and concurrent medication assessments were reviewed by the investigator.

Reviewer's Note: The rationale for measurement of PFTs in this study is not clear and was not provided by the sponsor.

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 into 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, 27:2, 57]:

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

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 qd doses (and respectively, the dose of FP/actuation) were the same as those utilized in FLTA 3010. A matching placebo bottle which was identical in appearance to that of active medication was utilized for the double dummy technique employed in this study which required an identical appearance between active and placebo drug.

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 at 8:00 a.m. and 8:00 p.m.) [NDA 20-121, S-009, 27:57].

For the remainder of the study, clinic visits consisted of evaluations as delineated in the study flow chart in Appendix I of this review. In addition to the evaluation of patient-self rated and physician rated TNSS and the individual nasal symptoms, physicians recorded their patients' overall response to treatment (as in FLTA 3010, FLN 350 and 351) at the final study visit using the 7-point ordinal scale summarized in Figure 2 below [NDA 20-121, S-009, 27:59]:

Figure 2: Physician Rating of Patients' Overall Response to Therapy Evaluation Using an Ordinal Scale [NDA 20-121, S-009, 27:59]:

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

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For the purposes of this study, which was to assess the therapeutic response of perennial allergic rhinitis patients, while pollen counts were not collected on a daily basis by the sponsor or recorded in a log, the number of hours of exposure to perennial allergens (the daily environmental exposure) was to be recorded by all patients in the study as part of the patient diary [NDA 20-121, S-009, 27:77].

With regard to safety analysis, 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: ENT changes such as nasal/septal ulcerations and/or candidiasis, cataracts, glaucoma), Cortrosyn stimulation testing with standard dose synthetic ACTH (250 µg I.M. or I.V.) was performed prior to dosing with a.m. study medication at the screening and final visits of the study-- visit 14 (plasma levels drawn between 6:30 a.m. and 9:30 a.m.) [NDA 20-121, S-009, 27:60] and measurement of a.m. plasma cortisol were performed at screening and visits 4, 7, 11, and 14 (weeks 0, 4, 12, and 24 of the study). Tests of adrenal response were repeated at the follow-up visit (week 26) if the response during visit 14 was found to be abnormal.

An a.m. cortisol level of at least 7 µg/dL was required for study entry [NDA 20-121, S-009, 27:60, 69] and an a.m. plasma cortisol level ranging from 5-18 µg/dL was considered in the normal range [NDA 20-121, S-009, 27:60]. Patients were instructed to fast overnight (~ 8 hours) for all clinical laboratory tests.

8.4.3.2. Clinical Endpoints:

The primary efficacy variable, as pre-specified in study FLN 310 by the sponsor consisted of [NDA 20-121, S-009, 27:67-68, 73]:

- (1) The physician-rated average reflective daily TNSS (=sum of rhinorrhea, nasal obstruction, sneezing, and nasal itch) for each week of the double-blind period for the intent-to-treat (ITT) population. **Because the powering of the study was based on this endpoint according to the sponsor, this efficacy variable was taken to be the 'primary efficacy variable' for study FLN 310 by the sponsor (see medical reviewer comments below).**

Additionally, pre-specified as a primary efficacy endpoint by the sponsor was the:

- (2) Physician-rated overall evaluation of response to therapy at the final study visit (visit 14=week 24).

Reviewer's Note: The primary efficacy variable of physician-rated overall evaluation of clinical response was regarded as a primary efficacy variable by the sponsor for the reasoning that these scores were obtained in a controlled setting (the investigator's clinic) [NDA 20-121, S-009, 27:58]. The medical reviewer, nonetheless considered this endpoint to be a secondary efficacy endpoint since powering of the study was not based on this variable

and thus in this review physician-rated overall evaluation of response was treated as a secondary efficacy endpoint.

Secondary efficacy variables, as specified by the sponsor, consisted of the following (ITT population):

- (1) The patient-rated average reflective daily TNSS (=sum of rhinorrhea, nasal obstruction, sneezing, and nasal itch) for each week of the double-blind period.
- (2) The physician-rated average reflective daily individual nasal symptom scores: rhinorrhea, nasal obstruction, sneezing, nasal itching, and a.m. nasal obstruction for each week of the double-blind period.
- (3) 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.
- (4) Use of rescue medication, as recorded by patients on daily diary cards.
- (5) Nasal examinations performed during clinic visits before and after treatment which evaluated appearance of the nasal turbinates, polyps, nasal septum, and nasal mucosa; along with an evaluation of nasal secretions (consistency, color, quantity). These parameters were scored subjectively by the examining physician on a 0-3 scale (none, minimal, moderate, and severe).

Reviewer's Note: Given a symptom score range of 0-100 for any individual PAR symptom, patients could achieve a TNSS ranging from 0-400, based on a composite of 4 nasal symptoms: rhinorrhea, nasal obstruction, sneezing, and nasal itch. The efficacy endpoint and primary comparison of interest was not specified by the sponsor in either the study protocol or study report but was taken by the medical reviewer to be the comparison between the FP 100 µg bid vs. FP 200 µg qd. Given that the study was powered on the 'mean change in physician-rated TNSS from baseline', this endpoint was taken to be the primary efficacy endpoint for FLN 310 by the sponsor.

Review of the Mayo Clinic Proceedings study on which FLN 310 was patterned (see medical reviewer comments below in section 8.4.3.1. 'Statistical Analysis') examined patient self-rated nasal symptoms rated on a 0-6 (and not 0-100) scale to ragweed allergen (a seasonal allergen) and focused on a non-perennial allergen which was rated using a different scoring system and on an efficacy endpoint that was different from that chosen for powering by the sponsor of FLN 310. Recognizing, as the sponsor states in their study report [NDA 20-121, S-009, 27:73] that extrapolation of the data from this study was done by changing an analog scale of 0-24 to the 0-100 scale of FLN, this extrapolation appears acceptable from a review standpoint, however the inherent differences between these 2 study designs should be pointed out.

8.4.3.1. Statistical Analysis [NDA 20-121, S-009, 3:63, 27:67-68,73]:

The study was conducted with a target enrollment of 360 patients. A minimum sample size of 120 patients per treatment arm (or 360 patients total) was calculated in order to detect a treatment difference of at least 30 points in the **physician-rated TNSS symptom score**, between placebo and the 2 FP treatment groups, based on a 2-sided $\alpha=0.05$, a power of 80%, and an estimated standard deviation of 75 points for the TNSS. This estimated sample size was based on results from a published SAR study in which beclomethasone, flunisolide, and cromolyn were compared in relieving ragweed allergy symptoms (*Welsh PW, Stricker WE, Chu C-P, Naessens JM, Reese ME, Reed CE, and Marcoux JP, Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy, Mayo Clinic Proceedings, 1987; 62:125-134*) [NDA 20-121, S-009, 27:73, 117].

Three different, but complementary analyses were performed on the primary efficacy variable of physician-rated TNSS for the double-blind treatment period. These consisted of: (1) ANCOVA of the change from baseline at week 1, week 2, week 4, week 6, week 8, week 10, week 12, week 16, week 20, week 24, and the endpoint visit, with pretreatment baseline score as covariate, followed by pairwise comparisons of treatment groups, (2) analysis of change from baseline score to endpoint (endpoint defined as either week 24 or the final visit for patients who discontinued early), and (3) a repeated measure model across visits [NDA 20-121, S-009, 27:68]. Least square means were used to compare all pairs of treatments. F-tests based on pairwise comparisons were performed on patient-rated symptoms of PAR scores.

The Cochran-Mantel-Haenszel test was used to compare pairs of treatments for overall physician evaluation of response to treatment, nasal exam, changes in nasal cytology, and use of rescue medication to detect statistically significant differences between treatment groups [NDA 20-121, S-009, 27:68]. Investigator effect was adjusted for in all analyses except the repeated measures analysis of physician-rated PAR symptoms. No adjustments were made for multiple comparisons.

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, 27:67]. An 'evaluable' efficacy population (all patients who had no major protocol violations as determined by the investigator(s)), e.g. received study drug for ≥ 2 weeks, had not received prednisone for treatment of an acute asthma attack, or were not lost to follow-up) [NDA 20-121, S-009, 27:68] 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, and 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].

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. Pairwise treatment group comparisons using the least squares means, based on the mean square error from ANOVA (pretreatment) or ANCOVA was utilized in order to determine significant differences between treatment groups.

