Table X.

Efficacy of Flonase Nasal Spray vs. Placebo: **Patient Self-Rated A.M and P.M. Rhinorrhea Score**
Secondary Efficacy Variable: Intent-to-Treat (ITT) Population: Double-blind Treatment Period
[NDA 20-121, S-009, 3:150, 153-154]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. Pre-treatment	210	208	211	208						
Rhinorrhea Score										
Day -6 to 0 (Pre-treatment) (n, mean score ± SE):										
A.M.	210 57.4 ± 1.9	208 59.3 ± 1.9	211 61.0 ± 1.8	208 57.6 ± 1.8	0.236	0.090	0.732	0.615	0.399	0.177
P.M.	210 62.5 ± 1.7	208 63.4 ± 1.8	211 65.6 ± 1.6	207 62.4 ± 1.7	0.462	0.123	0.810	0.424	0.620	0.195
Day 1-7 (n, Δ ln score ± SE):										
A.M.	210 -11.2 ± 1.5	204 -18.4 ± 1.6	207 -17.9 ± 1.6	205 -14.6 ± 1.6	<0.001	<0.001	0.089	0.780	0.062	0.110
P.M.	210 -12.8 ± 1.4	204 -19.3 ± 1.6	207 -19.1 ± 1.6	204 -15.6 ± 1.5	<0.001	0.002	0.153	0.884	0.073	0.098
(n, Δ ln score ± SE):										
A.M.	208 -14.9 ± 1.9	200 -24.3 ± 1.9	204 -21.9 ± 1.9	204 -20.1 ± 1.7	<0.001	0.003	0.026	0.309	0.081	0.463
P.M	208 -17.2 ± 1.8	201 -25.6 ± 1.9	204 -26.0 ± 1.9	56 -23.0 ± 1.7	<0.001	<0.001	0.014	0.946	0.280	0.249
Day 15-21 (n, Δ ln score ± SE):										
A.M.	203 -18.3 ± 1.8	192 -25.9 ± 2.0	201 -24.9 ± 2.0	200 -22.9 ± 1.8	0.002	0.006	0.060	0.667	0.197	0.383
P.M.	203 -21.2 ± 1.6	192 -28.4 ± 2.0	201 -28.2 ± 1.9	202 -26.1 ± 1.8	<0.002	<0.003	0.033	0.820	0.291	0.401
Day 22-28 (n, Δ ln score ± SE):										
A.M.	203 -19.2 ± 2.0	191 -29.1 ± 2.1	197 -27.3 ± 2.0	198 -24.8 ± 1.9	<0.001	0.001	0.031	0.431	0.071	0.305
P.M.	203 -22.1 ± 1.8	191 -31.5 ± 2.1	197 -30.2 ± 1.9	198 -28.3 ± 1.9	<0.001	0.001	0.014	0.523	0.149	0.417

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

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Table XI.

Efficacy of Flonase Nasal Spray vs. Placebo: **Patient Self-Rated A.M and P.M. Sneezing Score**

Secondary Efficacy Variable: Intent-to-Treat (ITT) Population: Double-blind Treatment Period

NDA 20-121, S-009, 3:150, 153-154]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. Pre-treatment	210	208	211	208						
Sneezing Score										
Day -6 to 0 (Pre-treatment) (n, mean score ± SE):										
A.M.	210 27.1 ± 1.9	208 28.6 ± 1.9	211 29.1 ± 1.9	208 25.4 ± 1.7	0.450	0.379	0.627	0.905	0.216	0.173
P.M.	210 30.3 ± 1.9	208 31.5 ± 1.9	211 32.9 ± 1.8	207 29.8 ± 1.7	0.534	0.252	0.969	0.603	0.510	0.238
Day 1-7 (n, Δ in score ± SE):										
A.M.	210 -4.5 ± 1.2	204 -10.5 ± 1.3	207 -9.4 ± 1.3	205 -8.4 ± 1.2	<0.001	0.003	0.023	0.536	0.208	0.519
P.M.	210 -4.1 ± 1.2	204 -10.4 ± 1.4	207 -10.1 ± 1.3	205 -8.8 ± 1.2	<0.001	<0.001	0.006	0.868	0.345	0.434
[illegible] 4 (n, score ± SE):										
A.M.	208 -7.7 ± 1.4	200 -13.6 ± 1.6	204 -11.6 ± 1.5	204 -11.4 ± 1.4	0.003	0.048	0.068	0.322	0.253	0.879
P.M.	208 -6.6 ± 1.4	201 -13.9 ± 1.6	204 -12.9 ± 1.6	204 -12.7 ± 1.4	<0.001	0.002	0.003	0.594	0.537	0.933
Day 15-21 (n, Δ in score ± SE):										
A.M.	203 -9.2 ± 1.5	192 -14.2 ± 1.7	201 -13.0 ± 1.5	200 -12.1 ± 1.5	0.017	0.062	0.176	0.583	0.293	0.611
P.M.	203 -9.4 ± 1.4	192 -15.0 ± 1.8	201 -14.2 ± 1.6	202 -14.1 ± 1.6	0.008	0.022	0.027	0.689	0.633	0.939
Day 22-28 (n, Δ in score ± SE):										
A.M.	203 -9.2 ± 1.6	191 -15.8 ± 1.7	197 -13.9 ± 1.6	198 -12.1 ± 1.6	0.017	0.062	0.176	0.583	0.293	0.611
P.M.	203 -9.6 ± 1.6	191 -17.1 ± 1.8	197 -15.5 ± 1.6	198 -15.3 ± 1.6	<0.001	0.008	0.012	0.455	0.374	0.887

