awakening; thus twice daily recordings of nasal obstruction were available (though not submitted as daily scores or line listings) for study FLN 311.

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, 29:64].

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 nasal 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, 29:64]. 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, 29:64].

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 $\geq$ 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, 29:65].

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 [redacted] 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 (FEV_1, FVC, $FEF_{25-75\%}$ recorded) [NDA 20-121, S-009, 29:69]. Adverse events and concurrent medication assessments were reviewed by the investigator.

Reviewer's Note: Similar to study FLN 310, 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 4 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:		
	DOSING	
STUDY GROUPS	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) Beclomethasone dipropionate nasal spray 168 µg bid (42 µg/actuation)	BDP 168 µg 2 sprays	BDP 168 µg 2 sprays
(4) Placebo	Placebo 2 sprays	Placebo 2 sprays

Blinding of the 4 study medications (including the BDP active comparator) 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, or conversely contained only BDP or placebo [NDA 20-121, S-009, 29:53; 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 and in the other NAPR and PAR studies analyzed in this efficacy supplement. A matching placebo bottle which was identical in appearance to that of the active medications 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, 29:63].

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, 351, and 310) at the final study visit using the 7-point ordinal scale summarized in Figure 2 below [NDA 20-121, S-009, 29:66]:

Figure 2: Physician Rating of Patients' Overall Response to Therapy Evaluation Using an Ordinal Scale [NDA 20-121, S-009, 29:66]:

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

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, 29:159-160].

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 was 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.) and measurement of a.m. plasma cortisols were performed at screening and visits 4, 7, 11, and 14 (weeks 0, 4, 12, and 24 of the study) [NDA 20-121, S-009, 29;67]. 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, 29:67] and an a.m. plasma cortisol level ranging from 5-18 μg/dL was considered in the normal range [NDA 20-121, S-009, 29:67]. Patients were instructed to fast overnight (~ 8 hours) for all clinical laboratory tests.

8.5.3.2. Clinical Endpoints:

Determination of primary and secondary efficacy variables by the sponsor was identical to the approach taken for study FLN 311. Thus, the primary efficacy variable, as pre-specified in study FLN 310 by the sponsor consisted of [NDA 20-121, S-009, 29:64-65]:

(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. **Again, 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 311 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, 29:64]. 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. 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 doses. 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 311 by the sponsor.

8.5.3.3. Statistical Analysis [NDA 20-121, S-009, 29:74-76, 79-80]:

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 α=0.05, a power of 80%, and an estimated standard deviation of 75 points for the TNSS. The criteria defined in this study (FLN 311) for statistical analysis are the same as those for study FLN 310. 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, 29:79-80].

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 for the double-blind period from baseline, 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, 29:75-76]. 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 compared 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, 29:75]. 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, 29:74-75]. An 'evaluable' efficacy population (all patients who had no major protocol violations as determined by the investigator(s)), e.g. received study drug for $\geq$ 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, 29:75] 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 studies FLTA 3010 and FLN 310, missing symptom scores in FLN 311 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 studies FLTA 3010, FLN 350 and 351 the powering of study FLN 311 (and FLN 310) were based on a mean score difference of 30 points was somewhat lower than that proposed in these other studies (~ 70 points). Most importantly, 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 311 than physician-rated TNSS by the medical reviewer and was treated as such in the efficacy analysis of FLN 311.**

8.5.4. Results

8.5.4.1. Patient Demographics

(A) A total of 466 patients with a history of PAR were randomized into the study (met the target 360 patient enrollment). One hundred and thirteen (113) patients were randomized to placebo, 119 were assigned to FP 100 µg bid, 118 were assigned to FP 200 µg qd, and 116 were assigned to BDP 168 µg bid [NDA 20-121, S-009, 29:82] and these patients comprised the intent-to-treat population (ITT). Three hundred and sixty patients (360, or 77% of all patients randomized into the double-blind portion of the study) completed the double-blind portion of the study and 106 patients withdrew from the study prior to study completion: 32 from the placebo group, 27 from the FP 100 µg bid, 16 from the FP 200 µg qd group, and 32 from the BDP 168 µg bid group [NDA 20-121, S-009, 29:82].
A distribution of the patient population is summarized in Table II. below:

Table II. Patient Disposition [NDA 20-121, S-009, 29:82]

	DOUBLE-BLIND TREATMENT PERIOD				
PATIENT DISPOSITION	Placebo	FP 100 µg bid	FP 200 µg qd	BDP 168 µg bid	Total
Enrolled Patients	113	119	118	116	466
Intent-to-Treat	**113**	**119**	**118**	**116**	**466**
Safety Evaluable (same as ITT)	113	119	118	116	466
Completed Study	81	92	102	85	360

(B) As discussed above, a total of 106 patients withdrew from the double-blind portion of the study prior to study completion, leaving 360 patients who completed the entire double-blind portion of the study (with 1 patient withdrawn (patient #5112) prior to entry into the double-blind period for a protocol violation [NDA 20-121, S-009, 29:82]. The overall degree of patient withdrawal (23% of enrolled patients for all 4 groups combined) was quite high. 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 (28%) of discontinuation was noted in the placebo group and BDP 168 µg bid group [NDA 20-121, S-009, 29:82]. This data is summarized in Table III. [NDA 20-121, S-009, 29:82] and in Tables 3 and 4 of the sponsor's submission [NDA 20-121, S-009, 29:136-147].

Table III. Number and Percentage (%) of Randomized Patients Who Discontinued the Study with Reasons for Discontinuation, ITT Population [NDA 20-121, S-009, 29:82]:

	DOUBLE-BLIND TREATMENT PERIOD				
	Placebo	FP 100 µg bid	FP 200 µg qd	BDP 168 µg bid	Total
Number Enrolled	113	119	118	116	466
Number (%) Withdrawn	32 (28%)	27 (23%)	16 (14%)	32 (28%)	107 (23%)
Reason for Discontinuation					
Adverse event	7 (6%)	6 (5%)	4 (3%)	10 (9%)	27 (6%)
Lack of Efficacy	10 (9%)	4 (3.4%)	4 (3%)	6 (5%)	24 (5%)
*Other	15 (13%)	17 (14.3%)	8 (7%)	16 (14%)	56 (12%)
ALL REASONS	32 (28%)	27 (23%)	16 (14%)	32 (28%)	107 (23%)

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

Reviewer's Note: The total % of patient discontinuation was significantly higher than 10% of the total number of patients randomized into the study (~23%)-i.e. a higher percentage of patients withdrawing from the study than seen in the other NAPR studies or PAR study FLN 310. The discontinuation rate for the 2 FP treatment arms was comparable and a greater number of patient discontinuations were noted in the placebo and BDP group. Overall, the reasons for early patient discontinuation were deemed acceptable by the medical reviewer but it is not clear from the study itself why so many

patients dropped out of the study based on these reasons, although a frequent reason for discontinuation in this study appeared to be the 'patient not meeting double-blind entry criteria'.

(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, 29:157-158]:

Variable	Placebo (n=113)	FP 100 µg bid (n=119)	FP 200 µg qd (n=118)	BDP 168 µg bid (n=116)	P-Value
Gender: (n, (%))					0.924
Male	55 (49%)	55 (46%)	58 (49%)	59 (51%)	
Female	58 (51%)	64 (54%)	60 (51%)	57 (49%)	
Race: (n, (%))					0.886
Caucasian	105 (93%)	108 (91%)	104 (88%)	107 (92%)	
Black	2 (2%)	4 (3%)	5 (4%)	3 (3%)	
Hispanic	4 (4%)	5 (4%)	6 (5%)	6 (5%)	
Other	2 (2%)	2 (2%)	3 (3%)	0	
Age: (yrs)					0.703
Mean ± SE	36.0 ± 11.4	36.9 ± 11.8	35.3 ± 12.3	37.0 ± 12.6	
Range	13-70	12-68	12-71	14-68	
Weight: (lbs.)					0.168
Mean ± SE	165.0 ± 36.1	165.3 ± 35.6	156.5 ± 30.7	166.5 ± 43.3	
Range	97.9-280.1	100.5-310.0	77.0-290.2	104.9-350.0	
History of perennial rhinitis:					0.539
Unknown	5 (4%)	1 (1%)	2 (2%)	2 (2%)	
< 1 year	0	0	1 (1%)	0	
1-5 years	17 (15%)	17 (14%)	17 (14%)	22 (19%)	
6-10 years	18 (16%)	22 (18%)	16 (14%)	15 (13%)	
11-20 years	34 (30%)	24 (20%)	35 (30%)	31 (27%)	
> 20 years	39 (35%)	55 (46%)	47 (40%)	46 (40%)	

P-value for gender, ethnic origin, and history of PAR based on the Cochrna-Mantel-Haenzel 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 4 treatment groups. Again, the majority of study patients were Caucasian (≥ 88% of total). Patients down to the age of 12 were included in the 2 FP 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 (83-91%) in each treatment group had concurrent medical conditions at the time of randomization and a majority (90-94%) 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), antibiotics, and bronchodilators (used in 15%-24% of

all study patients for the latter drug class) [NDA 20-121, S-009, 29:161, 163-165]. Likewise, in terms of possible pollen exposure, the majority of patients in all 4 treatment groups spent the majority of hours at home, as compared with 'other buildings', outside or in a vehicle [NDA 20-121, S-009, 29:159-160] although similar to PAR study FLN 310, there was a slight trend to spend fewer hours at home and more hours outside for all 4 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 4 treatment groups (range of TNSS: [redacted] with no statistically significant differences amongst the 4 treatment groups [NDA 20-121, S-009, 29:205]. In particular the 2 FP treatments had pre-treatment TNSS scores very similar to one another (198.9 for the FP 100 μg bid group and 198.5 for the FP 200 μg qd group) [NDA 20-121, S-009, 29:205]. Additionally, only small numerical differences in the patient-self rated individual rhinitis scores and physician-rated TNSS scores was noted, and which were found to be statistically insignificant amongst the 4 treatment groups [NDA 20-121, S-009, 29:188, 206-211].