Reviewer's Note: Compared with study FLTA 3010, FLN 350 and 351 the powering of the study based on a mean score difference of 30 points was somewhat lower than that proposed in these other studies (~ 70 points). Most importantly, the choice of the sponsor's primary efficacy variable was based on the consistency of having physician's rate patient symptoms in a clinic setting, however review of the Mayo Clinic Proceedings study on which powering of study FLN 310 was based indicated that patient self-rated and not physician-rated nasal symptom scores were utilized in assessing clinical efficacy (Welsh PW, Stricker WE, Chu C-P, Naessens JM, Reese ME, Reed CE, and Marcoux JP, Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy, Mayo Clinic Proceedings, 1987; 62:126-127). Given this information, the patient-self rated TNSS was deemed to be a more clinically and statistically relevant primary efficacy endpoint for analysis of FLN 310 than physician-rated TNSS by the medical reviewer and was treated as such in the efficacy analysis of FLN 310.

8.4.4. Results

8.4.4.1. Patient Demographics

(A) A total of 365 patients with a history of PAR were randomized into the study (met the target 360 patient enrollment). One hundred and sixteen (116) patients were randomized to placebo, 121 were assigned to FP 100 µg bid, and 128 were assigned to FP 200 µg qd [NDA 20-121, S-009, 27:75] and these patients comprised the intent-to-treat population (ITT). Two hundred and ninety nine patients (299, or 82% of all patients randomized into the double-blind portion of the study) completed the double-blind portion of the study and 66 patients withdrew from the study prior to study completion: 24 from the placebo group, 23 from the FP 100 µg bid, and 19 from the FP 200 µg qd group.

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

Table II. Patient Disposition [NDA 20-121, S-009, 27:75]

PATIENT DISPOSITION	DOUBLE-BLIND TREATMENT PERIOD			Total
	Placebo	FP 100 µg bid	FP 200 µg qd	
Enrolled Patients	116	121	128	365
Intent-to-Treat	116	121	128	365
Safety Evaluable (same as ITT)	116	121	128	365
Completed Study	92	98	109	299

(B) As discussed above, a total of 66 patients withdrew from the double-blind portion of the study prior to study completion, leaving 299 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 'other reasons' and not 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, 27:75]. This data is summarized in Table III. [NDA 20-121, S-009, 27:75] and in Tables 3 and 4 of the sponsor's submission [NDA 20-121, S-009, 27:122-132].

Table III. Number and Percentage (%) of Randomized Patients Who Discontinued the Study with Reasons for Discontinuation, ITT Population [NDA 20-121, S-009, 27:75]:

	DOUBLE-BLIND TREATMENT PERIOD			Total
	Placebo	FP 100 µg bid	FP 200 µg qd	
Number Enrolled	116	121	128	365
Number (%) Withdrawn	24 (21%)	23 (19%)	19 (15%)	66 (18%)
Reason for Discontinuation				
Adverse event	5 (4%)	7 (6%)	6 (5%)	18 (5%)
Lack of Efficacy	2 (2%)	2 (2%)	1 (1%)	5 (1%)
*Other	17 (15%)	14 (12%)	12 (9%)	43 (12%)
ALL REASONS	24 (21%)	23 (19%)	19 (15%)	66 (18%)

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

Reviewer's Note: The total % of patient discontinuation was somewhat greater than 10% of the total number of patients randomized into the study (~18%)-i.e. a higher percentage of patients withdrawing from the study than seen in the NAPR studies. The discontinuation rate for the 3 treatment arms was comparable, albeit with a greater number of patient discontinuations noted in the placebo group. 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:

Table IV. Patient Demographics for the ITT Population-Double Blind Treatment Period [NDA 20-121, S-009, 27:142-143]:

Variable	Placebo (n=93)	FP 100 µg bid (n=98)	FP 200 µg qd (n=95)	P-Value
Gender: (n, (%))				
Male	58 (50%)	57 (47%)	69 (54%)	0.662
Female	58 (50%)	64 (53%)	59 (46%)	
Race: (n, (%))				
Caucasian	109 (94%)	115 (95%)	120 (94%)	0.627
Black	5 (4%)	6 (5%)	4 (3%)	
Hispanic	1 (1%)	0 (0%)	2 (2%)	
Other	1 (1%)	0 (0%)	2 (2%)	
Age: (yrs)				
Mean ± SE	35.6 ± 13.1	34.7 ± 11.6	36.2 ± 12.7	0.391
Range	12-74	12-66	12-66	
Weight: (lbs.)				
Mean ± SE	154.5 ± 36.1	161.6 ± 34.3	160.7 ± 36.6	0.282
Range	86.9-298.1	96.8-260.0	88.0-260.0	
History of perennial rhinitis:				
Unknown	5 (4%)	3 (2%)	7 (5%)	0.942
1-5 years	16 (14%)	15 (12%)	19 (15%)	
6-10 years	20 (17%)	23 (19%)	25 (20%)	
11-20 years	36 (31%)	40 (33%)	34 (27%)	
> 20 years	39 (34%)	40 (33%)	43 (34%)	

P-value for gender, ethnic origin, and history of PAR based on the Cochran-Mantel-Haenszel 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. Again, the majority of study patients were Caucasian (≥ 94% of total). Patients down to the age of 12 were included in all 3 treatment groups. The majority of patients had a long-standing history of PAR (≥ 10 years). While not presented in this table, the majority of patients (80-85%) in each treatment group had concurrent medical conditions at the time of randomization and a majority (91-95%) 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. Likewise, in terms of possible pollen exposure, the majority of patients in all 3 treatment groups spent the majority of hours at home, as compared with 'other buildings', outside or in a vehicle [NDA 20-121, S-009, 27:144-146, 148-150] although there was a slight trend to spend fewer hours at home and more hours outside for all 3 treatment groups as the study progressed.

(D) Patient distribution by disease severity at pre-treatment in the ITT population, as assessed by average patient self-rated total nasal symptom scores (TNSS) and the individual nasal symptoms of nasal obstruction, rhinorrhea,

sneezing, and nasal itching for the pre-treatment period; revealed small numerical differences between the treatment groups with statistically significant differences between the placebo group and the FP 100 µg bid group ($p=0.032$) and between the 2 FP treatment groups ($p < 0.001$) [NDA 20-121, S-009, 27:187]. but failed to reveal a statistically significant difference in between the 3 treatment groups for the pre-defined primary efficacy variable of physician-rated TNSS [NDA 20-121, S-009, 21:170] and the individual pre-treatment nasal symptoms as rated by the physician [NDA 20-121, S-009, 21:171-174].

(E) Patient Validity

Patients diary data were invalidated in study FLN 310 for the following 3 main reasons: (1) if patients took prednisone (e.g. for an acute asthma exacerbation), failed to meet the minimal requirement for compliance (defined as \geq using at least 14 consecutive days of treatment during the double-blind period), or (3) were lost to follow-up and did not return for the final evaluation visit [NDA 20-121, S-009, 27:76]. 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 (these are listed on [27:76] had data that was invalidated during the study.

Reviewer's Note: Overall, the criteria for excluding patients from efficacy analysis were appropriate and consistent with other rhinitis trials reviewed in this efficacy supplement.

(F) Duration of Study Medication Exposure

The extent of exposure to study medication of at least 24 weeks of double-blind treatment period for all 3 treatment groups combined was 299/365 patients or approximately 82% [NDA 20-121, S-009, 27:75, 91]. Of these 299, 92 patients received placebo treatment, 98 received FP 100 µg bid and 109 received FP 200 µg qd. Therefore, a total of 207 patients received a total daily dose of FP 200 µg for 24 weeks.

(G) Patient Compliance [NDA 20-121, S-009, 27:75-76]

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 but this information was not provided in tabular form in the sponsor's submission. For inclusion in the efficacy database, patients were required to have completed at least 14 consecutive days of treatment with study medication [NDA 20-121, S-009, 27:76].

8.4.4.2. Efficacy Endpoint Outcomes

(I) Primary Efficacy Variable:

The purpose of reviewing efficacy in PAR study FLN 310 with respect to the FLONASE NAPR efficacy supplement was in order to compare efficacy of the

FP 200 µg qd treatment to the FP 100 µg bid treatment and to demonstrate comparable efficacy between the 2 treatments in decreasing PAR symptoms and comparable efficacy at the end-of-dosing interval (unfortunately which could only be assessed by 1 parameter in the study—the patient self-rated a.m. nasal obstruction score). These results then could be used for bridging to the NAPR studies in which only bid dosing of FP was evaluated.