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

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Table XII.

Efficacy of Flonase Nasal Spray vs. Placebo: **Physician-rated Nasal Symptom Score**

Secondary Efficacy Variable: Intent-to-Treat (ITT) Population: Double-blind Treatment Period

NDA 20-121, S-009, 3:156]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. at screening	210	208	211	208						
Total Nasal Symptom Score:										
Visit 2=Baseline (n, mean score ± SE)	210 193.8 ± 3.3	207 202.1 ± 3.3	210 200.2 ± 3.3	208 197.6 ± 3.5	0.073	0.116	0.367	0.820	0.372	0.503
Visit 3= Day 14 (n, Δ in score ± SE)	204 -48.9 ± 5.0	192 -71.0 ± 5.4	198 -68.6 ± 5.1	198 -59.6 ± 5.2	0.003	0.003	0.160	0.917	0.106	0.128
Visit 4= Day 28 (n, Δ in score ± SE)	199 -56.8 ± 4.9	187 -85.5 ± 5.5	196 -70.7 ± 5.4	194 -79.6 ± 5.7	<0.001	0.040	0.002	0.039	0.334	0.268
Nasal Obstruction Score:										
Visit 2=Baseline (n, mean score ± SE)	210 64.3 ± 1.6	207 69.3 ± 1.4	210 67.3 ± 1.4	208 67.8 ± 1.4	0.011	0.125	0.049	0.302	0.555	0.658
Visit 3= Day 14 (n, Δ in score ± SE)	204 -14.7 ± 1.9	192 -25.3 ± 2.1	198 -20.2 ± 1.9	198 -21.7 ± 2.1	<0.001	0.040	0.012	0.094	0.217	0.655
Visit 4= Day 28 (n, Δ in score ± SE)	199 -16.4 ± 2.0	187 -29.3 ± 2.0	196 -22.6 ± 2.0	194 -28.0 ± 2.2	<0.001	0.021	<0.001	0.013	0.626	0.043
Nasal Drip Score:										
Baseline (n, mean score ± SE)	210 70.5 ± 1.5	207 70.6 ± 1.6	210 70.8 ± 1.5	208 69.4 ± 1.5	0.937	0.840	0.476	0.780	0.528	0.361
Visit 3= Day 14 (n, Δ in score ± SE)	204 -19.3 ± 2.1	192 -23.0 ± 2.2	198 -23.9 ± 2.1	198 -18.8 ± 2.1	0.264	0.087	0.739	0.567	0.151	0.043
Visit 4= Day 28 (n, Δ in score ± SE)	199 -22.0 ± 2.0	187 -27.5± 2.2	196 -24.7 ± 2.1	194 -25.9 ± 2.3	0.042	0.304	0.210	0.306	0.426	0.820
Rhinorrhea Score:										
Visit 2=Baseline (n, mean score ± SE)	210 59.0 ± 1.9	207 62.2 ± 1.7	210 62.1 ± 1.7	208 60.4 ± 1.9	0.210	0.152	0.514	0.86	0.546	0.436
Visit 3= Day 14 (n, Δ in score ± SE)	204 -14.8 ± 2.2	192 -22.8 ± 2.3	198 -24.4 ± 2.1	198 -19.0 ± 2.2	0.012	0.001	0.193	0.471	0.217	0.049
Visit 4= Day 28 (n, Δ in score ± SE)	199 -18.4 ± 2.2	187 -28.6 ± 2.4	196 -23.4 ± 2.3	194 -25.7 ± 2.3	<0.001	0.083	0.022	0.106	0.293	0.570

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

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able XIII.

ff of Flonase Nasal Spray vs. Placebo: **Overall Physician Evaluation**

rin... Efficacy Variable: Evaluable Patient Population for the Double-blind Treatment Period