(E) Patient Validity

Patients diary data were invalidated in study FLN 311 for the following 3 main reasons: (1) if patients took prednisone (e.g. for an acute asthma exacerbation), (2) patients who failed to meet the minimal requirement for compliance (defined as using study medication for less than 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, 29:83].

Based on these criteria, there were 11 placebo group patients, 11 FP 100 μg bid group patients, 1 FP 200 μg qd group patients, and 10 BDP 168 μg bid group patients who were considered study 'nonevaluable' [NDA 20-121, S-009, 29:83]. Thus, the proportion of patients excluded from the evaluable population was 9-10% for the 3 treatment groups, excluding the FP 200 μg qd group, of which only 1% of patients were considered 'nonevaluable'.

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. The number of 'nonevaluable' patients was marginally reasonable for the 3 treatment groups where ~9-10% of patients were termed 'nonevaluable' and very reasonable for the FP 200 μg qd group.

(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 360/466 patients or approximately 77% [NDA 20-121, S-009, 29:100]. Of these 360, 81 patients received placebo treatment, 92 received FP 100 μg bid, 102 received FP 200 μg qd, and 85 received BDP 168 μg bid for a total of 24 weeks. Therefore, a total of 194 patients received a total daily dose of FP 200 μg for 24 weeks (6 months).

(G) Patient Compliance [NDA 20-121, S-009, 29:83]

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, 29:83]. The methodology employed for assessment of patient compliance in this study (FLN 311) was identical to that of FLN310.

8.5.4.2. Efficacy Endpoint Outcomes

(I) Primary Efficacy Variable:

The purpose of reviewing efficacy in PAR study FLN 311 (as also 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 determine if there is 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, n=119 for the FP 100 μg bid group, n=118 for the FP 200 μg bid group, and n=116 for the BDP 168 μg bid group). Based on the sponsor's interpretation of powering of study FLN 311 (as 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 <u>each week</u> 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 <u>each week</u> 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.

In summary, efficacy review of FLN 311 was performed in the same manner as that for FLN 310, with the addition of assessing the efficacy response for the active comparator BDP 168 μg bid group.

For the comparison with baseline of the mean physician-rated average daily reflective TNSS for each week of the double-blind treatment period, the 100 μg bid dose of FP nasal spray and the 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, although for the physician-rated TNSS the mean numerical scores for TNSS were slightly but consistently higher for the FP 200 μg qd group. Overall, the numerical difference between the 2 FP groups with regard to the physician-rated TNSS was smaller in FLN 311 than was seen in FLN 310. The overall decrease in TNSS with FP treatment was comparable to that shown in FLN 310 which was marginal at best, however a similar decrease was also seen for the BDP treatment group; hence these findings indicated that none of the active treatments were particularly effective in decreasing TNSS substantially in terms of the numerical value during the double-blind treatment period. Furthermore, the pre-treatment (baseline) TNSS for all 4 treatment groups were similar, with slightly lower mean TNSS seen in the BDP group (which were not statistically significantly different from that of the other 3 treatment groups). These data are presented in Table V of the medical officer review [NDA 20-121, S-009, 29:188].

Importantly, no statistical difference was demonstrated between the 3 active treatments (including the BDP group) 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, and additional comparable efficacy of the 2 FP groups to the BDP 168 μg bid group. Statistically significant efficacy compared to placebo was demonstrable by week 1 of treatment for the 2 FP groups and the BDP group and TNSS continued to progressively decrease for the duration of the study for all 3 active treatments.

Similar to study FLN 310, the mean change in symptom scores was not presented in tabular form for FLN 311, and only the mean TNSS symptom scores for each clinic visit were displayed. Importantly, for the post-treatment visit (~ 2 weeks post-discontinuation of study medication), all treatment groups showed worsening of TNSS (as manifested by higher symptom scores), and the BDP treatment group showed the greatest increase in mean physician-rated TNSS of the 4 treatment groups. Of note, the physician-rated TNSS for the efficacy evaluable patient population were numerically similar to that of the ITT population [NDA 20-121, S-009, 29:194].

Review of the individual physician-rated nasal symptom scores and eye symptoms [NDA 20-121, S-009, 29:189-193] for the 4 treatment groups revealed no statistically significant difference in scores between FP 100 μg bid treatment

vs. FP 200 μg qd treatment (and conversely, for the 2 FP groups vs. the BDP group) for the entire double-blind treatment period for all individual symptoms of: nasal obstruction, rhinorrhea, sneezing, nasal itching, and eye symptoms. The numerical symptom score values for all 3 active treatment groups were very similar, with slightly smaller mean symptom scores for the BDP group, followed by the FP 100 μg bid group, and lastly, the FP 200 μg qd group. For the entire double-blind treatment period, all 3 active treatment groups demonstrated statistically significantly greater efficacy than placebo treatment for physician-rated individual nasal symptoms (but not eye symptoms) at the majority of study visits, although the numerical differences (as for the physician-rated TNSS) were marginal. Nasal obstruction, followed by rhinorrhea, contributed most heavily in terms of numerical score value in computation of the physician-rated TNSS [NDA 20-121, S-009, 29:189-190]. Numerically, sneezing was the least important in terms of numerical value in determination of the physician-rated TNSS [NDA 20-121, S-009, 29:191]. Eye symptom scores were generally similar between the placebo treated group and the 3 active treatments. Similar to the primary efficacy endpoint results, small numerical differences between the physician-rated individual nasal symptom scores (and eye symptoms) were noted for the 2 active FP treatment groups and BDP treatment and these symptom scores tended to progressively decrease for the duration of the study.

With respect to the perhaps more clinically relevant primary efficacy variable of patient self-rated TNSS, results were consistent statistically with the physician-rated TNSS, although for this endpoint, the FP 200 μg qd group demonstrated a consistently slightly smaller mean numerical TNSS than the FP 100 μg bid group—the opposite of the finding seen for the physician-rated TNSS (Table VI) [NDA 20-121, S-009, 29:205]. At pre-treatment (i.e. at baseline), no statistically significant differences were seen between the 4 treatment groups, although similar to the physician-rated TNSS, the BDP group was seen to have a numerically slightly lower TNSS than the other 3 treatment groups. Similar to the physician-rated TNSS, these symptom scores tended to progressively decrease for the duration of the study for all 4 treatment groups, but increased 2 weeks post-discontinuation of treatment (the post-treatment visit). Subgroup analysis of the primary efficacy variables was not performed in this study.

Review of the individual patient self-rated nasal symptom scores revealed that the nasal symptom scores were generally statistically significantly lower after treatment with the 2 FP treatments compared with placebo treatment, however the FP 200 μg qd treatment was generally numerically superior to the FP 100 μg bid treatment groups and demonstrated a greater number of statistically significant time points, compared with placebo treatment than did the FP 100 μg bid group [NDA 20-121, S-009, 29:206-209]. Again, the nasal obstruction, followed by the rhinorrhea score contributed the most numerically in the determination of the patient-rated TNSS. For the patient-rated a.m. nasal obstruction score, statistically significant improvement compared with placebo throughout the double-blind treatment period was seen for all 3 active treatments, with a

tendency for the BDP 168 μg bid group to have numerically slightly lower mean symptom scores than the 2 FP treatment groups [NDA 20-121, S-009, 29:211]. Additionally, as seen for the physician-rated individual symptom scores, no statistically significant difference (or difference in terms of the numerical value) was seen amongst the 4 treatment groups for the eye symptom score [NDA 20-121, S-009, 29:210].

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 group and the FP 100 μg bid treatment group would suggest that they demonstrate similar efficacy in decreasing nasal symptoms of PAR, with physician-rated nasal symptom analyses (composite and individual symptoms) favoring slightly the FP 100 μg bid treatment group and the patient-rated nasal symptom analyses favoring slightly the FP 200 μg qd treatment group. Of note, neither of these numerical differences between the 2 FP treatments were statistically significant and overall, the numerical differences between the 2 FP treatments were tighter than that seen in PAR study FLN 310, supportive of the comparability of the 2 dosing regimens of FP Nasal Spray.

(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 (26% vs. 27%, respectively) [NDA 20-121, S-009, 29:203]. Results of this analysis are summarized in Table VII. and no statistically significant differences were seen between the 2 active FP treatments but were seen between the 2 FP treatments and the placebo group. The number of patients reporting 'significant improvement' was numerically slightly greater for the 2 FP treatment groups, compared to the BDP group (23% for the latter).

A number of secondary endpoints were evaluated by the sponsor which consisted of: rescue medication use [NDA 20-121, S-009, 29:194], 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, 29:195-201].