All efficacy analyses in this review were based on the intent-to-treat (ITT) population (n=113 for the placebo group (3 patients dropped out prior to having one post-baseline visit), n=121 for the FP 100 µg bid group, and n=128 for the FP 200 µg bid group). Based on the sponsor's interpretation of powering of study FLN 310, the primary efficacy variable was defined as: (1) the physician-rated average reflective daily TNSS (=sum of rhinorrhea, nasal obstruction, sneezing, and nasal itch) for each week of the double-blind period (24 weeks total), the endpoint visit and the post-treatment visit (week 26) 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 PAR indication) vs. the FP 200 µg qd group. Based on all the NAPR studies reviewed, actual powering of this study based on this endpoint and not the physician-rated TNSS, and the importance of patient-self rated symptom scores in assessing clinical efficacy, the medical reviewer also included the patient-rated average reflective daily TNSS (=sum of rhinorrhea, nasal obstruction, sneezing, and nasal itch) for each week of the double-blind period (24 weeks total), the endpoint visit and the post-treatment visit (week 26) as the more important primary efficacy endpoint. All other variables presented by the sponsor were treated as secondary efficacy endpoints.

For the mean physician-rated daily reflective TNSS for each week of the double-blind treatment period, the 100 µg bid dose of FP nasal spray and FP 200 µg qd dose both demonstrated statistically significant efficacy in decreasing TNSS for all clinic visits compared to placebo treatment during the double-blind treatment period and in general were found to have similar numerical values during each of these study visits. These data are presented in Table V of the medical officer review [NDA 20-121, S-009, 27:170]. Importantly, no statistical difference was demonstrated between these 2 active treatments throughout the study when compared against one another; thus supportive of the comparable efficacy of the FP 100 µg bid treatment to FP 200 µg qd for this primary efficacy endpoint. Statistically significant efficacy compared to placebo was demonstrable by week 1 of treatment and TNSS continued to progressively decrease for the duration of the study for both active treatments. Unlike studies FLTA 3010, FLN 350 and 351, the mean change in symptom scores was not presented in tabular form for FLN 310, and only the TNSS symptom scores for each clinic visit were displayed. Interestingly, for the post-treatment visit (~ 2 weeks post-discontinuation of study medication), while the 2 FP treatment group's patient showed worsening of TNSS (as manifested by higher symptom scores), the

placebo treatment group's TNSS continued to decrease, suggestive of a true placebo effect.

Review of the individual physician-rated nasal symptom scores [NDA 20-121, S-009, 27:171-174] for the 3 treatment groups revealed no statistically significant difference in scores between FP 100 μ g bid treatment vs. FP 200 μ g qd treatment for the entire double-blind treatment period for all 4 individual symptoms of: nasal obstruction, rhinorrhea, sneezing, nasal itching. Likewise no statistically significant difference in scores between FP 100 μ g bid treatment vs. FP 200 μ g qd treatment for the entire double-blind treatment period was noted for the physician-rated composite score of eye symptom scores [NDA 20-121, S-009, 27:175]. Similar to the primary efficacy endpoint results, small numerical differences between the individual nasal symptom scores were noted for the 2 active FP treatment groups and these symptom scores tended to progressively decrease for the duration of the study.

With respect to the perhaps more clinically relevant and statistically relevant primary efficacy variable of patient self-rated TNSS, results were somewhat different from that of the physician-rated TNSS, in that only at weeks 4, 8, 10, 23, 26, 20, 24, and at post-treatment was no statistically significant difference seen between the FP 100 μ g bid treatment and the FP 200 μ g qd treatment (Table VI) [NDA 20-121, S-009, 27:187]. At pre-treatment (i.e. at baseline), and at weeks 1, 2, and 6; statistically significant differences were seen between the 2 active FP treatment groups. Numerically, for most of the double-blind treatment period, the FP 200 μ g qd treatment group had slightly higher patient self-rated TNSS symptoms than did the FP 100 μ g bid treatment group, though the magnitude of this difference was generally small (~ 2-4 points between treatment groups) and well within the standard errors. While the general trend favored showing comparability between the 2 active FP treatments, data for this endpoint were less consistent than those for the physician-rated TNSS discussed above. Subgroup analysis of the primary efficacy variables was not performed in this study.

Review of the individual patient self-rated nasal symptom scores revealed the following: (1) for the patient self-rated nasal obstruction score, statistically significant differences were noted between the FP 100 μ g bid treatment and the FP 200 μ g qd treatment at pre-treatment, and at weeks 1, 2, and 6, which favored the FP 100 μ g bid treatment, generally by 1-2 points over the FP 200 μ g qd treatment [NDA 20-121, S-009, 27:188], (2) for the patient self-rated rhinorrhea score, statistically significant differences were noted between the FP 100 μ g bid treatment and the FP 200 μ g qd treatment at weeks 4 and 6, with a magnitude of symptom score difference between the 2 groups of ~ 5-6 points [NDA 20-121, S-009, 27:189], (3) for the patient self-rated sneezing score, statistically significant differences were noted between the FP 100 μ g bid treatment and the FP 200 μ g qd treatment at pre-treatment and week 4, with a magnitude of symptom score difference of ~ 1 point [NDA 20-121, S-009, 27:190], (4) for the patient self-rated nasal itching score, statistically significant differences were noted between the FP 100 μ g bid treatment and the FP 200 μ g qd treatment at the pre-treatment period

only (~ 6 point difference) [NDA 20-121, S-009, 27:191], and (5) for the patient self-rated a.m. nasal obstruction score, statistically significant differences were noted between the FP 100 µg bid treatment and the FP 200 µg qd treatment at pre-treatment, and at weeks 1, 2, 4, and 6, (with a magnitude of symptom score difference of ~ 1-4.8 points) [NDA 20-121, S-009, 27:193]. Importantly, for the a.m. nasal obstruction score, which represented an evaluation of the end-of-dosing interval for the FP 200 µg qd treatment arm, both FP treatments demonstrated statistically significantly less nasal obstruction than the placebo group at all treatment time points (an ~ 8-12 point magnitude of difference in symptom scores), however statistically significant differences were seen between the means of the 2 FP treatment groups at baseline as well as differences in mean scores for the first 6 weeks of the double-blind period, with the FP 100 µg bid treatment group having lower scores than the FP 200 µg qd treatment group, [NDA 20-121, S-009, 27:193]. After week 6, the mean scores in the 2 FP groups were very similar.

Review of the patient self-rated composite eye symptom score revealed that a statistically significant difference in symptom scores was noted between the FP 100 µg bid treatment and the FP 200 µg qd treatment at weeks 1 and 16 [NDA 20-121, S-009, 27:192].

Reviewer's Note: Based on the data for patient-rated TNSS and physician-rated TNSS the overall trend of efficacy between the FP 200 µg qd treatment and the FP 100 µg bid treatment would suggest that they demonstrate similar efficacy in decreasing nasal symptoms of PAR, however lack of consistent comparability for the patient-rated TNSS between the 2 FP regimens for the entire duration of the double-blind period makes this argument weaker for study FLN 310.

(II) Secondary Efficacy Variables:

The physician-rated overall clinical evaluation (specified as a primary efficacy endpoint by the sponsor but considered a secondary efficacy endpoint by the medical reviewer), revealed comparable degrees of significant improvement in overall condition for the FP 100 µg bid treatment and the FP 200 µg qd treatment groups (34% vs. 33%, respectively [NDA 20-121, S-009, 27:185]. Results of this analysis are summarized in Table VII. and no statistically significant differences were seen between the 2 active FP treatments.

A number of secondary endpoints were evaluated by the sponsor which consisted of: rescue medication use [NDA 20-121, S-009, 27:194], along with change in the nasal exam (change in nasal turbinates, mucosa, nasal polyps, the nasal septum, and evaluation of nasal secretions: consistency, color, and color). The nasal exam findings were scored on a 0-3 scale (0=none, 1=minimal, 2=moderate, and 3=severe) [NDA 20-121, S-009, 27:195-201].