DA 20-121, S-009, 3:158]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. at Baseline	210	208	211	208						
Total # of Evaluable Pts.	208	203	205	204						
Patient Response to Treatment:					0.074	0.223	<0.001	0.993	0.283	0.297
Significant Improvement	21 (10%)	33 (16%)	32 (16%)	36 (18%)	NA	NA	NA	NA	NA	NA
Moderate Improvement	46 (22%)	52 (26%)	56 (27%)	54 (26%)	NA	NA	NA	NA	NA	NA
Mild Improvement	58 (28%)	57 (28%)	57 (28%)	73 (36%)	NA	NA	NA	NA	NA	NA
No change	73 (35%)	48 (24%)	50 (24%)	33 (16%)	NA	NA	NA	NA	NA	NA
Mildly Worse	7 (3%)	6 (3%)	5 (2%)	2 (<1%)	NA	NA	NA	NA	NA	NA
Moderately Worse	1 (<1%)	5 (2%)	3 (1%)	5 (2%)	NA	NA	NA	NA	NA	NA
Significantly Worse	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)	NA	NA	NA	NA	NA	NA

P... sone propionate. P-values based on the Cochran-Mantel-Haenszel test controlling for investigator. Percentages are based on the number of ev... patients. NA=Not available (i.e. analysis not performed).

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At pre-treatment (i.e. baseline), for the total patient self-rated a.m. nasal symptom scores (TNSS), overall the 4 treatment groups were reasonably similar in symptom severity (with no statistically significant difference noted between the 4 treatment groups), although the FP 50 μg bid and FP 100 μg bid treatment groups had slightly higher symptom scores than the other 2 treatment groups (205.2 and 202.6, respectively vs. 197.6 for the placebo group and 198.1 for the FP 200 μg bid treatment group) (overall p-value for the 4 treatment groups=0.252 by F-test) [Table VII, Medical officer review or Table 15 in efficacy supplement, NDA 20-121, S-009, 3:150]. Similar to the patient self-rated p.m. total nasal symptom scores (TNSS), the decrement in a.m. TNSS was progressively greater with each subsequent week, reaching maximal decrease for the double-blind treatment period by week 4 of treatment. Also similar to the p.m. TNSS, the FP 50 μg bid group demonstrated the greatest mean change in the a.m. TNSS for each respective week and showed the greatest mean decrement in a.m. TNSS by week 4 of treatment (-88.7 points), compared with a mean decrement of -57.1 points for the placebo treatment group ($p < 0.001$) [Table VII, Medical officer review or Table 15 in efficacy supplement, NDA 20-121, S-009, 3:150].

Comparison of a.m. vs. p.m. patient self-rated TNSS showed that in general, the p.m. TNSS was slightly lower than the a.m. TNSS, both at pre-treatment and at all subsequent weekly visits. Daily a.m. symptom scores which could be used to assess onset of action of FP were not provided as data in this efficacy supplement. Furthermore, no direct dose response based on a.m. or p.m. TNSS could be concluded for the 3 different FP treatment groups.

Review of the individual patient self-rated nasal symptom scores for the a.m. (as for the p.m. individual patient self-rated nasal symptom scores) revealed that postnasal drip, closely followed by nasal obstruction, had a slightly higher symptom score than did rhinorrhea [Table VIII, Medical Officer Review, NDA 20-121, S-009, 3:150].

For the a.m. individual nasal symptoms at pre-treatment, a marginally statistically significant difference in severity of nasal obstruction, compared to placebo, was noted for the FP 50 μg bid treatment group (p=0.052) (Table VIII). During the double-blind treatment period, evaluation of all 3 FP treatment groups during all weekly intervals for the a.m. individual nasal symptom scores (week 1 through week 4) demonstrated that the 3 FP treatments had statistically significantly greater efficacy in decreasing each of the 4 individual nasal symptoms compared with placebo with the exception of: (1) the FP 100 μg bid treatment group vs. placebo at days 15-21 (week 3) for the sneezing endpoint (p=0.062), (2) the FP 200 μg bid treatment group vs. placebo at days 8-14 (week 2) for the sneezing endpoint (p=0.068), and (3) the FP 200 μg bid treatment group vs. placebo at days 1-7 (week 1) and days 15-21 (week 3) for the rhinorrhea endpoint (p=0.089 and p=0.060, respectively) [Tables VIII-XI, Medical Officer Review, NDA 20-121, NAPR Efficacy Supplement, p. 1, NDA 20-121, S-009, 3:150, 153-154].