Review of rescue medication use amongst the 4 treatment groups revealed a general tendency for the active treatments to use numerically less rescue medication (with the lowest amount used by the BDP 168 μg bid group), but these differences between the 4 groups were not consistently statistically significant [NDA 20-121, S-009, 29:212].

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, decreasing slightly toward the end of the trial.

Review of the nasal exam findings, which while interesting as supportive data, in addition to the symptom score measurements, were not felt to represent an efficacy endpoint by the medical reviewer, as already noted during the review of FLN 310 in which identical analyses were performed by the sponsor. Nonetheless, these assessments revealed that for most time points, again no statistically significant difference was noted between the 2 FP treatments (and between the 2 FP treatments and the BDP treatment), using the sponsor's 0-3 scale scoring system [NDA 20-121, S-009, 29:213-240]. Generally, for all nasal parameters examined (turbinates, mucosa, septum, polyps, and secretions: quantity, consistency, and color), little numerical difference in the respective score was seen in patients randomized to the 3 active treatments and the placebo group.

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 statistically significant endpoints for the majority of study time points 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 of FP Nasal spray that had been based on the primary efficacy variable—that is, either FP 100 μg bid or FP 200 μg qd.

Analysis of Duration of Effect:

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 preferable to qd dosing in terms of reducing the a.m. nasal obstruction symptom score; though no statistically significant difference was found between the FP 100 μg bid treatment and the FP 200 μg qd treatment at pre-treatment or weeks 1-24 of the double-blind treatment period [NDA 20-121, S-009, 29:211]. Overall, these results were consistent with those seen in FLN 310. In addition, the BDP treatment group demonstrated a numerically slightly greater decrease in a.m. nasal obstruction than either the FP 100 μg bid treatment group of the FP 200 μg qd treatment group. As previously stated in the medical officer review of FLN 310, this information, because focused on only 1 symptom, cannot be exclusively interpreted as showing that bid dosing is preferable to qd dosing of FLONASE Nasal Spray but does tend to support this conclusion for this clinical endpoint.

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 311.

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, 29:188]

	TREATMENT GROUPS									
	Placebo	[1]FP 100 µg bid	FP 200 µg qd	[2]BDP 168 µg bid	P vs. FP 100	P vs. FP 200	P vs. BDP 168	FP 100 vs. FP 200	FP 100 vs. BDP 168	FP 200 vs. BDP 168
Total Nasal Symptom Score (TNSS): **Composite of Rhinorrhea + Nasal Obstruction + Sneezing + Nasal Itch**										
Pre-Treatment (n, mean score ± [3]SE)	111 190.0 ± 6.19	116 192.6 ± 6.33	118 193.1± 6.82	113 184.5 ± 6.45	.839	.845	.627	.993	.487	.490
Week 1 (n, mean score ± SE)	110 171.1 ± 6.39	115 146.7 ± 7.01	117 150.9 ± 7.02	113 146.9 ± 6.67	<.001	.006	.009	.597	.536	.923
Week 2 (n, mean score ± SE)	108 161.4 ± 7.01	114 143.4 ± 7.07	116 137.7 ± 7.56	112 127.9 ± 6.16	.020	.003	<.001	.505	.233	.593
Week 4 (n, mean score ± SE)	107 163.9 ± 7.29	111 133.9 ± 6.84	117 134.2 ± 7.03	106 118.6 ± 6.81	<.001	<.001	<.001	.928	.260	.293
Week 6 (n, mean score ± SE)	100 145.6 ± 6.97	105 118.8 ± 7.66	115 125.0 ± 7.01	104 116.8 ± 7.03	.003	.012	.005	.558	.836	.709
Week 8 (n, mean score ± SE)	95 143.1 ± 7.38	103 114.1 ± 6.95	111 129.5 ± 7.62	102 120.4 ± 6.89	.002	.105	.037	.112	.292	.606
Week 10 (n, mean score ± SE)	92 144.9 ± 7.71	101 113.3 ± 7.28	110 124.2 ± 7.66	101 111.2 ± 6.17	<.001	.016	.002	.305	.867	.393
Week 12 (n, mean score ± SE)	91 143.6 ± 8.51	101 108.2 ± 6.85	108 120.9 ± 6.87	96 104.5 ± 6.94	<.001	.007	<.001	.243	.943	.221
Week 16 (n, mean score ± SE)	90 130.4 ± 8.29	98 107.2 ± 7.74	105 111.8 ± 7.46	91 101.2 ± 7.25	.026	.042	.014	.814	.774	.602
Week 20 (n, mean score ± SE)	84 133.2 ± 9.13	96 102.4 ± 7.01	104 111.1 ± 7.40	87 99.0 ± 6.67	.002	.012	.002	.519	.930	.473
Week 24 (n, mean score ± SE)	81 128.3 ± 8.50	91 94.4 ± 7.08	102 105.4 ± 6.89	84 98.9 ± 6.81	<.001	<.001	<.001	.340	.480	.834
Endpoint (n, mean score ± SE)	111 137.9 ± 7.22	116 106.6 ± 6.89	118 106.4 ± 6.36	113 100.1 ± 6.00	<.001	<.001	<.001	.911	.671	.753
Post-treatment (Week 26) (n, mean score ± SE)	105 142.9 ± 6.85	109 141.8 ± 7.55	116 138.9 ± 7.03	107 154.0 ± 7.19	.846	.539	.120	.673	.079	.028

[1]FP=Fluticasone propionate. [2]BDP=Beclomethasone dipropionate. [3]SE=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, 29:205]

	TREATMENT GROUPS									
	Placebo	[1]FP 100 µg bid	FP 200 µg qd	[2]BDP 168 µg bid	P vs. FP 100	P vs. FP 200	P vs. BDP 168	FP 100 vs. FP 200	FP 100 vs. BDP 168	FP 200 vs. BDP 168
Total Nasal Symptom Score (TNSS): Composite of Rhinorrhea + Nasal Obstruction + Sneezing + Nasal Itch										
Pre-Treatment (n, mean score ± [3]SE)	112 199.6 ± 4.63	117 198.9 ± 5.09	118 198.5± 5.65	114 195.8 ± 4.66	.842	.836	.587	.994	.729	.733
Week 1 (n, mean score ± SE)	112 194.3 ± 5.48	116 167.0 ± 5.56	116 168.7 ± 6.46	112 166.1 ± 5.41	<.001	<.001	<.001	.659	.814	.840
Week 2 (n, mean score ± SE)	108 181.3 ± 5.64	114 158.7 ± 6.83	116 146.1 ± 6.62	113 143.9 ± 5.87	.003	<.001	<.001	.116	.089	.888
Week 4 (n, mean score ± SE)	108 174.6 ± 6.18	111 147.5 ± 7.23	115 135.4 ± 6.59	106 132.7 ± 6.33	<.001	<.001	<.001	.130	.148	.971
Week 6 (n, mean score ± SE)	104 162.6 ± 6.22	109 136.2 ± 7.20	116 135.8 ± 6.70	107 132.8 ± 6.48	.001	.002	.001	.916	.986	.930
Week 8 (n, mean score ± SE)	95 156.5 ± 6.84	104 130.1 ± 7.05	116 128.5 ± 6.85	104 127.6 ± 6.43	.003	.002	.003	.936	.954	.890
Week 10 (n, mean score ± SE)	92 156.0 ± 6.81	103 129.7 ± 7.75	114 130.8 ± 7.04	102 121.5 ± 6.12	.001	.004	<.001	.677	.687	.408
Week 12 (n, mean score ± SE)	91 152.0 ± 7.14	99 120.6 ± 7.56	110 124.3 ± 6.82	99 121.3 ± 6.48	<.001	<.001	.001	.582	.607	.981
Week 16 (n, mean score ± SE)	91 145.5 ± 6.75	98 117.4 ± 7.64	108 114.6 ± 6.65	93 122.0 ± 6.93	.002	<.001	.018	.642	.499	.250
Week 20 (n, mean score ± SE)	90 141.8 ± 7.23	96 113.7 ± 7.46	104 115.5 ± 7.15	89 116.1 ± 6.99	.001	<.001	.007	.976	.654	.669
Week 24 (n, mean score ± SE)	85 140.8 ± 7.74	94 112.5 ± 7.11	103 110.1 ± 6.64	86 112.4 ± 7.10	.002	<.001	.003	.669	.860	.550
Post-treatment (Week 26) (n, mean score ± SE)	80 151.8 ± 7.14	90 138.2 ± 7.98	99 139.1 ± 6.79	83 145.0 ± 7.60	.036	.019	.240	.821	.079	.028

[1]FP=Fluticasone propionate. [2]BDP=Beclomethasone dipropionate. [3]SE=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 VII.
Efficacy of Flonase Nasal Spray vs. Placebo: **Overall Physician Evaluation at Week 24 of the Study;** Intent-to-Treat (ITT) for the Double-blind Treatment Period
[NDA 20-121, S-009, 29:203]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 100 µg bid	FP 200 µg qd	[2]BDP 168 µg bid	P vs. FP 100	P vs. FP 200	P vs. BDP 168	FP 100 vs. FP 200	FP 100 vs. BDP 168	FP 200 vs. BDP 168
Total # Randomized Pts.	113	119	118	116						
Total # of Evaluable Pts:	108	114	118	108						
Patient Response to Treatment					.002	.001	<.001	.854	.199	.227
Significant Improvement	11 (10%)	30 (26%)	32 (27%)	25 (23%)	NA	NA	NA	NA	NA	NA
Moderate Improvement	19 (18%)	27 (24%)	30 (25%)	32 (30%)	NA	NA	NA	NA	NA	NA
Mild Improvement	33 (31%)	27 (24%)	26 (22%)	33 (31%)	NA	NA	NA	NA	NA	NA
No change	38 (35%)	27 (24%)	25 (21%)	15 (14%)	NA	NA	NA	NA	NA	NA
Mildly Worse	4 (4%)	2 (2%)	2 (2%)	2 (2%)	NA	NA	NA	NA	NA	NA
Moderately Worse	2 (2%)	1 (1%)	2 (2%)	1 (1%)	NA	NA	NA	NA	NA	NA
Significantly Worse	1 (1%)	0 (0%)	1 (1%)	0 (0%)	NA	NA	NA	NA	NA	NA

[1]FP=Fluticasone propionate. [2]BDP=Beclomethasone propionate. P-values based on the Cochran-Mantel-Haenszel test. Percentages are based on the number of evaluable patients. NA=Not available (i.e. analysis not performed). P-values are not adjusted for multiple comparisons.