Review of rescue medication use amongst the 3 treatment groups revealed no significant numerical difference between the 3 groups and no statistically

significant difference between the 2 FP treatments, or between the FP 100 µg bid treatment and placebo, or between the FP 200 µg qd treatment and placebo [NDA 20-121, S-009, 27:194]. Rescue medication use was slightly higher during the run-in period of the trial and remained fairly consistent for the duration of the double-blind treatment period for all 3 treatment groups.

Review of the nasal exam findings, which while interesting and supportive data in addition to the symptom score measurements, were not felt to represent an efficacy endpoint by the medical reviewer. Nonetheless, these assessments revealed that for most time points, again no statistically significant difference was noted between the 2 FP treatments, using the 0-3 sponsor's scoring system [NDA 20-121, S-009, 27:88, 161-169, 202-222].

Reviewer's Note: Of note, the nasal exam/nasal secretions assessment was neither evaluated numerically nor treated as an efficacy endpoint in any of the NAPR studies but rather analyzed categorically as a supportive finding. 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 24 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 PAR 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 µg qd).

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Table V.
 Efficacy of Flonase Nasal Spray vs. Placebo:
Physician-Rated Daily Total Nasal Symptom Score; Primary Efficacy Variable
 Intent-to-Treat (ITT) for the Double-blind Treatment Period [NDA 20-121, S-009, 27:170]

	TREATMENT GROUPS					
	Placebo	FP 100 µg bid	FP 200 µg qd	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg qd	FP 100 µg bid vs. FP 200 µg qd
Total Nasal Symptom Score (TNSS): Composite of Rhinorrhea + Nasal Obstruction + Sneezing + Nasal Itch						
# of Pts at Screening	113	121	128			
Pre-Treatment						
(n, mean score ± ² SE)	113 211.6 ± 6.96	121 215.8 ± 6.37	128 209.4 ± 6.11	0.542	0.635	0.266
Week 1						
(n, mean score ± SE)	112 191.1 ± 7.18	119 152.9 ± 6.86	128 155.4 ± 6.60	<0.001	<0.001	0.641
Week 2						
(n, mean score ± SE)	108 181.0 ± 7.36	120 143.1 ± 7.30	126 153.7 ± 6.85	<0.001	0.004	0.204
Week 4						
(n, mean score ± SE)	104 170.8 ± 7.49	116 127.1 ± 7.20	122 133.9 ± 6.66	<0.001	<0.001	0.550
Week 6						
(n, mean score ± SE)	102 168.4 ± 7.78	109 124.7 ± 7.48	121 130.4 ± 5.87	<0.001	<0.001	0.540
Week 8						
(n, mean score ± SE)	100 151.7 ± 8.54	108 121.9 ± 7.49	117 122.7 ± 6.26	0.006	0.003	0.849
Week 10						
(n, mean score ± SE)	99 143.1 ± 8.08	107 119.8 ± 7.85	116 121.5 ± 6.27	0.041	0.029	0.918
Week 12						
(n, mean score ± SE)	98 147.1 ± 7.78	102 114.5 ± 7.75	113 116.2 ± 6.81	0.004	0.003	0.999
Week 16						
(n, mean score ± SE)	95 134.9 ± 7.71	101 108.6 ± 7.00	112 104.3 ± 6.76	0.015	<0.001	0.376
Week 20						
(n, mean score ± SE)	94 132.7 ± 8.44	100 110.6 ± 6.77	112 100.5 ± 6.38	0.049	<0.001	0.123
Week 24						
(n, mean score ± SE)	91 143.0 ± 9.13	96 95.6 ± 7.61	108 103.5 ± 6.81	<0.001	<0.001	0.756
Endpoint						
(n, mean score ± SE)	113 147.6 ± 8.12	121 103.2 ± 7.19	128 108.8 ± 6.50	<0.001	<0.001	0.605
Post-treatment (Week 26)						
(n, mean score ± SE)	101 138.4 ± 7.51	107 143.3 ± 8.41	120 140.4 ± 7.05	0.550	0.803	0.711

¹FP=Fluticasone propionate. ²SE=Standard Error. P-values are based on scores at pre-treatment and on changes from pre-treatment at other time points. Pairwise comparisons were based on the least significant difference (LSD) using the MSError from ANOVA (pre-treatment) or ANCOVA. No adjustments were made for multiple comparisons.

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, 27:187]

	TREATMENT GROUPS					
	Placebo	FP 100 µg bid	FP 200 µg qd	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg qd	FP 100 µg bid vs. FP 200 µg qd
Total Nasal Symptom Score (TNSS): Composite of Rhinorrhea + Nasal Obstruction + Sneezing + Nasal Itch						
# of Pts at Screening	111	120	127			
Pre-Treatment						
(n, mean score ± SE)	113 201.5 ± 5.49	121 215.1 ± 5.27	128 195.0 ± 4.70	0.032	0.235	<0.001
Week 1						
(n, mean score ± SE)	109 187.6 ± 5.74	119 163.0 ± 6.13	127 162.2 ± 5.33	<0.001	<0.001	0.037
Week 2						
(n, mean score ± SE)	107 184.0 ± 6.62	116 147.3 ± 6.46	126 150.7 ± 6.02	<0.001	<0.001	0.042
Week 4						
(n, mean score ± SE)	104 173.2 ± 6.96	113 128.9 ± 6.18	121 136.2 ± 5.80	<0.001	<0.001	0.071
Week 6						
(n, mean score ± SE)	102 171.3 ± 7.19	109 118.7 ± 6.53	118 132.0 ± 5.59	<0.001	<0.001	0.013
Week 8						
(n, mean score ± SE)	100 162.1 ± 7.59	109 124.2 ± 6.60	117 126.3 ± 5.95	<0.001	<0.001	0.384
Week 10						
(n, mean score ± SE)	100 151.5 ± 7.13	107 116.4 ± 6.47	116 120.4 ± 6.10	<0.001	0.001	0.391
Week 12						
(n, mean score ± SE)	97 149.1 ± 7.75	104 114.6 ± 6.89	113 116.9 ± 6.22	<0.001	0.002	0.505
Week 16						
(n, mean score ± SE)	95 138.6 ± 7.48	103 106.5 ± 6.19	113 108.6 ± 6.10	<0.001	0.002	0.597
Week 20						
(n, mean score ± SE)	94 139.5 ± 7.48	98 108.6 ± 6.46	112 106.3 ± 6.46	<0.001	<0.001	0.871
Week 24						
(n, mean score ± SE)	94 134.3 ± 7.17	99 106.2 ± 6.63	110 104.2 ± 6.21	0.002	<0.001	0.771
Post-treatment (Week 26)						
(n, mean score ± SE)	89 140.5 ± 7.66	96 136.3 ± 7.61	109 131.2 ± 6.47	0.555	0.548	0.995

¹FP=Fluticasone propionate. ²SE=Standard Error. P-values are based on scores at pre-treatment and on changes from pre-treatment at other time points. Pairwise comparisons were based on the least significant difference (LSD) using the MSE error from ANOVA (pre-treatment) or ANCOVA. No adjustments were made for multiple comparisons.

Analysis of Duration of Effect (see below):

Analysis of the end-of-dosing interval efficacy (or duration of drug effect) was only assessed by the a.m. nasal obstruction endpoint (assessed on awakening by study patients) which showed that the bid dosing was comparable to qd dosing in terms of reducing the a.m. nasal obstruction symptom score; with small numerical differences in the symptom scores between the 2 dosing regimens (an ~ 1-4 point magnitude of difference between scores, that were generally within the standard error), despite a statistically significant difference found between the FP 100 µg bid treatment and the FP 200 µg qd treatment at pre-treatment and weeks 1-6 of the double-blind treatment period [NDA 20-121, S-009, 27:193]. From week 6 onward (till week 24 of the study), no statistically significant difference between a.m. nasal obstruction (the end-of-dosing interval) was seen between these 2 active treatment groups. Because of the small numerical differences in a.m. nasal obstruction score and because assessment of duration of effect focused on only 1 symptom, these data cannot be exclusively interpreted as showing that bid dosing is preferable to qd dosing of FLONASE Nasal Spray.

When evaluating the duration of drug effect via comparison of the 3 treatment groups (FP 100 µg bid, FP 200 µg qd, and placebo) with respect to rescue medication use throughout the study, the proportion of patients using rescue medication (i.e. chlorpheniramine 4 mg tablets) during the pretreatment run-in period was similar among all 3 treatment groups (~ 44-56% of patients required rescue medication use) but moreso between the FP 200 µg qd group and placebo; Numerically, the FP 100 µg bid group required the most rescue medication at pre-treatment (56% of patients in this group). Hence, rescue medication use between the 3 groups at pre-treatment, while not statistically significantly different was numerically different between the 3 groups.