Statistically insignificant differences for the 3 FP treatment groups compared to placebo treatment were likewise noted for weekly assessments of the majority of the p.m. individual nasal symptom scores (week 1 through week 4), with the exception of the following: (1) the FP 100 μg bid treatment group vs. placebo at days 1-7 (week 1) and days 15-21 (week 3) for the postnasal drip endpoint and (2) the FP 200 μg bid treatment group vs. placebo at days 1-7 (week 1) for the postnasal drip endpoint, and (3) the FP 200 μg bid treatment group vs. placebo at days 1-7 (week 1) for the rhinorrhea endpoint [Appendix II, Medical Officer Review, NDA 20-121, NAPR Efficacy Supplement, p. 2, NDA 20-121, S-009, 3:153-154].

Evaluation of the secondary efficacy endpoints of physician-rated TNSS and the physician-rated individual nasal symptom scores of: nasal obstruction, postnasal drip, and rhinorrhea at week 2 and 4 post-treatment with study medication, revealed that for the TNSS statistically significant differences in efficacy compared with placebo were achieved for all 3 FP treatment groups with the exception of the FP 200 μg bid treatment group at the day 14 (week 2) clinic visit (p=0.160) [Appendix II, Medical Officer Review, NDA 20-121, NAPR Efficacy Supplement, p. 3, NDA 20-121, S-009, 3:156]. Again, the greatest mean difference is TNSS (at both the week 2 and week 4 visits) was seen in the FP 50 μg bid treatment group (-71.0 mean point decrease for week 2 and -85.5 mean point decrease for week 4, compared with -48.9 mean point decrease for week 2 and -56.8 mean point decrease for week 4 in the placebo group) [Appendix II, Medical Officer Review, NDA 20-121, NAPR Efficacy Supplement, p. 3, NDA 20-121, S-009, 3:156].

For the physician-rated individual nasal symptom score of nasal obstruction, all 3 FP treatment groups afforded statistically greater efficacy than the placebo group at both week 2 and 4, but again the FP 50 μg bid treatment group demonstrated a slightly greater mean decrease in nasal obstruction than the other 2 FP treatment groups (-25.3 mean point decrease at week 2 vs. -14.7 mean point decrease for the placebo group and a -29.3 mean point decrease at week 4 vs. a -16.4 mean point decrease for the placebo group). With the exception of the FP 50 μg bid treatment group at day 28 only (week 4), none of the other FP treatment groups showed statistically significantly greater efficacy in decreasing postnasal drip, as compared with placebo treatment. For the rhinorrhea endpoint, with the exception of the FP 100 μg bid treatment group at day 28 (week 4) and the FP 200 μg bid treatment group at day 14, all 3 FP treatment group showed statistically significantly greater efficacy in decreasing rhinorrhea during the 2 clinic visits [Appendix II, Medical Officer Review, NDA 20-121, NAPR Efficacy Supplement, p. 3, NDA 20-121, S-009, 3:156].

Finally, for the fourth secondary efficacy endpoint—the overall physician evaluation of patients' response to treatment, only the FP 200 μg bid treatment group demonstrated statistically significantly greater efficacy in improving nasal symptoms, compared to placebo treatment ($p< 0.001$) [Appendix II, Medical Officer Review, NDA 20-121, NAPR Efficacy Supplement, p. 4, NDA 20-121, S-009, 3:158].

(III) Assessment of Efficacy During the Open-Label Treatment Period

Assessment of efficacy during the open-label treatment period, while not a primary objective, was performed using the same symptom assessments as for the double-blind treatment period (e.g. patient self-rated and physician-rated assessments). All NAPR symptom assessments were calculated as the change from the baseline symptom score which was defined as the respective symptom score on clinic visit 4 (week 4 of the double-blind period).

The main utility of assessment of efficacy during the open-label treatment period was the following: (1) to ascertain that patients continued to respond to the FP treatment long-term (albeit at a higher than the recommended dose of 100 μg bid or 200 μg), (2) that patients continued to experience progressive improvement in nasal symptoms with FP treatment, beyond the 4 week double-blind period, and (3) that no significant differences were notable with respect to long-term efficacy depending on which active treatment patients were initially randomized into for the double-blind treatment period.