8.5.4.2. Nasal Cytology Studies

Similar to the NAPR studies, nasal cytology studies were conducted in study FLN 311 (as in FLN 310) in order to assess the proportion of patients enrolled in FLN 311 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 4 treatment groups had evidence of low numbers of eosinophils (grade 1; or scattered eosinophils noted on nasal smear: 59% of placebo group patients, 51% of FP 100 μg bid patients, 55% of FP 200 μg qd patients, and 52% of BDP 168 μg bid patients) [NDA 20-121, S-009, 29:241], 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=0.683), between placebo and the FP 200 μg bid group (p=0.769), or between placebo and the BDP 168 μg bid group at screening [NDA 20-121, S-009, 29:241]. Furthermore, the percentage of nasal smears with no eosinophils increased in each of the 3 active treatment groups (including the BDP group) by week 24 but increased less in the placebo group (25% of placebo group patients, 48% of FP 100 μg bid patients, 41% of FP 200 μg qd patients, and 67% of BDP 168 μg qd patients) [NDA 20-121, S-009, 29:241]. These results of distribution of nasal eosinophilia are similar to those seen in the pivotal NAPR study FLTA 3010 and PAR study FLN 310 (although the % decrease in nasal eosinophils in FLN 311 was slightly lower than that seen in FLN 310). 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 and the BDP treatment group [NDA 20-121, S-009, 29:242].

Regarding the distribution of other cell types, namely neutrophils, it appeared that treatment with FP and BDP Nasal Spray decreased the percentage of neutrophils in nasal secretions (compared to placebo) by week 24 of treatment [NDA 20-121, S-009, 29:244]. Consistent with 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, 29:245]. 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.

8.5.4.3. Safety Analysis

The safety data for study FLN 311 (as for FLN 310) had been previously reviewed during the evaluation of NDA 20-121 for FLONASE Nasal Spray for NDA approval. Since these data were not the primary focus for approval of the NAPR efficacy supplement, safety results for study FLN 311 will only be summarized with respect to pertinent findings.

Similar to the NAPR studies, safety analysis for study FLN 311 consisted of an evaluation of adverse events, standard laboratory tests (along with special safety studies such as a.m. plasma cortisols 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, 29:66-70]. In this trial, the safety evaluable population was the same as the ITT population. All 466 patients who received study medication were included in the safety database and comprised the intent-to-treat population (n=113 for the placebo group, n=119 for the FP 100 μg bid group, n=118 for the FP 200 μg qd group, and n= for the BDP 116 μg bid 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: 106 patients withdrew from the study prematurely, leaving 360 patients (out of 466 patients, or 77% of total) who completed the entire 6 month double-blind treatment period) [NDA 20-121, S-009, 29:100].

The overall incidence of adverse events (AEs) were generally similar for all 4 treatment groups but with a slightly higher incidence in the FP 200 μg qd treatment group (78-85% range, highest in the FP 200 μg qd group-85%). Of note, these overall AE ranges were similar to that of pivotal NAPR study FLTA 3010 and the PAR study FLN 310 and included as most common AEs: headache (10-17% incidence for the 4 treatment groups, highest in the FP groups), epistaxis (9-18% incidence for the 4 treatment groups, highest in the FP groups), URIs (8-15% incidence for the 4 treatment groups, highest in the BDP group), and sore throat (10-151% incidence for the 4 treatment groups, highest in the placebo group) [NDA 20-121, S-009, 29:254, 255, 262]. With regard to other individual/specific AEs, the incidence of AEs were also similar across all 4 treatment groups, with the exception of a slight increase in the incidence of nasopharyngitis in the higher dose FP treatment group-200 μg qd (11% range) over placebo (5%) [NDA 20-121, S-009, 29:254]. Of note, this type of result was also seen for FLN 310. Reports of sinusitis were rare for all 4 treatment groups [NDA 20-121, S-009, 29:254], but were higher in the FP 200 μg qd group (6%) and not reported in the BDP group (0% incidence). Nasal septal or mucosal ulcers (3 cases in the FP 100 μg bid group and 1 case in the placebo group

reported as AEs) were likewise rare or altogether not reported in all 4 treatment groups, as were lack of cataract AE reports [NDA 20-121, S-009, 29:255].

In summary, the safety profile for the double-blind period for FP Nasal Spray in study FLN 311 was unremarkable and consistent with findings of other NAPR and PAR studies performed with FLONASE, 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, 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 27 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, 29:100]. In 2 of these patients, AEs were considered 'serious' but unrelated to study medication (patient # 5105- FP 200 μg qd group-hospitalized for gangrenous bowel and patient # 5006-BDP 168 μg bid group-hospitalization for fever and tonsillitis) [NDA 20-121, S-009, 29:102, 251, 252]. The majority of reasons for discontinuation were reasons associated with worsening rhinitis or asthma symptoms (or lack of effficacy) or intercurrent illness. None of these patients were deemed by the principal investigators to have had AEs that could have been induced by drug treatment.

[5]Serious AEs were reported for 8 patients in study FLN 311 (1 placebo group patient (broken left jaw), 3 FP 100 μg bid group patients (abdominal pain/diarrhea, squamous cell carcinoma of the left lower extremity, and double fracture of the pelvis), 3 FP 200 μg qd group patients (worsening left shoulder pain, upper abdominal pain with twisted gangrenous bowel, and one case of minor trauma), and 1 BDP 168 μg bid group patient (fever/tonsillitis) [NDA 20-121, S-009, 29:249-252]. None of the serious AEs were considered to be related to study medication. No deaths were reported in this study [NDA 20-121, S-009, 29:100].

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 with normal range by week 24 of the study, with only minor variability in a number of parameters by week 24 of testing in all 4 treatment groups: monocyte counts (which increased slightly (< 1%) with treatment in all 4 treatment groups at week 24), peripheral eosinophil counts (which decreased with treatment), and minor decrements in platelet counts, which was more pronounced in the BDP group

[5] 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.

[NDA 20-121, S-009, 29:118]. Interestingly, a similar trend in these 3 laboratory values was noted in PAR study FLN 310.

With regard to laboratory outliers, laboratory abnormalities which in rare instances met the definition of 'clinically significant' per the sponsor's normal laboratory range [NDA 20-121, S-009, 29:466-470, 30:255-259] were seen among the 4 treatment groups, but with no pattern or trend evident for any particular laboratory abnormality or for any particular treatment group. Two patients in the FP 100 μg bid group were withdrawn from the study because of abnormal liver function laboratory values which were not deemed by the principal investigators to be clinically significant: (1) patient # 5104: a 33 year old female with an increased SGPT on screening (to 81 U/L) but normal SGOT (32 U/L) who was withdrawn from the study on day 12 due to an increase in LFTs to an SGPT of 186 U/L and SGOT of 77 U/L which was felt to be possibly related to hepatitis, and (2) patient # 5431: a 37 year old male in the FP 100 μg bid group with normal range screening SGPT and SPOT who was withdrawn from the study due to an increase in SGPT to 57 U/L and increase in SGOT to 40 U/L at day 29 of the study (the patient's LFTs reverted to normal range post-discontinuation of study drug) [NDA 20-121, S-009, 30:106, 108].

Adrenal function was evaluated in FLN 311 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, 29:114-118] revealed a no significant mean change (decrease) in a.m. plasma cortisol levels post-treatment with either of the 4 treatments at week 12 and 24 (Table VIII). In fact, the mean a.m. plasma cortisol concentrations were similar in all treatment groups (range of means: 15.4 μg/dL-17.1 μg/dL) values [NDA 20-121, S-009, 29:376]. For purposes of this study, a normal a.m. plasma cortisol level was defined as: a cortisol level between 5-18 μg/dL. These results are in mild contrast to FLN 310 in which the FP 200 μg qd patients demonstrated a slight decrease in a.m. plasma cortisol levels, compared with the FP 100 μg bid group and placebo. Based on the patient line listings and outlier results [NDA 20-121, S-009, 29:115-118, 378-429], a number of patients in all 4 treatment groups (including placebo patients) manifested a.m. plasma cortisol outliers, or a.m. plasma cortisol levels < 7 μg/dL (frequency of outliers for all 4 treatment groups 9-11% range) and this number was lowest in the FP 200 μg qd group (FP 200 μg qd group =9%, FP 100 μg bid=11%, BDP 168 μg bid group=11%, placebo=11%) [NDA 20-121, S-009, 29:378]. Similar results were demonstrable for the ACTH stimulation tests (Table IX) in which mean plasma cortisol levels post-ACTH stimulation were similar and within the expected range in all 4 treatment groups (Table IX) [NDA 20-121, S-009, 29:115, 377]. Based on individual patient line listings, 6-15% of patients in all 4 treatment groups

demonstrated an inadequate response to ACTH stimulation, using the sponsor's pre-defined criteria of an adequate adrenal response (8% of placebo patients failed to have an adequate adrenal response, 7% of FP 100 μg bid patients failed to have an adequate adrenal response, 10% of FP 200 μg qd patients failed to have an adequate adrenal response, and 4% of BDP 168 μg bid patients failed to demonstrate an adequate adrenal response) [NDA 20-121, S-009, 29:378].