Correspondingly, rescue medication use decreased most in the FP 100 µg bid (to 48% of patients requiring use at week 24, from 56% of patients at week 0). While numerically, the proportion of patients requiring rescue medication use for the FP 200 µg qd group increased at week 24 from the pretreatment proportion, the difference in week 24 rescue medication use was not statistically significantly different between the FP 100 µg bid and FP 200 µg qd groups.

Conversely, rescue medication use remained approximately the same as for the pretreatment period for the placebo group (59% of patients required rescue medication use) [NDA 20-121, S-009, 27:87, 194].

Importantly, comparisons between the 3 treatment groups for the other study time points (e.g. week 1, 2, 4, etc. till week 12) show no significant numerical of statistical difference in rescue medication use between the 2 active FP groups: the FP 100 µg bid and FP 200 µg qd groups. (After week 12, rescue medication use appeared to increase more in the FP 200 µg qd group patients than the FP 100 µg bid patients [NDA 20-121, S-009, 27:87, 194])

Hence the rescue medication use data more strongly support the efficacy and duration of effect of the 2 active FP treatments over, at least weeks 1-12 [NDA

20-121, S-009, 27:194], when rescue medication use is considered. 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 310.

8.4.4.2. Nasal Cytology Studies

Similar to the NAPR studies, nasal cytology studies were conducted in study FLN 310 in order to assess the proportion of patients enrolled in FLN 310 that might have NARES (non-allergic rhinitis with eosinophilia), a disorder different in etiology from perennial allergic rhinitis. Prevalence of eosinophils in nasal secretions were assessed at screening (week -4), week 24 (last week of the double-blind treatment period), and the endpoint visit (the patient's last clinic visit). Based on these [redacted] studies; at screening, the majority of patients enrolled into the 3 treatment groups had evidence of low numbers of eosinophils (grade 1; or scattered eosinophils noted on nasal smear: 62% of placebo group patients, 59% of FP 100 µg bid patients, and 61% of FP 200 µg qd patients) [NDA 20-121, S-009, 27:223], 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 ($p=0.260$) or between placebo and the FP 200 µg bid group ($p=0.561$) at screening [NDA 20-121, S-009, 27:223].

Furthermore, the percentage of nasal smears with no eosinophils increased in each of the 2 active treatment groups by week 24 but increased less in the placebo group (39% of placebo group patients, 69% of FP 100 µg bid patients, and 68% of FP 200 µg qd patients) [NDA 20-121, S-009, 27:223]. These results of distribution of nasal eosinophilia are similar to those seen in the pivotal NAPR study FLTA 3010. Similar results to that of eosinophil distribution in nasal smears was also seen with regard to nasal basophil distribution—the greatest decrease in numbers with double-blind treatment was noted to occur in the 2 FP treatment groups [NDA 20-121, S-009, 27:224].

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 week 24 of treatment [NDA 20-121, S-009, 27:226]. In contrast to one of the NAPR studies (FLN 310), this finding was not associated with a respective increase in the number of bacteria by week 24 of treatment in the FP Nasal Spray treatment groups (the overall number of bacteria in nasal secretions remained relatively constant over the double-blind period) [NDA 20-121, S-009, 27:226]. Results of this study, in terms of neutrophil and bacteria number in nasal secretions would suggest that 6 month treatment with FP nasal spray with either of the 2 dosing regimens would not tend to significantly depress ingress of immune cells and/or increase bacterial colonization in the nares, although similar outcomes were not shown in all studies reviewed in this NAPR submission.

8.4.4.3. Safety Analysis

The safety data for study FLN 310 had been previously reviewed during the evaluation of NDA 20-121 for FLONASE Nasal Spray for NDA approval. These data were not the primary focus for approval of the NAPR efficacy supplement, therefore safety results for study FLN 310 will only be summarized with respect to pertinent findings.

Similar to the NAPR studies, safety analysis for study FLN 310 consisted of an evaluation of adverse events, standard laboratory tests (along with special safety studies such as a.m. plasma cortisol and Cortrosyn stimulation testing pre- and post-treatment with study drug), vital signs, pulmonary function tests, 12-lead ECGs, and changes in physical examination (especially with regard to oropharyngeal, nasal, and eye 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, 27:91-113]. In this trial, the safety evaluable population was the same as the ITT population. All 365 patients who received study medication were included in the safety database and comprised the intent-to-treat population (n=116 for the placebo group, n=121 for the FP 100 µg bid group, and n=128 for the FP 200 µg qd group).

As discussed previously, there were no statistically significant differences among the treatment groups with regard to the demographic variables of age, gender, race, weight, or history of PAR.

The extent of exposure to study medication in study patients is summarized in the following statement: 66 patients withdrew from the study prematurely, leaving 299 patients (out of 365 patients, or 82% of total) who completed the entire 6 month double-blind treatment period) [NDA 20-121, S-009, 27:91].

The overall incidence of adverse events (AEs) were generally similar for all 3 treatment groups but with a slightly higher incidence in the 2 FP treatment groups (71-80% range, highest in the FP 200 µg qd group). Of note, these overall AE ranges were similar to that of pivotal NAPR study FLTA 3010 and included as most common AEs: headache, epistaxis, URIs, sore throat, and acute nasopharyngitis [NDA 20-121, S-009, 27:235-236]. 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 nasopharyngitis in the 2 FP treatment groups (7-8% range) over placebo (3%) [NDA 20-121, S-009, 27:235]. Reports of sinusitis were rare for all 3 treatment groups [NDA 20-121, S-009, 27:235]. Nasal septal or mucosal ulcers were likewise rare or altogether not reported in all 3 treatment groups, as were cataracts [NDA 20-121, S-009, 27:236].

In summary, the safety profile for period for FP nasal in study FLN 310 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. Adverse event stratification by demographics was not performed in this study.

Regarding patient discontinuation, a total of 18 patients discontinued treatment prematurely during the run-in and the 24 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, 27:134-136]. The majority of reasons for discontinuation were reasons associated with worsening rhinitis or asthma symptoms. None of these patients were deemed by the principal investigators to have had AEs that could have been induced by drug treatment.

⁴Serious AEs were reported for 8 patients in study FLN 310 (1 placebo group patient (femur fracture), 1 FP 100 µg bid group patient (pneumonia) and 6 FP 200 µg qd group patients (2 cases of increased asthma, 1 death, 1 case of dizziness/nausea/vomiting, 1 case of bilateral inguinal hernia, and 1 case of left inner ear inflammation) [NDA 20-121, S-009, 27:91-98]. None of the serious AEs were considered to be related to study medication. One death was reported in this study (patient #5346) which was due to a commercial airline crash [NDA 20-121, S-009, 27:91, 136:1].

Review of routine laboratory tests performed during pre-treatment (screening visit), day 1 of the double-blind treatment period, week 4, 12, and upon completion of double-blind period of the study (week 24) through analysis of mean values, shift tables, and evaluation of laboratory 'outliers', failed to reveal any laboratory test signals, as the mean values of all analytes tested remained within normal range by week 24 of the study, with only minor variability in a number of parameters by week 24 of testing in all 3 treatment groups: lymphocyte counts (which increased with treatment), peripheral eosinophil counts (which decreased with treatment), and minor decrements in platelet counts [NDA 20-121, S-009, 27:104-109]. Importantly, minor laboratory abnormalities were seen among the 3 treatment groups, with no pattern or trend evident for any particular treatment group. No patients were withdrawn from the study because of abnormal laboratory values.

Adrenal function was evaluated in FLN 310 by measurement of 2 adrenal response parameters: (1) a.m. plasma cortisol levels at screening (visit 1), pre-treatment (week 0), weeks 4, 12, and post-24 weeks of treatment with study drug (or at early patient discontinuation and (2) standard dose (250 µg) Cortrosyn stimulation testing before pre- (screening visit) and post-treatment (week 24).