Because patients enrolled into the open-label portion of the study were recruited from each of the 4 treatment groups, including placebo, patients' baseline NAPR symptoms were not stratified at baseline visit 4 and thus dissimilar at the start of the open-label period [NDA 20-121, S-009, 3:70]. In particular, patients enrolled from the placebo treatment group had higher baseline self-rated ((placebo group patient self-rated p.m. TNSS= 144.7 ± 7.9 vs. FP 50 μg bid group patient self-rated p.m. TNSS= 126.4 ± 8.7, vs. FP 100 μg bid group patient self-rated p.m. TNSS= 125.9 ± 9.5, vs. FP 200 μg bid group patient self-rated p.m. TNSS= 117.4 ± 8.0) [Table XV, Medical Officer Review, NDA 20-121, S-009, 3:262], and placebo group patient self-rated a.m. TNSS= 145.2 ± 8.1 vs. FP 50 μg bid group patient self-rated a.m. TNSS= 126.9 ± 8.7, vs. FP 100 μg bid group patient self-rated a.m. TNSS= 122.7 ± 9.6, vs. FP 200 μg bid group patient self-rated a.m. TNSS= 118.2 ± 8.5) [Table XIV, Medical Officer Review, NDA 20-121, S-009, 3:259]) or physician-rated total nasal symptoms (placebo group physician-rated TNSS (visit 4)= 150.0 ± 8.7 vs. FP 50 μg bid group physician-rated TNSS= 128.9 ± 9.0, vs. FP 100 μg bid group physician-rated TNSS= 128.8 ± 9.0, vs. FP 200 μg bid group physician-rated TNSS= 122.8 ± 7.8) [Table XX, Medical Officer Review, NDA 20-121, S-009, 3:265] than either of the active treatment groups.

Once enrolled into the open-label portion of the study, all patients were treated with FP 200 μg bid and rated the severity of nasal symptoms only during each of the 7 days (1 week) immediately preceding the scheduled clinic visit for the purpose of providing efficacy data to justify the validity of the safety evaluations. Statistical comparisons were made by grouping data based on each patient's previous treatment assignment (i.e. placebo group, FP 50 μg bid group, etc.) [NDA 20-121, S-009, 3:74].

A summary of clinical efficacy data for the 5 efficacy endpoints: (1) patient self-rated change from baseline (visit 4) in a.m. TNSS and in individual nasal symptom scores for the open-label period, (2) patient self-rated change from baseline (visit 4) in p.m. TNSS and in individual nasal symptom scores for the open-label period, (3) physician-rated change from baseline (visit 4) in TNSS and in individual nasal symptom scores, (4) overall patient-rated evaluation of response to treatment, and (5) overall physician-rated evaluation of response to treatment, is presented in Tables XIV-XXII of this review [NDA 20-121, S-009, 3:259-260, 262, 266-267].

Results for the open-label efficacy period indicate that: (1) there was some imbalance with regard to pre-treatment symptom scores for the 4 treatment groups that comprised the open-label group, with a higher baseline score in the placebo group (Tables XIV-XXII), (2) for most efficacy endpoints, a continued decrement in nasal symptom scores occurred throughout the open-label treatment period (Tables XIV-XX), (3) the greatest mean change in patient-self rated nasal symptom scores for all 4 treatment groups occurred at Visit 10 (~ Day 183 after completion of the double-blind treatment period) (Tables XIV-XIX), (4) the mean change in patient-self rated nasal symptom scores (total and individual) was comparable between the 4 different treatment groups, with a slightly greater mean change in nasal symptom scores evident in the placebo group, once randomized to open-label FP 200 μg bid (Tables XIV-XIX), (5) a slightly greater mean change in the patient-self rated a.m. and p.m. nasal obstruction and postnasal drip scores was evident in all 4 treatment groups throughout the study (Tables XVI-XVII), followed by the rhinorrhea score (Table XVIII), and then the sneezing score (Table XIX); a general trend which was the same as for the double-blind treatment period, (6) the patient-self rated a.m. compared to p.m. nasal symptom scores were not consistently higher or lower than one another (as previously noted for the double-blind period), (7) overall evaluation of nasal symptom improvement (patient and physician-rated, Tables XXI and XX) revealed no statistically significant difference between the 4 treatment groups during the open-label post-treatment with FP 200 μg bid.

Hence, the open-label efficacy data, while limited in interpretability, support the continued efficacy of FP at a dose of 200 μg bid in decreasing the nasal symptoms of NAPR and suggest that NAPR symptoms may continue to progressively decrease in those patients who continue treatment with this regimen.