Reviewer's Note: Results of adrenal assessment detected mild to no adrenal suppression based on review of mean data and patient outlier results. The results seen in FLN 311 are slightly different from FLN 310, in that patients in the latter study demonstrated greater blunting of the adrenal response (in particular with ACTH stimulation testing) with the higher dose of FP Nasal Spray-200 μg qd.

Table VIII. A.M. Plasma Cortisol Levels Pre- and Post-Treatment with Study Drug (FLONASE Aqueous Nasal Spray); ITT Population [NDA 20-121, 009, 29:376]

A.M. PLASMA CORTISOL (µg/dL)	Placebo Pre-Rx, n=112 Week 4, n=111 Week 12, n=100 Week 24, n=90 Endpoint, n=112 (mean ± SE)	FP 100 µg bid Pre-Rx, n=116 Week 4, n=115 Week 12, n=109 Week 24, n=99 Endpoint, n=116 (mean ± SE)	FP 200 µg qd Pre-Rx, n=118 Week 4, n=116 Week 12, n=115 Week 24, n=106 Endpoint, n=118 (mean ± SE)	BDP 168 µg bid Pre-Rx, n=113 Week 4, n=112 Week 12, n=102 Week 24, n=91 Endpoint, n=113 (mean ± SE)	P-Values					
					P vs. FP 100	P vs. FP 200	P vs. BDP	FP 100 vs. FP 200	FP 100 vs. BDP	FP200 vs.BDP
Pre-Rx (Screening)	16.3 ± 0.71	16.6 ± 0.80	16.6 ± 0.74	15.5 ± 0.65	0.713	0.750	0.437	0.958	0.250	0.270
Week 4	16.0 ± 0.76	15.9 ± 0.74	16.4 ± 0.79	15.6 ± 0.65	0.575	0.845	0.756	0.444	0.384	0.970
Week 12	16.1 ± 0.84	15.7 ± 0.79	17.1 ± 0.89	15.5 ± 0.77	0.618	0.294	0.764	0.112	0.847	0.173
Week 24	16.5 ± 0.88	16.1 ± 0.70	16.6 ± 0.84	15.8 ± 0.73	0.646	0.856	0.803	0.769	0.837	0.938
Endpoint visit	16.5 ± 0.77	16.8 ± 0.74	16.9 ± 0.81	15.4 ± 0.65	0.864	0.907	0.596	0.955	0.482	0.515

Pre-Rx=Pre-treatment. P=Placebo, FP=Fluticasone Propionate Nasal Spray, BDP=Beclomethasone dipropionate.
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 MSError form ANOVA (pre-treatment) or ANCOVA. P-values are not adjusted for multiple comparisons.

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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, 29:377]

A.M. PLASMA CORTISOL (µg/dL)	Placebo Week -4, n=104 Week 24, n=81 Endpoint, n=104 (mean ± SE)	FP 100 µg bid Week -4, n=108 Week 24, n=90 Endpoint, n=108 (mean ± SE)	FP 200 µg qd Week -4, n=114 Week 24, n=101 Endpoint, n=114 (mean ± SE)	BDP 168 µg bid Week -4, n=104 Week 24, n=83 Endpoint, n=104 (mean ± SE)	P-Values P vs. FP 100	P vs. FP 200	P vs. BDP	FP 100 vs. FP 200	FP 100 vs. BDP	FP200 vs.BDP
Week -4:										
--Baseline	15.7 ± 0.63	15.1 ± 0.71	14.9 ± 0.68	14.2 ± 0.64	0.680	0.345	0.655	0.170	0.970	0.162
--Post-Cortrosyn	31.2 ± 0.74	30.4 ± 0.86	30.9 ± 0.76	29.4 ± 0.62						
--Difference	15.5 ± 0.45	15.3 ± 0.47	16.0 ± 0.38	15.2 ± 0.42						
Week 24:										
--Baseline	16.7 ± 0.94	16.3 ± 0.73	16.4 ± 0.86	15.7 ± 0.74	0.512	0.156	0.315	0.442	0.708	0.713
--Post-Cortrosyn	31.3 ± 1.07	30.4 ± 0.81	30.0 ± 0.92	29.5 ± 0.83						
--Difference	14.6 ± 0.61	14.1 ± 0.51	13.7 ± 0.48	13.7 ± 0.70						
Endpoint visit:										
--Baseline	16.5 ± 0.80	16.6 ± 0.70	16.8 ± 0.83	15.4 ± 0.66	0.433	0.167	0.490	0.555	0.928	0.500
--Post-Cortrosyn	31.1 ± 0.89	30.6 ± 0.72	30.6 ± 0.88	29.4 ± 0.78						
--Difference	14.6 ± 0.55	14.0 ± 0.48	13.8 ± 0.45	14.0 ± 0.61						

Pre-Rx=Pre-treatment. P=Placebo, FP=Fluticasone Propionate Nasal Spray, BDP=Beclomethasone dipropionate.
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 MSError 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, 29:124-126].

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 or BDP at the 2 different doses of FP Nasal Spray, although several patients in each of the treatment groups developed either nasal ulcerations or perforations per physical examination reports (see discussion below) [NDA 20-121, S-009, 29: 255, 316, 338]. Patients receiving the 2 active treatments generally experienced a decrease in the size of nasal turbinates and nasal secretions. Eye exams revealed that at pre-treatment, ~ 10% of patients in the 2 FP groups and in the placebo group had some ophthalmic abnormality recorded as did 20% of BDP patients. The majority of these findings were corneal or retinal changes with only a few small lens opacities (congenital, nonprogressive per consult ophthalmologists) noted in this patient group. After 12 weeks of treatment with study medication, posterior subcapsular cataracts were not noted in any patients in either of the 4 treatment groups. Lenticular opacities (not deemed to be associated with steroid use) were seen in 1 patient each in the placebo, FP 200 µg qd and BDP 168 µg bid group, and 2 patients in the FP 100 µg bid group at the end of the double-blind period by week 24 [NDA 20-121, S-009, 29:126, 256]. No cases of glaucoma were reported [NDA 20-121, S-009, 29:126-127].

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. The slight increase in the incidence of sinusitus in the FP 200 µg qd group compared with placebo and the other 2 active comparators was previously discussed in the section addressing adverse event (AE) frequencies.

Evaluation of the ear, nose, and throat (ENT exam) to rule out nasal or oral candidiasis and results of these examinations revealed that only 1 patient in the FP 100 µg bid group who developed nasal candidiasis during treatment with study drug and 1 patient in the BDP 168 µg bid group (post-24 weeks of treatment) [NDA 20-121, S-009, 29:123, 269]. Two cases of oral candidiasis were detected on physical examination (patient # 5210:placebo group (post-treatment visit), and patient # 5323: FP 100 µg bid group (post-1 week of treatment) [NDA 20-121, S-009, 29:123]. Clinical evaluation for presence of nasal septal ulcers or perforations revealed 1 case of a nasal ulceration in a placebo group patient and 2 cases in the FP 200 µg qd group [NDA 20-121, S-009, 29:255], and 1 case each of nasal septal perforations in the FP 100 µg bid and FP 200 µg qd groups [NDA 20-121, S-009, 29:255, 316, 338]. In study FLN 311, ear exams to assess perforations and serous effusions were not performed (as had been for study FLTA 3010).

8.5.5. 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 almost all efficacy endpoints (primary and secondary; exception the week 2 interval for the patient self-rated nasal itch score) 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). The numerical differences in mean symptom scores for the FP 100 µg bid and FP 200 µg qd doses were minimal for most endpoints. 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 demonstrable throughout the duration of the study, again supportive of the comparability of qd vs. bid dosing of FP Nasal Spray. End-of-dosing assessment with the a.m. patient-self rated nasal obstruction score was likewise able to support comparability between the 2 FP regimens, though favoring slightly greater efficacy for the FP 100 µg bid dosing regimen.

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 that were clearly a result of study medication taken. 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 Table: Efficacy Variables for the ITT Population and Treatment with FLONASE Aqueous Nasal Spray for the Perennial Allergic Rhinitis (PAR) Indication (**STUDY FLN 311**)

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:	No: All time points.
Secondary Efficacy Variables	
1. Overall Physician Evaluation	No
2. Patient-rated average daily nasal obstruction score	No: All time points.
3. Patient-rated average a.m. nasal obstruction score	No: All time points.
4. Patient-rated average daily rhinorrhea score	No: All time points.
5. Patient-rated average daily sneezing score	No: All time points.
6. Patient-rated average daily nasal itch score	Yes: Week 2. No: Week 1, 3-24.
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: Turbinates Nasal mucosa Nasal septum Nasal polyps	No: All time points. All time points. All time points. All time points.
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,.