Review of mean A.M. plasma cortisol measurements (pre- and post-treatment) for the double-blind treatment period and as a list of patient outlier values [NDA 20-121, S-009, 27:327, 329, 330-370] revealed a significant mean change (decrease) in a.m. plasma cortisol levels post-treatment with the FP 200 µg qd group compared to the placebo ($p=0.053$) and compared to the FP 100 µg bid group ($p=0.019$). For purposes of this study, a normal a.m. plasma cortisol level

⁴ 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.

was defined as: a cortisol level between 5-18 $\mu\text{g/dL}$. Based on the patient line listings and outlier results [NDA 20-121, S-009, 27:330-370], a number of patients in all 3 treatment groups manifested a.m. plasma cortisol outliers (5-11% range) however, this number was highest in the FP 200 $\mu\text{g qd}$ group (placebo=8%, FP 100 $\mu\text{g bid}$ =5%, FP 200 $\mu\text{g qd}$ group=11%) [NDA 20-121, S-009, 27:329]. Similar results were demonstrable for the ACTH stimulation tests (Table IX) in which the FP 200 $\mu\text{g qd}$ group tended to have slightly greater blunting of the adrenal response (though not statistically significant) than either the placebo or FP 100 $\mu\text{g bid}$ group [NDA 20-121, S-009, 27:328-329]. Based on individual patient line listings, 6-15% of patients in all 3 treatment groups demonstrated an inadequate response to ACTH stimulation, using the sponsor's pre-defined criteria of an adequate adrenal response (6% of placebo patients failed to have an adequate adrenal response, 15% of FP 100 $\mu\text{g bid}$ patients failed to have an adequate adrenal response, and 9% of FP 200 $\mu\text{g qd}$ patients failed to have an adequate adrenal response) [NDA 20-121, S-009, 27:329, 330-370].

Reviewer's Note: Results of adrenal assessment detected a greater degree (albeit low) of adrenal suppression than the NAPR studies reviewed in this efficacy supplement. The reason for this possible discrepancy, other than sampling error, is not entirely clear but a possible additional etiology is the longer duration of treatment with corticosteroid and consequent monitoring for adrenal suppression in FLN 310 (6 months vs. 4 weeks) which would be more likely to detect abnormalities than in trials of shorter duration.

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Table VIII. A.M. Plasma Cortisol Levels Pre- and Post-Treatment with Study Drug (FLONASE Aqueous Nasal Spray); ITT Population [NDA 20-121, S-009, 27:327]

A.M. PLASMA CORTISOL (µg/dL)	Placebo Pre-Rx, n=110 Week 4, n=110 Week 12, n=100 Week 24, n=95 Endpoint, n=110 (mean ± SE)	FP 100 µg bid Pre-Rx, n=117 Week 4, n=115 Week 12, n=108 Week 24, n=99 Endpoint, n=117 (mean ± SE)	FP 200 µg qd Pre-Rx, n=125 Week 4, n=122 Week 12, n=118 Week 24, n=110 Endpoint, n=125 (mean ± SE)	P-Values		
				P vs. FP 100	P vs. FP 200	FP 100 vs. FP 200
Pre-Rx (Screening)	16.8 ± 0.85	16.9 ± 0.73	14.7 ± 0.63	0.711	0.053	0.019
Week 4	17.1 ± 0.79	17.8 ± 0.83	15.6 ± 0.68	0.337	0.761	0.503
Week 12	16.6 ± 0.78	17.9 ± 0.82	15.0 ± 0.62	0.117	0.971	0.113
Week 24	17.6 ± 0.89	19.1 ± 0.95	16.2 ± 0.72	0.315	0.681	0.537
Endpoint visit	17.3 ± 0.81	18.8 ± 0.90	15.9 ± 0.70	0.097	0.897	0.117

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 at other time points. Pairwise comparisons were based on the least significant difference (LSD) using the MSE error form ANOVA (pre-treatment) or ANCOVA. P-values are not adjusted for multiple comparisons.

Table IX. Plasma Cortisol Levels Pre- and Post-Treatment Cortrosyn Stimulation Testing before and after treatment with study drug (FLONASE Aqueous Nasal Spray); ITT Population [NDA 20-121, S-009, 27:328]

A.M. PLASMA CORTISOL (µg/dL)	Placebo Week -4, n=103 Week 24, n=91 Endpoint, n=103 (mean ± SE)	FP 100 µg bid Week -4, n=105 Week 24, n=95 Endpoint, n=105 (mean ± SE)	FP 200 µg qd Week -4, n=120 Week 24, n=108 Endpoint, n=120 (mean ± SE)	P-Values		
				P vs. FP 100	P vs. FP 200	FP 100 vs. FP 200
Week -4:						
–Baseline	16.5 ± 0.85	17.1 ± 0.82	15.3 ± 0.71	0.784	0.998	0.773
–Post-Cortrosyn	31.4 ± 0.88	32.1 ± 0.80	30.3 ± 0.79			
–Difference	14.9 ± 0.46	14.4 ± 0.43	15.0 ± 0.47			
Week 24:						
–Baseline	17.5 ± 0.91	19.2 ± 0.99	16.4 ± 0.73	0.088	0.363	0.386
–Post-Cortrosyn	31.3 ± 1.01	32.0 ± 0.99	29.7 ± 0.85			
–Difference	13.8 ± 0.57	12.8 ± 0.58	13.3 ± 0.59			
Endpoint visit:						
–Baseline	17.3 ± 0.86	19.1 ± 0.96	16.1 ± 0.71	0.021	0.191	0.272
–Post-Cortrosyn	31.4 ± 0.98	31.7 ± 0.98	29.3 ± 0.83			
–Difference	14.1 ± 0.55	12.6 ± 0.55	13.2 ± 0.55			

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 at other time points. Pairwise comparisons were based on the least significant difference (LSD) using the MSE error form ANOVA (pre-treatment) or ANCOVA. P-values are not adjusted for multiple comparisons.

Furthermore, evaluation of change in the physical examination, vital signs, pulmonary function tests, and 12 lead ECGs performed patients on during the 24 week double-blind period revealed no significant trends in physical findings or in the diagnostic studies performed and only minor changes on physical exam. In general, results of these evaluations at completion of the study were consistent with those on screening [NDA 20-121, S-009, 27:109-113].

With regard to the ENT exam, no significant change in nasal exam (including incidence of ulcerations, polyps, etc.) was seen in the FP treated patients, compared to placebo at the 2 different doses of FP Nasal Spray [NDA 20-121, S-009, 27:88]. Patients receiving the 2 active treatments generally experienced a decrease in the size of nasal turbinates and nasal secretions. Eye exams and intraocular pressure monitoring failed to reveal new cases of cataracts or glaucoma in either of the 3 treatment groups which might have developed on study medication [NDA 20-121, S-009, 27:109-112-113], though 1 patient in the FP 200 µg qd group developed a vacuolar crescent opacity in his left eye by week 12 and 24 of treatment (patient # 5081), and 1 additional FP 200 µg qd group patient developed an increase in right eye intraocular pressure (patient #5219) by week 12 to 23 mm Hg from a previous reading of 14 mm Hg at baseline (follow-up intraocular pressure in this patient who continued on therapy at week 24 was 15 mm Hg) [NDA 20-121, S-009, 27:113].

With respect to infections, 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 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, 27:109]. Clinical evaluation for presence of nasal septal ulcers or perforations revealed 1 case of a nasal ulceration in a FP 200 µg qd group patient [NDA 20-121, S-009, 27:235] and 1 case of a nasal septal ulceration in a placebo group patient [NDA 20-121, S-009, 27:235]. In study FLN 310, ear exams to assess perforations and serous effusions were not performed (as had been for study FLTA 3010).

8.4.5. 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 PAR (nasal obstruction, rhinorrhea, sneezing, and nasal itch) in adults and children 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 dosing at 100 µg bid vs. dosing at 200 µg qd did not demonstrate statistically significant different efficacy when compared to

one another (but did demonstrate statistically significant efficacy when compared to placebo treatment). Importantly, however, for patient self-rated TNSS which was felt to represent the most appropriate primary efficacy endpoint, consistent similarity between the 2 active FP treatments was not demonstrable throughout the duration of the study, indicating that at least for study FLN 310 at earlier time points (weeks 1, 2, and 6) the FP 100 µg bid treatment group afforded slightly greater efficacy in decreasing patient self-rated TNSS than did FP 200 µg qd. End-of-dosing assessment with the a.m. patient-self rated nasal obstruction score was comparable between the 2 FP regimens, favoring slightly greater efficacy for the FP 100 µg bid dosing regimen which was minimal in terms of the numerical difference in a.m. nasal obstruction score between these 2 dosing regimens.