Table XIV.
Efficacy of Flonase Nasal Spray vs. Placebo: **Patient Self-Rated A.M. Total Nasal Symptom Score**
Open-label Period Efficacy Variable: Intent-to-Treat (ITT)
[NDA 20-121, S-009, 3:259-260]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. entering the Open-label	72	68	73	76						
Total Nasal Symptom Score (TNSS): Composite of Rhinorrhea + Nasal Obstruction + Postnasal Drip										
Visit 4=Day 28 (Pre-treatment) (n, mean score ± SE)	72 142.5 ± 8.1	68 126.9 ± 8.7	72 122.7 ± 9.6	76 118.2 ± 8.5	0.082	0.180	0.052	0.658	0.879	0.547
Visit 5 (day 61) (n, Δ ln score ± SE)	62 -56.9 ± 7.0	59 -41.1 ± 10	65 -25.6 ± 7.1	63 -42.7 ± 8.2	0.031	0.006	0.170	0.610	0.418	0.182
Visit 6 (day 122) (n, Δ ln score ± SE)	52 -56.3 ± 8.4	55 -46.0 ± 10	59 -39.7 ± 6.8	56 -51.6 ± 7.9	0.334	0.331	0.596	0.980	0.654	0.671
Visit 10 (day 183) (n, Δ ln score ± SE)	50 -61.5 ± 8.7	55 -51.6 ± 10	61 -39.9 ± 7.4	53 -52.8 ± 8.1	0.420	0.139	0.515	0.516	0.880	0.429

[1]FP = fluticasone propionate. P-values at pre-treatment for the open-label period (day 28) were based on mean scores at baseline, and at subsequent visits p-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

Table XV.
Efficacy of Flonase Nasal Spray vs. Placebo; **Patient Self-Rated P.M. Total Nasal Symptom Score**
Open-Label Period Efficacy Variable: Intent-to-Treat (ITT)
NDA 20-121, S-009, 3:262]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. entering the Open-Label	72	68	73	76						
Total Nasal Symptom Score (TNSS): Composite of Rhinorrhea + Nasal Obstruction + Postnasal Drip										
Visit 4=Day 28 (Pre-treatment) (n, mean score ± SE)	72 144.7 ± 7.9	68 126.4 ± 8.7	72 125.9 ± 9.5	76 117.4 ± 8.0	0.048	0.203	0.023	0.454	0.815	0.320
Visit 5 (day 61) (n, Δ in score ± SE)	62 -61.2 ± 7.0	59 -41.9 ± 9.4	65 -30.3 ± 7.2	63 -43.6 ± 8.0	0.022	0.008	0.092	0.777	0.533	0.359
Visit 6 (day 122) (n, Δ in score ± SE)	52 -60.8 ± 8.3	55 -45.6 ± 10	59 -42.7 ± 6.6	56 -55.1 ± 7.5	0.160	0.229	0.481	0.805	0.471	0.632
Visit 10 (day 183) (n, Δ in score ±	50 -64.3 ± 8.5	55 -52.0 ± 11	61 -45.2 ± 8.6	52 -52.8 ± 8.4	0.439	0.229	0.387	0.688	0.920	0.772

[1]Fluticasone propionate. P-values at pre-treatment for the open-label period (day 28) were based on mean scores at baseline, and at subsequent visits p-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table XVI.

E[ ]y of Flonase Nasal Spray vs. Placebo: **Patient Self-Rated A.M and P.M. Nasal Obstruction Score** Op[ ]Label Period: Intent-to-Treat (ITT)

NDA 20-121, S-009, 3:259-260, 262]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. entering the Open-label	72	68	73	76						
Nasal Obstruction Score										
Visit 4=Day 28 (Pre-treatment) (n, mean score ± SE): A.M.	72 52.8 ± 3.2	68 46.8 ± 3.4	72 44.6 ± 3.6	76 42.4 ± 3.1	0.123	0.106	0.041	0.975	0.651	0.669
Visit 4=Day 28 (Pre-treatment) (n, mean score ± SE): P.M.	72 50.7 ± 3.1	68 45.0 ± 3.5	72 43.7 ± 3.6	76 41.2 ± 3.1	0.140	0.163	0.065	0.904	0.748	0.654
Visit 5 (day 61) (n, Δ in score ± SE): A.M.	62 -23.4 ± 3.1	59 -16.0 ± 3.8	65 -8.8 ± 2.5	63 -15.3 ± 3.0	0.025	<0.001	0.051	0.274	0.748	0.154
Visit 5 (d[ ]61) ([ ] score ± [ ]M.	62 -23.5 ± 3.2	59 -15.4 ± 3.6	65 -9.6 ± 2.5	63 -14.7 ± 2.8	0.022	0.001	0.030	0.390	0.893	0.317
Visit 6 (day 122) (n, Δ in score ± SE): A.M.	52 -22.7 ± 4.0	55 -17.1 ± 3.9	59 -11.8 ± 2.9	56 -19.1 ± 3.1	0.216	0.060	0.367	0.540	0.727	0.340
Visit 6 (day 122) (n, Δ in score ± SE): P.M.	52 -22.9 ± 3.8	55 -16.7 ± 4.0	59 -11.7 ± 2.6	56 -19.2 ± 2.9	0.134	0.026	0.305	0.490	0.624	0.241
Visit 10 (day 183) (n, Δ in score ± SE): A.M.	50 -25.5 ± 3.8	55 -19.4 ± 3.9	61 -12.5 ± 2.9	53 -19.2 ± 3.3	0.279	0.017	0.229	0.195	0.893	0.257
Visit 10 (day 183) (n, Δ in score ± SE): P.M.	50 -25.3 ± 3.5	55 -19.2 ± 3.8	61 -13.2 ± 3.1	52 -18.3 ± 3.3	0.291	0.019	0.160	0.208	0.714	0.391