Summary:

Based on the results of this PAR trial, FP Nasal Spray given at a dose of 100 µg bid vs. 200 µg qd did consistently show statistically insignificant differences in efficacy for the primary efficacy endpoints, in contrast to study FLN 310 where the numerical differences between the 2 FP dosing regimens were not always statistically insignificant, though the trend was toward similarity of the 2 regimens.

From the safety perspective, the 2 doses were overall well-tolerated with an unremarkable adverse event profile that was consistent with that seen in other studies reviewed in this efficacy supplement submission.

Hence, results of this study support comparability of 100 µg bid and 200 µg qd dosing of FLONASE Nasal Spray 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.

REVISED
STUDY SCHEDULE (FLOWCHART)
CGBA-368

	Pre-Study	Single-Blind Baseline			Double-Blind Treatment											F/U
VISIT NUMBER	0	1[a]	2	3	4[f]	5	6	7	8	9	10	11	12	13	14[g]	15[h]
WEEK NUMBER	-4	-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)
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	
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		
Observe/Interview for Adverse Experience		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

8.6. Summaries of Controlled, Non-U.S. Perennial Rhinitis Trials (PAR and NAPR):

A number of controlled studies in which allergic and non-allergic rhinitis were not differentiated (i.e. patients with either could have been enrolled in the study(ies)) were reviewed briefly in terms of the overall efficacy and safety trends. The summaries of these studies are presented in the ensuing section and overall demonstrated efficacy in decreasing many rhinitis symptoms compared with placebo treatment (in the studies where a placebo arm was included) with a safety profile similar to the NAPR and PAR studies previously reviewed in this efficacy supplement (sections 8.1-8.5).

8.6.1. Protocol No. FLIP07 (report # GRP/88/032): A dose-ranging, parallel-group study comparing FP Nasal Spray 50 μg, 100 μg, 200 μg, and 400 μg bid with placebo in perennial rhinitis [NDA 20-121, S-009, 32:4, 7-8].

This was a multi-center (European), randomized, double-blinded, stratified (by results of skin prick testing), placebo-controlled, parallel group study of 4 different doses of FP Nasal Spray vs. placebo for the treatment of symptoms of perennial rhinitis in adult patients. Patients were treated with 1 of the 5 treatments for up to 4 weeks. The goal of the study was to establish the minimum effective bid dose of FP Nasal Spray for the control of perennial rhinitis symptoms, along with an assessment of the safety and tolerability of FP Nasal Spray.

A total of 254 patients were enrolled into the trial, of which 226 completed the study. Enrolled patients ranged from 15-74 years of age. Patients recorded their daily symptoms which consisted of: nasal discharge, nasal blockage, nasal itching, and sneezing using a 4 point scale, and eye irritation/watering using a 3 point scale. The primary efficacy endpoint was defined as: the percentage of symptom-free days (symptoms defined as: nasal discharge, nasal blockage, nasal itching, sneezing, and eye irritation/watering) as recorded on patient diary cards. The primary comparison of interest was between the 4 FP treatment groups and placebo treatment.

Statistical analysis of the intent-to-treat population, in terms of the % of 'symptom-free days', provided no evidence of a dose-response effect for FP Nasal Spray. Patients receiving FP Nasal Spray did however demonstrate a greater increase in the % of 'symptom-free days' in terms of the individual nasal symptoms of nasal discharge and nasal blockage than did patients receiving placebo. None of the comparisons between FP Nasal Spray and placebo were statistically significant with the exception of nasal blockage with the FP 100 μg bid dose ($p < 0.05$) and with the FP 400 μg bid dose ($p < 0.01$). Hence, this study overall only provided marginal evidence, based on all nasal symptoms and the eye symptoms of perennial rhinitis, that FP Nasal Spray at either of the 4 doses studied was efficacious in the treatment of perennial rhinitis symptoms.

With regard to the safety analysis, adverse events (AEs) were generally mild and similar between the treatment groups. The most commonly reported AEs were headache and epistaxis. A.M. plasma cortisol levels were likewise measured in this study, with no patient in either of the 4 FP treatment groups demonstrating a statistically significant response from placebo treatment. There was no evidence that increasing the dose of FP Nasal Spray produced a decrease in the a.m. plasma cortisol levels.

8.6.2. Protocol No. FLNT43 (report # GRP/90/032): A double-blind comparison of FP Nasal Spray 200 µg qd, FP Nasal Spray 200 µg bid, with BDP 200 µg bid, and with placebo aqueous nasal spray in the treatment of patients with perennial rhinitis [NDA 20-121, S-009, 32:4, 11-281].

This was a multi-center (European), randomized, double-blinded, placebo-controlled, parallel group study to compare the safety and efficacy of FP Nasal Spray 200 µg qd, vs. FP Nasal Spray 200 µg bid, vs. BDP 200 µg bid, and vs. placebo nasal spray in adult patients with perennial rhinitis. The study was designed with a 2 week run-in period, followed by a 12 week treatment period, and a 2 week follow-up period.

A total of 516 patients ranging in age from 10-83 years of age with 2 or more symptoms of perennial rhinitis and a history of moderate-severe rhinitis were randomized into the study, with 453 completing the study. Patients recorded nasal blockage on awakening in the a.m., nasal blockage for the remainder of the day, along with rhinorrhea, sneezing, and an overall assessment of their symptoms using a 4 point scale (0-3 rating of symptoms). The primary efficacy endpoints were based on the analysis of the % of 'symptom-free days' for symptoms of nasal blockage on awakening, nasal blockage during the day, and rhinorrhea. Use of rescue medication (terfenadine) was recorded on diary cards, was tabulated, and compared between treatments.

Analysis of the primary efficacy endpoints showed that FP Nasal Spray 200 µg qd or FP 200 µg bid was statistically significantly better in reducing symptoms of rhinorrhea and nasal blockage during the day, compared with placebo but not so for the nasal blockage on awakening endpoint. There was no significant difference between FP 200 µg qd or FP 200 µg bid and placebo for any of the rhinitis symptoms or for the overall assessment of symptoms. The FP 200 µg bid treatment generally provided a greater numerical decrease in rhinitis symptoms than did the FP 200 µg qd treatment group, although statistical comparison between these 2 groups was not defined a priori to study initiation and was therefore not performed by the sponsor.

Safety analysis revealed similar findings seen in the other perennial rhinitis trials reviewed in the sponsor's efficacy supplement submission. Namely, adverse events (AEs) were generally mild and consistent with those noted previously. Most patient withdrawals from the study were due to 'lack of efficacy' in the

placebo group and not AEs. No untoward findings were seen with regard to routine laboratory tests.

8.6.3. Protocol No. FLIT11 (report # GRP/90/022): A double-blind, parallel group study to assess the safety of long term use of FP Nasal Spray 200 μg bid compared with BDP 200 μg bid in the treatment of perennial rhinitis [NDA 20-121, S-009, 34:1-302].

This was a multi-center (European), randomized, double-blinded, parallel group long-term (1 year) study to compare the safety and efficacy of FP Nasal Spray 200 μg bid, vs. BDP 200 μg bid in patients with perennial rhinitis. The study was designed with a 2 week run-in period, followed by a 1 year treatment period, and a 2 week follow-up period. Patients were randomized to the study such that every 2 patients received FP Nasal Spray for every 1 patient who received BDP Nasal Spray. The primary objective of the study was to assess the safety of longer term therapy with FP Nasal Spray.

A total of 242 patients 16 years of age and older with a history of moderate-severe rhinitis were randomized into the study (159 into the FP treatment group and 83 into the BDP treatment group), with a total of 179 patients completing the study. At each clinic visit (8 in total) patients recorded their symptoms of nasal blockage, rhinorrhea, sneezing, nasal itching, and eye watering/irritation using a 4 point scale (0-3 rating of symptoms). Use of rescue medication (terfenadine) was recorded on diary cards, was tabulated, and compared between treatments.
It appears from the study report that a primary efficacy endpoint was not pre-defined and analysis of the nasal and eye symptoms were equally rated using data from clinic visits 3, 4, and 7 [NDA 20-121, S-009, 34:27]. The proportional odds model was used to model the effects of treatment and country on symptom grade at clinic visits 3, 4, and 7. Grades 2 and 3 (symptom score rating) were combined into a single grade since few patients were graded as 3 for a particular nasal symptom. Based on this statistical analysis of efficacy, and based on comparable baseline symptom scores between the FP and BDP treatment groups, at clinic visit 7 (post-52 weeks of treatment), FP treatment afforded a statistically significantly greater improvement in nasal blockage ($p=0.002$), rhinorrhea ($p=0.002$), and eye watering/irritation ($p=0.048$) than did BDP treatment, and numerically greater but marginally statistically greater improvement in nasal itching ($p=0.052$) than BDP treatment. Although a placebo group was not included in this study's design, comparison with the active comparator BDP for the clinical endpoints listed above, which showed greater efficacy for the FP treated patients, is supportive of efficacy for FP Nasal Spray.