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Summary Table: Efficacy Variables for the ITT Population and Treatment with FLONASE Aqueous Nasal Spray for the Perennial Allergic Rhinitis (PAR) Indication (STUDY FLN 310)

EFFICACY VARIABLE	Statistically Significant Response (FP 100 µg bid vs. FP 200 µg qd) Yes/No
Primary Efficacy Variable	
1. Physician-rated average daily reflective TNSS:	No: All time points.
2. Patient-rated average daily reflective TNSS:	Yes: Pre-treatment, Week 1, 2, and 6. No: Week 4, 8, 10, 12, 16, 20, 24.
Secondary Efficacy Variables	
1. Overall Physician Evaluation	No: All time points.
2. Patient-rated average daily nasal obstruction score	Yes: Pre-treatment, Week 1, 2, and 6. No: Week 4, 8, 10, 12, 16, 20, and 24.
3. Patient-rated average a.m. nasal obstruction score	Yes: Pre-treatment, Week 1, 2, 4, and 6. No: Week 8, 10, 12, 16, 20, and 24.
4. Patient-rated average daily rhinorrhea score	Yes: Week 6 and 8. No: Pre-treatment, Week 1, 2, 4, 10, 12, 16, 20, and 24.
5. Patient-rated average daily sneezing score	Yes: Pre-treatment and Week 2. No: Week 4, 24.
6. Patient-rated average daily nasal itch score	Yes: Pre-treatment. No: Week 4, 24.
7. Physician-rated nasal obstruction score	No: All time points.
8. Physician-rated rhinorrhea score	No: All time points.
9. Physician-rated sneezing score	No: All time points.
10. Physician-rated nasal itch score	No: All time points.
11. Rescue medication use	No: All time points.
12. Nasal exam assessments: Turbinate Nasal mucosa Nasal septum Nasal polyps	Yes: Week 1, 2, 4, and 16. Week 16, 24, endpoint visit. No visits. Week 2 and 4.
13. Nasal secretion assessments: Quantity, consistency, color	No: All visits.

Important efficacy variables for the approval of FLONASE AQ Nasal Spray for PAR are represented in bold italics. Sx=Symptom.

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 occurred in patients treated with FP Nasal Spray using either of 2 dosing regimens. No significant increase in oropharyngeal candidiasis or nasal septal ulcerations/perforations were seen in patients treated with FP Nasal Spray, compared with placebo. Twenty-four week treatment with FP Nasal Spray at either of the 2 dosing regimens did show a small numerical difference in mean a.m. plasma cortisol measurements post-treatment or after Cortrosyn stimulation testing, and a small increase in a.m. plasma

cortisol outliers in the 2 active treatments, compared with placebo but these changes were generally not shown to be statistically significant.

Summary:

Based on the results of this PAR trial, FP Nasal Spray given at a dose of 100 μ g bid vs. 200 μ g qd did not consistently show statistically insignificant differences in efficacy for the primary efficacy endpoints, although the overall trend between these 2 active treatments was that the different efficacy parameters measured were numerically and generally statistically similar for most time points throughout the study.

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

Hence, results of this study, which are important as a bridging data to support comparability of bid and qd dosing of FLONASE Nasal Spray, may be used to overall recommend an appropriate dose of FP Nasal of 100 μ g bid or 200 μ g qd (once daily regimen) for the PAR indication in adults and children 12 years of age and older based on the efficacy and safety data reviewed in this submission with the caveat that not all efficacy data stringently showed equivalency of the 2 dosing regimens.

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FIGURE 1
OVERALL TIME AND EVENT SCHEDULE

	Pre-Study	Double-Blind Treatment														F/U
		Single-Blind Baseline														
VISIT NUMBER	0	1 ^a	2	3	4 ^d	5	6	7	8	9	10	11	12	13	14 ^e	15 ^h
WEEK NUMBER	-1	-2	-1	0	0	1	2	4	6	8	10	12	16	20	24	26
DAY NUMBER	-(29-22)	-15	-8	-1	1	8	15	29	43	57	71	85	113	141	169	183
Informed Consent	X															
Medical History	X															
Physical Examination	X											X			X	(X)
Skin Testing ^b	X															
Laboratory Safety Tests (Chemistry, Hematology,																
Urinalysis) ^c	X ⁱ				X			X				X			X	(X)
Pregnancy Test	X														X	X
A.M. Plasma Cortisol ^c	X ⁱ				X			X				X			X	(X)
Synthetic ACTH Stimulation Test ^c	X ⁱ														X	(X)
12 Lead ECG ^c	X				X			X				X			X	(X)
Ophthalmic Exam		X										X			X	(X)
Pulmonary Function Test ^c		X						X				X			X	(X)
Nasal/Oropharynx Exam	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Nasal Cytology	X ^j														X	
Physician-Rated Symptom Assessment	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Diary Card Issued	X	X			X		X	X	X	X	X	X	X	X	X	
Chlorpheniramine Issued	X ^d															
Study Drug Issued		X ^e			X			X		X		X	X	X		
Observation/Interview for Adverse Experience		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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- a) Time between Prestudy screening and Visit 1 must have been between 7 and 14 days.
- b) At Visit 0 or within 12 months prior to Visit 0.
- c) Pre-dose
- d) Additional medication was issued if necessary at each office visit.
- e) Single-blind placebo
- f) Visit 4 was a continuation of the Visit 3 for patients who meet the criteria for entry into the double-blind phase of the study.
- g) Performed all final visit evaluations at this visit or at the time the patient was withdrawn from the study.
- h) A 2-week follow-up evaluation was required for all patients. (X) evaluations performed as needed.
- i) Test may have been repeated for patients with abnormal values on initial testing.
- j) Test may have been repeated if eosinophils not noted on the initial evaluation.

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PERENNIAL ALLERGIC RHINITIS (Bridging Trial):

- 8.5. Protocol No. FLN 311: A double-blind, randomized, parallel group, multi-center, placebo-controlled clinical trial to evaluate the efficacy and safety of once daily vs. twice daily intranasal administration of fluticasone propionate vs. aqueous beclomethasone dipropionate in patients with perennial allergic rhinitis (PAR).

Principal Investigator: None, multi-center study.

Participating Centers: 16 U.S. centers.

8.5.1 Objectives

The primary objective of this study was to investigate the safety and efficacy of a 24 week course of 2 different dosing regimens of fluticasone propionate (FP) nasal spray: FP 100 µg bid vs. FP 200 µg qd, vs. beclomethasone dipropionate (BDP) 168 µg bid, and vs. placebo nasal spray for the treatment of symptoms of perennial allergic rhinitis (PAR). This study constituted the 2nd of the 2 bridging studies for the PAR efficacy supplement for FLONASE Aqueous Nasal Spray whose objective (as also FLN 310) it was to demonstrate comparable clinical efficacy of the 200 µg qd regimen of FP Nasal Spray to the FP 100 µg bid regimen.

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

8.5.2. Study Design

The study was a phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group, with a 2 week placebo lead-in, safety and efficacy study of fluticasone propionate nasal spray (FP) 100 µg bid, vs. fluticasone propionate nasal spray (FP) 200 µg qd, vs. BDP 168 100 µg bid, and vs. placebo nasal spray bid given for a duration of 6 months (24 weeks) for the treatment of PAR in patients 12 years of age and older which was almost identical to the study design of study FLN 310 (with the exception of having the addition of an active comparator, beclomethasone (BDP) nasal spray. The 24 week double-blind treatment period was followed by a 2 week post-treatment assessment (weeks 24-26) [NDA 20-121, S-009, 29:57]. The overall study design of FLN 311 (also study FLN 310) was similar to that of studies FLN 350 and 351 with the exception that these former 2 trials were of longer duration (see below) and a number of additional parameters were assessed in FLN 311 (which were not evaluated in FLN 350 or 351, see below). While a number of amendments were made to the initial study protocol for FLN 311, the study design summary discussed in the medical officer review represents that of the final protocol for FLN 311 [NDA 20-121, S-009, 29:57-130, 30:308-394].