[1]FP=Fluticasone propionate. P-values at pre-treatment for the open-label period (day 28) were based on mean scores at baseline, and at subsequent visits p-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table XVII.
Efficacy of Flonase Nasal Spray vs. Placebo: **Patient Self-Rated A.M and P.M. Postnasal Drip Score**
Open-Label Period Efficacy Variable: Intent-to-Treat (ITT)
NDA 20-121, S-009, 3:259-260, 262]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. entering the Open-label Period	72	68	73	76						
Postnasal Drip Score										
Visit 4=Day 28 (Pre-treatment) (n, mean score ± SE): A.M.	72 53.3± 3.4	68 46.0 ± 3.4	72 43.3 ± 3.6	76 43.4 ± 3.5	0.094	0.081	0.105	0.980	0.921	0.900
Visit 4=Day 28 (Pre-treatment) (n, mean score ± SE): P.M.	72 53.7 ± 3.3	68 46.4 ± 3.3	72 44.2 ± 3.5	76 43.5 ± 3.4	0.089	0.090	0.070	0.955	0.952	0.906
Visit 5 (day 61) (n, Δ in score ± SE): A.M.	62 -20.6 ± 2.7	59 -13.9 ± 3.7	65 -9.7 ± 3.1	63 -14.3 ± 3.2	0.043	0.023	0.193	0.865	0.458	0.355
Visit 5 (day 61) (n, Δ in score ± SE): P.M.	62 -21.4 ± 2.6	59 -14.1 ± 3.4	65 -10.4 ± 3.2	63 -15.0 ± 3.4	0.051	0.027	0.216	0.855	0.463	0.353
Visit 6 (day 122) (n, Δ in score ± SE): A.M.	52 -20.7 ± 3.3	55 -15.2 ± 4.0	59 -15.0 ± 3.0	56 -17.8 ± 3.3	0.297	0.412	0.629	0.798	0.566	0.747
Visit 6 (day 122) (n, Δ in score ± SE): P.M.	52 -21.5 ± 3.2	55 -15.4 ± 3.9	59 -15.8 ± 2.8	56 -20.1 ± 3.1	0.264	0.384	0.802	0.776	0.376	0.543
Visit 10 (day 183) (n, Δ in score ± SE): A.M.	50 -22.2 ± 3.8	55 -17.1 ± 4.0	61 -13.8 ± 3.2	53 -19.5 ± 3.5	0.391	0.169	0.762	0.623	0.577	0.294
Visit 10 (day 183) (n, Δ in score ± SE): P.M.	50 -22.1 ± 3.6	55 -17.4 ± 4.2	61 -15.5 ± 3.5	52 -20.4 ± 3.5	0.584	0.334	0.855	0.690	0.716	0.444

[1]FP=Fluticasone propionate. P-values at pre-treatment for the open-label period (day 28) were based on mean scores at baseline, and at subsequent visits p-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table XVIII.
Efficacy of Flonase Nasal Spray vs. Placebo: **Patient Self-Rated A.M and P.M. Rhinorrhea Score**
Open-label Period Efficacy Variable: Intent-to-Treat (ITT)
NDA 20-121, S-009, 3:259-260, 262]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. entering the Open-label Period	72	68	73	76						
Rhinorrhea Score										
Visit 4=Day 28 (Pre-treatment) (n, mean score ± SE): A.M.	72 36.6 ± 3.3	68 34.1 ± 3.2	72 38.1 ± 3.8	76 33.1 ± 2.9	0.251	0.849	0.276	0.179	0.931	0.205
Visit 4=Day 28 (Pre-treatment) (n, mean score ± SE): P.M.	72 40.3 ± 3.4	68 34.9 ± 3.2	72 35.1 ± 3.9	76 32.8 ± 3.2	0.075	0.983	0.048	0.069	0.885	0.048
Visit 5 (day 61) (n, Δ in score ± SE): A.M.	62 -13.0 ± 2.4	59 -11.2 ± 3.3	65 -10.2 ± 2.9	63 -13.9 ± 2.9	0.153	0.152	0.808	0.957	0.233	0.247
Visit 5 (day 61) (n, Δ in score ± SE): P.M.	62 -16.3 ± 2.4	59 -12.4 ± 3.0	65 -7.5 ± 2.8	63 -13.3 ± 3.1	0.073	0.135	0.348	0.714	0.384	0.604
Visit 6 (day 122) (n, Δ in score ± SE): A.M.	52 -12.9 ± 2.7	55 -13.7 ± 3.4	59 -15.2 ± 2.6	56 -16.0 ± 2.7	0.982	0.591	0.761	0.575	0.741	0.824
Visit 6 (day 122) (n, Δ in score ± SE): P.M.	52 -16.6 ± 2.8	55 -13.6 ± 3.3	59 -12.9 ± 2.5	56 -15.1 ± 2.6	0.309	0.835	0.616	0.206	0.595	0.472
Visit 10 (day 183) (n, Δ in score ± SE): A.M.	50 -13.9 ± 2.9	55 -15.1 ± 3.4	61 -16.6 ± 3.2	53 -14.1 ± 2.9	0.998	0.816	0.999	0.816	0.997	0.816
Visit 10 (day 183) (n, Δ in score ± SE): P.M.	50 -17.0 ± 2.9	55 -15.4 ± 3.6	61 -13.6 ± 3.0	52 -14.3 ± 2.6	0.305	0.632	0.929	0.550	0.350	0.704