With regard to safety, approximately 1 year of monitoring of FP Nasal Spray use in patients failed to reveal any new, untoward effects (that were not already seen in other studies reviewed); the most common AEs being URI, epistaxis, nasal irritation, and headache. With regard to routine laboratory tests, a total of 9 patients had laboratory tests considered to be possibly related to study drug. Of

these 9 patients, 3 patients in the FP group had abnormal renal function and 1 had abnormal liver function tests [NDA 20-121, S-009, 34:4]. Results of ACTH stimulation testing revealed no patients in either the FP treatment group or BDP group (47 total who underwent testing in the FP group and 23 in the BDP group) who showed a statistically significant decrease in plasma cortisol level after 1 year of treatment.

8.6.4. Protocol No. FLIT22 (report # GRP/92/012): A parallel group comparison of FP Nasal Spray compared with placebo in patients with non-seasonal allergic rhinitis with symptoms all year round [NDA 20-121, S-009, 34:303-305].

This was a single center (The Netherlands), randomized, double-blinded, placebo-controlled, parallel group long-term (1 year) study to compare the safety and efficacy of FP Nasal Spray 100 μg bid, vs. placebo in adult patients with perennial non-allergic rhinitis. Additionally, changes in nasal mucosal histology and T cell subsets isolated from nasal mucosa were assessed in this study. The study was designed with a 4 week run-in period, followed by a 1 year treatment period, and a 2 week follow-up period.

A total of 42 patients were randomized into the study, though no information was provided in the study report as to how many patients completed the study. Rescue medication use (with a maximum dose of terfenadine 60 mg bid) was allowed in this study for troublesome symptoms. At each clinic visit both the patient and physician assessed symptoms of: nasal blockage, rhinorrhea, sneezing, nasal itching, and eye irritation using a 4 point (0-3) rating scale. A primary efficacy endpoint was not pre-defined for this study as its' objective was primarily to assess the effect of FP Nasal Spray treatment on changes in nasal mucosa and immunologically active cells in the nasal mucosa.

Nonetheless, efficacy analysis (statistical analysis was performed) for this study revealed that long-term treatment with FP Nasal Spray 100 μg bid was more efficacious than placebo at decreasing some of the symptoms of non-seasonal allergic rhinitis (PAR). For example, FP Nasal Spray 100 μg bid was statistically more effective than placebo at decreasing physician-rated scores of sneezing at visits 3, 10, and 11 ($p=0.029$, $p=0.045$, and $p=0.018$, respectively), physician-rated nasal discharge at visit 8 ($p=0.039$), and physician-rated nasal itching at visit 11 ($p=0.024$). With regard to patient rated symptoms, no statistically significant difference in symptom scores compared with placebo was seen for nasal blockage, rhinorrhea, sneezing, nasal itching, and eye watering/irritation. Based on these results, FP Nasal Spray at a dose of 100 μg bid was not found to be consistently more efficacious than placebo for many of the symptom scores analyzed.

Safety analysis supported the tolerability of FP Nasal Spray and the adverse event profile was consistent with that shown in other PAR and NAPR studies reviewed in this submission. No patients reported any serious AEs during the study and few laboratory abnormalities were recorded. Histopathological

examination revealed improvement in nasal mucosa architecture in patients treated with FP Nasal Spray compared with placebo.

8.6.5. Protocol No. FLNP57 (report # GRP/92/002): A double-blind, single center, parallel group study to investigate the influence of FP Nasal Spray 200 µg qd given once daily, on nasal mucosal inflammation in PAR [NDA 20-121, S-009, 34:306-309].

This was a single center (United Kingdom), randomized, double-blinded, placebo-controlled, parallel group study to compare the safety and efficacy of FP Nasal Spray 200 µg qd, vs. placebo in adult patients with perennial allergic rhinitis (PAR). The study was designed with a 2 week run-in period, followed by a 6 week treatment period. Nasal biopsies with analysis of cell numbers in the nasal mucosa and submucosa were also performed in study patients pre- and post-treatment.

A total of 38 patients were randomized into the study and all 38 patients completed the study. Rescue medication use (with a maximum dose of terfenadine 60 mg bid) was allowed in this study for troublesome symptoms. The patient assessed symptoms of: nasal blockage on awakening (the a.m.), nasal blockage throughout the day, and rhinorrhea. Primary efficacy endpoints were based on these 3 symptom scores (change from baseline) and analyzed as the 'median decrease in symptom scores from baseline to the end of treatment. Additionally, sneezing, nasal itching, and sense of smell were assessed as secondary efficacy endpoints.

Efficacy analysis revealed a statistically significant median decrease for nasal blockage on awakening (p=0.073), nasal blockage throughout the day (p=0.064), sneezing (p=0.019), and nasal itch (p=0.021). Hence, for the majority of symptom scores, the FP Nasal Spray group demonstrated greater efficacy in reducing the respective symptom score, compared with placebo treatment. No numerically significant differences were noted between the 2 treatment groups with respect to nasal biopsy cell numbers, although a trend towards reduction in mast cell numbers was noted in the nasal submucosa of FP treated patients.

Safety analysis was again consistent with that of the other rhinitis studies reviewed; namely that FP Nasal Spray was overall well tolerated, with no serious AEs or serious trends in laboratory parameters.

8.6.6. Protocol No. FLNP64 (report # GRP/94/020): A double-blind, single center, placebo-controlled, crossover study to investigate the effect of acute and chronic FP Nasal Spray 200 µg qd once daily treatment on nasal responses to histamine in patients with PAR [NDA 20-121, S-009, 34:1-10].

This was a single center (United Kingdom), randomized, double-blinded, placebo-controlled, crossover study to compare the safety and efficacy of FP Nasal Spray 200 µg qd, vs. placebo in adult patients with perennial allergic rhinitis (PAR). The study was designed with a 4 week treatment, followed by a 2

week washout period, in turn followed by an additional 4 week treatment period (crossover design).

A total of 13 patients were randomized into the study and 11 patients completed both phases of the study. Again, rescue medication use (with a maximum dose of terfenadine 60 mg bid) was allowed in this study for troublesome symptoms. The patients assessed nasal symptom scores using the same symptoms and rating scale as per previous studies reviewed. Importantly, however, these assessments were not utilized in the efficacy analysis as planned because efficacy analysis was not performed per study protocol and was disregarded. Hence this study became essentially a safety monitoring study only.

In terms of the safety analysis, no serious or unexpected AEs were reported and FP treatment was well-tolerated by study patients.

Summaries of Uncontrolled, Non-U.S. Perennial Rhinitis Trials (PAR and NAPR):

8.6.7. Protocol No. FLIT08 (report # GRP/90/023): The long-term safety and efficacy of FP Nasal Spray 200 µg bid in the management of perennial rhinitis [NDA 20-121, S-009, 35:12-185].

This was a single center (United Kingdom), open label study to establish the safety of FP Nasal Spray 200 µg bid, in the long-term management of perennial rhinitis in adult patients. The study was designed as a 52 week open label period where all enrolled patients were placed on FP Nasal Spray 200 µg bid.

A total of 60 patients were randomized into the study and 35 patients completed the study. Again, rescue medication use (with a maximum dose of terfenadine 60 mg bid) was allowed in this study for troublesome symptoms. While patients did assess nasal symptoms during this study these were not analyzed statistically, as this was primarily a safety study. In addition, secondary objectives of the study were to study olfaction, mucociliary clearance, total nasal resistance, respiratory function and the structure of the lateral end of the inferior turbinate of the nose, at baseline and after 1 year's treatment with FP Nasal Spray.

The overall trend for efficacy in this study was that symptom scores decreased for nasal blockage, sneezing, nasal itching, rhinorrhea, and eye symptoms, compared with baseline in FP treated patients.

In terms of the safety analysis, no serious or unexpected AEs were reported and FP treatment was well-tolerated by study patients. With regard to laboratory parameters, 3 patients had recorded an abnormal hematology test (2 had a decrease in white blood cell and neutrophil count and 1 had a decrease in the neutrophil differential count) which were thought to be possibly related to drug treatment [NDA 20-121, S-009, 35:13].

Summaries of Pediatric, Non-U.S. Perennial Rhinitis Trials (PAR and NAPR):

8.6.8. Protocol No. FLNT60 (report # GRP/92/008): A double-blind comparison of FP Nasal Spray 100 µg qd, FP Nasal Spray 200 µg qd, and placebo qd in the treatment of perennial rhinitis in children aged 4-11 years [NDA 20-121, S-009, 35:187-198].

This was a multi-center, multinational, randomized, double-blinded, placebo-controlled, parallel group study to compare the safety and efficacy of FP Nasal Spray 200 µg qd, vs. FP 100 µg qd in pediatric patients aged 4-11 years with perennial rhinitis. The study was designed with a 4 week treatment period, and a 2 week follow-up period.

A total of 415 pediatric patients with a history of moderate-severe perennial rhinitis were randomized into the study (138 into the FP 100 µg qd treatment group, 136 into the FP 200 µg qd treatment group, and 141 into the placebo group), with a total of 179 patients completing the study. Patients recorded their symptoms daily on a diary card which consisted of nasal blockage (on awakening and for the duration of the day), rhinorrhea, sneezing, nasal itching/nose rubbing and an overall assessment of symptoms, using a 4 point scale (0-3 rating of symptoms). Symptoms were also recorded by the investigator at clinic visits. Patients were given a supply of antihistamine tablets or syrup to taken as needed for the control of troublesome perennial rhinitis symptoms. Use of rescue medication was also recorded.