Same as study FLN 310, study FLN 311 consisted of a total of 16 patient visits: a screening visit (visit 0, day -29 to -22), visit 1 or 'the first day of the single-blind treatment period' (day -15), visit 2 (day -8), visit 3 (day -1), and visit 4 (day 1, week 0, the 1st day of the double-blind treatment period), visit 5 (day 8, week 1), visit 6 (day 15, week 2), visit 7 (day 29, week 4), visit 8 (day 43, week 6), visit 9 (day 57, week 8), visit 10 (day 71, week 10), visit 11 (day 85, week 12), visit 12 (day 115, week 16), visit 13 (day 141, week 20), visit 14 (day 169, week 24), and the post-treatment visit: visit 15 (day 183, week 26) [NDA 20-121, S-009, 30:311-312, 316-324, 388]. Patients were evaluated in clinic from between 6:30 a.m.-9:30 a.m. for each study visit. The duration of the study for a given patient was approximately 26 weeks. A flow chart of FLN 311 is provided in Figure 1 of the sponsor's submission and is inserted in this review as Appendix I [NDA 20-121, S-009, 30:311].

8.5.3. Protocol

8.5.3.1.a. Population: Male or female patients, ≥ 12 years of age, with PAR defined by the inclusion criteria listed below [NDA 20-121, S-009, 29:61].

- (I) Inclusion Criteria [NDA 20-121, S-009, 27:55, 29:61]:
1. Diagnosis of PAR as defined by the following criteria:
 - (a) evidence of a positive skin test at screening to a relevant perennial allergen (e.g. dust mite, animal dander) that the patient was exposed to on a continuous basis (positive response defined as a $\geq 2+$ skin test reaction per physician reading) in order to fulfill the diagnosis of perennial allergic rhinitis (PAR).
 - (b) presence of nasal eosinophilia on nasal cytology exam.
 2. A morning (a.m.) plasma cortisol level of at least $7 \mu\text{g/dL}$ on screening and a normal response to Cortrosyn stimulation using the standard $250 \mu\text{g}$ dose or cosyntropin (this was defined a priori as an increase in plasma cortisol concentration $\geq 7 \mu\text{g/dL}$ from baseline to a level of at least $18 \mu\text{g/dL}$, 30' after I.V. administration of Cortrosyn or 60' after I.M. administration of Cortrosyn).
 3. The patient's self-rated severity of disease for at least 8 out of the 14 days immediately prior to receiving double-blind study medication (the single-blind run-in period) would need to meet the entry criteria of: a patient-rated total nasal symptom score (TNSS defined as being comprised of nasal obstruction and rhinorrhea for the run-in period) of ≥ 100 points out of a maximum total of 200 points, based on a visual analog rating

scale for the daily TNSS. (Similar to the NAPR studies, this score was supposed to represent symptoms throughout the previous 24 hours, i.e. were to be scored reflectively by patients in the p.m. prior to dosing with study medication).

Reviewer's Notes: The same issues regarding inclusion criteria discussed for study FLN 310 apply to study FLN 311. Similar to the pivotal NAPR study FLTA 3010, 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, the specific allergens tested, nor the definition of a $\geq 2+$ skin test reaction. In addition, the antihistamine washout times prior to skin testing were not delineated in the study protocol for FLN 311.

(II) Exclusion Criteria [NDA 20-121, S-009, 29:61-62]:

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. Diagnosis of rhinosinusitis, rhinitis medicamentosa, vasomotor rhinitis, or NARES.
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: 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 hypersensitivity reactions to any intranasal, inhaled, or systemic corticosteroid therapy.
6. Concurrent bacterial or viral infection (e.g. URI) that could confound analysis of efficacy.
7. Use of any investigational new drug within 1 month prior to the screening visit.
8. Patients with an elevated intraocular pressure (> 22 mm Hg)
9. Patients with cataracts or lenticular opacities.
10. Patients starting immunotherapy who were not on stable doses of maintenance therapy.
11. History of previous enrollment in a PAR study with fluticasone propionate aqueous nasal spray.
12. 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 any capacity in the study report or study protocol.

(III). Concurrent Medication Restrictions [NDA 20-121, S-009, 29:62]:
The following medications were to be discontinued within the indicated time periods prior to visit 1, and were not allowed throughout the study duration:

<u>Medication</u>	<u>Time Discontinued Prior to Visit 1 (Screening visit)</u>
1. Intranasal sodium cromolyn	≥ 2 weeks
2. Intranasal, inhaled, or systemic corticosteroids	≥ 1 month
3. 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 and theophylline during the study for the treatment of asthma but use of these drugs was to be recorded on the case report forms (CRFs). 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 prescription or OTC drugs that could affect the course of rhinitis (e.g. decongestants, sinus medications, and including antihistamines with the exception of chlorpheniramine, which was allowed as a rescue medication during the run-in and double-blind treatment period) [NDA 20-121, S-009, 29:62, 73] would result in patient exclusion from participation in the trial.

Reviewer's Note: Again, similar to the pivotal study FLTA 3010, and PAR study FLN 310, 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 whose use was prohibited, such as: decongestants, expectorants, sinus medications, cold/cough preparations, along

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

8.5.3.1.b. Procedure

As stated above, the overall design of PAR study FLN 311 was essentially identical to study FLN 310. As reiterated for study FLN 310, study FLN 311 was likewise similar to that of studies FLTA 3010, FLN 350 and 351, with the exception of a number of caveats: a longer duration for study FLN 311 (6 months total; also applied to FLN 310), allowance for the use of rescue medication during the run-in and double-blind treatment periods of the study (chlorpheniramine 4 mg tablets q 6 h prn, up to a maximum allowed dose of 6 tablets qd for 'intolerable' symptoms), the inclusion of safety monitoring for glaucoma and cataracts (study visits 1, 11, and 14=weeks -2, 12, and 24), the performance of 12-lead ECGs (study visits 0, 4, 7, 11, and 14=weeks 0, 4, 7, 12, and 24), and the performance of PFTs during FLN 311 (study visits 1, 7, 11, and 14=weeks -2, 7, 12, and 24) [NDA 20-121, S-009, 29:388]. A summary of the study design for FLN 311 is provided below and delineated in Appendix I of this review) [NDA 20-121, S-009, 30:311, 388].

During the screening visit, a complete medical history and physical examination (to include ear and nasal exam which was 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, along with an evaluation for oral or nasal candidiasis (with cultures obtained if there was clinical evidence of candidiasis in order to confirm the diagnosis), nasal cytology studies (using the same scoring system as reviewed in NAPR studies FLTA 3010, FLN 350, 351, and 310), and ophthalmologic exam to include [redacted] (the latter also performed on visit 11=week 12 and visit 14=week 24) was performed [NDA 20-121, S-009, 29:69-70]. In addition, laboratory evaluation (to include a.m. plasma cortisol levels and pre-/post-Cortrosyn stimulation testing 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) [NDA 20-121, S-009, 29:67-68, 30:388].

Again, the purpose of the screening visit was to determine if prospective patients met the requisite inclusion/exclusion criteria to qualify for entry into the 2 week run-in period of the study, to be subsequently followed by the 24 week double-blind treatment period. Patients likewise underwent a self-rated nasal symptom assessment of rhinorrhea, nasal obstruction, sneezing, and nasal itch during screening which was used to compute a TNSS (total nasal symptom score consisting of a composite of rhinorrhea and nasal obstruction) that would determine if patients had PAR symptoms sufficiently severe in order to qualify for study entry (see study inclusion criteria, section 8.2.3.1.a.(I)) [NDA 20-121, S-009, 29:64-65].

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) nasal obstruction, (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, 29:64]. 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, 29:65]. Thus, nasal obstruction was rated both in the a.m. and p.m. prior to dosing with study medication.

Figure 1: Subjective PAR symptom rating scale:

PAR Symptoms	Visual Analog Scale
Rhinorrhea	0 ————— 100 (Symptom Absent) (Symptom most severe)
Nasal obstruction	0 ————— 100 (Symptom Absent) (Symptom most severe)
Nasal itching	0 ————— 100 (Symptom Absent) (Symptom most severe)
Sneezing	0 ————— 100 (Symptom Absent) (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 and rescue medication (only if absolutely necessary) throughout the double-blind treatment period.

Reviewer's Note: Similar to study FLN 310, in this study, postnasal drip was not rated by patients, making PAR studies FLN 310 and 311 somewhat different with respect to the nasal symptoms evaluated, compared with NAPR studies FLN 350 and 351. 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, sneezing, and nasal itch, allowing a maximum TNSS of 400. 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 4 PAR symptoms of rhinorrhea, sneezing, nasal itch, and nasal obstruction. As stated above, nasal obstruction was also scored in the morning, upon the patient's