The primary efficacy endpoint was defined as the percentage of 'symptom-free days' for patient assessments of nasal blockage on awakening, nasal blockage during the rest of the day, and rhinorrhea. The patient assessments of sneezing, nasal itching, and overall symptoms, use of rescue medication, and investigator rated rhinitis assessments were analyzed as secondary efficacy endpoints.

Based on the primary efficacy endpoints, children receiving either FP 100 µg qd or FP 200 µg qd reported a statistically significantly greater median percentage of symptom free days compared with placebo, along with a statistically significantly greater reduction in mean rhinorrhea scores compared with placebo ($p=0.014$ and $p=0.005$ for the FP 100 µg qd and FP 200 µg qd groups, respectively). While not statistically significantly higher than placebo, the 2 FP treatment groups demonstrated a numerically greater decrease in nasal blockage scores (both on awakening and during the day) than placebo. In this study, there was overall no significant difference between the 2 FP treatment groups with respect to most endpoints, supporting the comparability of both treatment regimens with respect to perennial rhinitis symptoms in the pediatric population (i.e. no dose response noted between the 2 FP treatments).

With respect to safety monitoring, the adverse event profile for the FP treatment groups (also placebo) was similar to that seen in adult patients; namely, the most common AEs consisted of epistaxis, headache, URI, and cough. No serious AEs were reported that were related to drug treatment and withdrawal from the study was generally due to intercurrent infection or underlying atopy (e.g. asthma exacerbation). Results of laboratory testing did not reveal any trends or significant laboratory abnormalities. Similarly no evidence of adverse effects

on vital signs or physical exam were seen with treatment. Hence, in summary, FP 100 μg qd or FP 200 μg qd were found to be well tolerated and generally safe in the pediatric age group for the duration tested in study FLNT60.

8.6.9. Protocol No. FLNT61 (report # GRP/92/000): A double-blind comparison of FP Nasal Spray 100 μg qd, FP Nasal Spray 100 μg bid, and BDP 200 μg bid in the treatment of perennial rhinitis in pediatric patients (aged 6-11 years) [NDA 20-121, S-009, 35:199-201].

This was a multi-center, multinational, randomized, double-blinded, active-controlled, parallel group study to compare the safety and efficacy of FP Nasal Spray 100 μg qd, vs. FP 100 μg bid in pediatric patients aged 6-11 years with perennial rhinitis. The study was designed with a open-label placebo run-in period, followed by a 12 week treatment period.

A total of 95 pediatric patients with a history of moderate-severe perennial rhinitis were randomized into the study (30 into the FP 100 μg qd treatment group, 35 into the FP 100 μg bid treatment group, and 35 into the BDP 200 μg bid group), with a total of 179 patients completing the study. Patients recorded their rhinitis symptoms daily on a diary card which consisted of recordings of: nasal blockage (on awakening and for the duration of the day), rhinorrhea, sneezing, nasal itching/nose rubbing and an overall assessment of symptoms, using a 4 point scale (0-3 rating of symptoms). Symptoms were also recorded by the investigator at clinic visits. Patients were given a supply of antihistamine tablets or syrup to taken as needed for the control of troublesome perennial rhinitis symptoms. Use of rescue medication was also recorded.

Similar to study FLNT60, the primary-efficacy endpoints for FLNT61 were defined as the percentage of 'symptom-free days' for patient assessments of nasal blockage on awakening, nasal blockage during the rest of the day, and rhinorrhea. These primary efficacy endpoints were also supplemented by an analysis of the % of days on which patients recorded their symptoms as being non-existent or 'mild'. The patient assessments of sneezing, nasal itching, overall symptoms, use of rescue medication, and investigator rated rhinitis assessments were analyzed as secondary efficacy endpoints.

All 3 active treatment groups demonstrated a decrease in symptoms of rhinitis from the placebo run-in period and analysis of the % of 'symptom-free days' which suggested that the 3 treatments were similarly effective in decreasing symptoms of nasal blockage (on awakening and throughout the day), rhinorrhea, in addition to sneezing and nasal itching. A dose response between the 2 FP doses was not seen.

With regard to safety monitoring, the adverse event profile was again similar to that demonstrated in study FLNT60 with epistaxis, headache, URI, and cough being the most commonly reported AEs. No serious AEs were reported in the study. No new laboratory test trends were seen and physical exams/vital signs were unremarkable throughout the study. These findings again support the tolerability and general safety of FP Nasal Spray in children given at a dose of

either FP Nasal Spray 100 µg qd, or FP 100 µg bid for the treatment of perennial rhinitis symptoms.

8.7. ONSET OF ACTION:

Onset of action of FLONASE Aqueous Nasal Spray was evaluated during review of the original NDA for FLONASE Aqueous Nasal Spray (NDA 20-121) and was based on a number of randomized, double-blind, placebo-controlled, parallel group SAR and PAR studies (FLN-202, FLN-203, FLN-204, FLN-301, FLN-305, FLN-306, FLN-320, and FLN-321); none of which were specifically designed to assess onset of action as an a priori primary efficacy endpoint but rather evaluated total nasal symptoms 12 hours after initiation of treatment. It was this 12 hour time point that was utilized in providing data that the onset of action of FLONASE "may occur as soon as 12 hours after starting therapy with FLONASE Nasal Spray" [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.1:4].

Since approval of NDA 20-121, 2 additional studies were performed (FLN-444 and FLN-445) which were replicate park studies that specifically evaluated onset of action of nasal symptom relief on a hourly basis for the first 7 hours of the study post-treatment with the 1st dose of study medication, followed by evaluation at 9, 12, and 23 hours post-treatment, and continuation of evaluation of total nasal and total SAR symptoms every 12 hours thereafter for a total duration of 7 days.

Hence, the medical officer review of onset of action for FLONASE Aqueous Nasal Spray for this Efficacy Supplement will focus on these 2 park studies and additionally incorporate findings from the other SAR, PAR and NAPR studies in which a 12 hour assessment of total nasal symptom scores was performed.

8.7.1. Protocol No. FLN 444: A double-blind, randomized, placebo-controlled parallel group park study to compare the onset of action of fluticasone propionate (FP) aqueous nasal spray 200 μg qd vs. beclomethasone dipropionate aqueous nasal spray (BDP) 168 μg bid in patients with seasonal allergic rhinitis (SAR).

Principal Investigator: None, multi-center study.

Participating Centers: 3 U.S. centers (San Diego, Minneapolis, Iowa City).

8.7.1.a. Objectives

The primary objective of this study was to investigate the onset of action of fluticasone propionate nasal spray vs. placebo and vs. an active comparator, BDP Nasal spray; though efficacy and safety for the duration of the 7 day period (days 3-7; the length of the trial) were also evaluated.

8.7.1.b. Study Design

The study was a multi-center, randomized, double-blind, placebo-controlled, parallel group onset of action park study of fluticasone propionate nasal spray (FP) 200 μg qd, vs. BDP 168 μg bid, and vs. placebo nasal spray bid conducted during the fall allergy season in 309 patients with SAR. After a screening period in which patients were required to have fulfilled certain pre-defined criteria (e.g. be ≥ 12 years of age and have a history of SAR for at least 1 season with a documented period in which onset and offset of symptoms was observed, and in which patients were to have documented a positive skin test within the prior 12 months to at least 1 fall allergen prevalent in the local area) [specifics of skin testing described in: NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:1], patients were randomly assigned to 1 of the 3 treatment groups delineated above using a double-dummy method for a 7 day treatment period [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:2]. The protocol and case report form are provided in Appendix 1 and 2, respectively, of volume 35.2 [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:32-96].

Patients at each site were assembled in a park setting for an 8 hour period for the 1st 2 consecutive days of the study (the 'acute' phase) where they self-assessed their SAR symptoms hourly via completion of diary cards. These hourly recordings were used to determine the onset of action. Patients rated rhinitis symptoms which consisted of the following: nasal stuffiness (left and right), number of nose blows, number of sneezes, sniffles and runny nose (left and right), itchy nose, post-nasal drip, watery eyes, itchy eyes, itchy ears/palate/throat, and cough. Each individual symptom was rated by the patient on a diary card and scored using a scale ranging from 0 (=none) to 10 (=severe, persistent, annoying distraction). For the number of sneezes and number of nose blows, patients recorded the number (0-10) which occurred in the past hour. Ten was recorded if more than 10 occurred [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:2]. The total nasal symptom score (TNSS=composite score comprised of the sum of the individual symptom scores of: nasal stuffiness (right nostril), nasal stuffiness (left nostril), number of nose blows, number of sneezes, sniffles/runny nose (right nostril), sniffles/runny nose (left nostril), post-nasal drip, and nasal itching) was defined as the primary efficacy endpoint utilized in determining the onset of action for study medication. These 8 symptoms combined yielded a TNSS scale which could range from score of 0 to 80 (maximum possible score) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:3].

All patients at each site were treated on the same date outdoors to control for confounding influences of different weather conditions and differing pollen counts. Pollen counts for the period and the geographic area from study initiation to the final patient visit were collected at each site. The frequency of rain was also recorded for the study period. In order to qualify for treatment on day 1, patients were to have a combined score of ≥ 8 for the sum of stuffy nose (left) and stuffy nose (right) prior to dosing with the 1st dose of study medication (between