[1]FP=Fluticasone propionate. P-values at pre-treatment for the open-label period (day 28) were based on mean scores at baseline, and at subsequent visits p-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table XIX.

3(/ of Flonase Nasal Spray vs. Placebo: **Patient Self-Rated A.M and P.M. Sneezing Score**

Op... Label Period Efficacy Variable: Intent-to-Treat (ITT)

NDA 20-121, S-009, 3:259-260, 262]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. entering the Open-label	72	68	73	76						
Sneezing Score										
Visit 4=Day 28 (Pre-treatment) (n, mean score ± SE): A.M.	72 18.7 ± 3.0	68 16.4 ± 2.6	72 17.3 ± 3.0	76 10.0 ± 1.7	0.213	0.799	0.016	0.315	0.267	0.033
Visit 4=Day 28 (Pre-treatment) (n, mean score ± SE): P.M.	72 22.0 ± 3.0	68 17.0 ± 2.5	72 19.8 ± 2.9	76 10.9 ± 1.7	0.042	0.609	0.002	0.120	0.341	0.012
Visit 5 (day 61) (n, Δ ln score ± SE): A.M.	61 -5.1 ± 1.7	59 -5.5 ± 2.1	65 -3.3 ± 2.4	63 -1.8 ± 1.6	0.751	0.581	0.291	0.828	0.464	0.599
Visit 5 (d... 61) (... score ± ... M.	61 -6.8 ± 1.8	59 -5.2 ± 2.0	65 -5.5 ± 2.3	63 -1.5 ± 1.5	0.213	0.687	0.047	0.383	0.465	0.106
Visit 6 (day 122) (n, Δ ln score ± SE): A.M.	51 -3.2 ± 1.3	55 -3.2 ± 2.3	59 -4.4 ± 2.0	56 -3.1 ± 1.8	0.997	0.383	0.918	0.381	0.914	0.330
Visit 6 (day 122) (n, Δ ln score ± SE): P.M.	51 -4.1 ± 1.8	55 -4.5 ± 2.3	59 -6.0 ± 1.8	56 -3.0 ± 1.7	0.919	0.334	0.613	0.385	0.536	0.140
Visit 10 (day 183) (n, Δ ln score ± SE): A.M.	50 -3.5 ± 1.3	55 -5.5 ± 2.2	61 -2.5 ± 1.8	53 -3.8 ± 2.0	0.448	0.972	0.938	0.405	0.492	0.908
Visit 10 (day 183) (n, Δ ln score ± SE): P.M.	50 -3.7 ± 1.6	55 -6.3 ± 2.2	61 -3.9 ± 1.8	52 -3.8 ± 1.7	0.305	0.632	0.929	0.550	0.350	0.704

[1]FP=Fluticasone propionate. P-values at pre-treatment for the open-label period (day 28) were based on mean scores at baseline, and at subsequent visits p-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table XX.
Efficacy of Flonase Nasal Spray vs. Placebo: **Physician-rated Nasal Symptom Scores**
Open-Label Period Efficacy Variable: Intent-to-Treat (ITT)
[NDA 20-121, S-009, 3:259-260, 262]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. entering the Open-label Period	72	68	73	76						
Total Nasal Symptom Score:										
Visit 4=Day 28 (n, mean score ± SE)	72 150 ± 8.7	68 128.9 ± 9.0	73 128.8 ± 9.0	76 122.8 ± 7.8	0.021	0.159	0.007	0.335	0.739	0.190
Visit 5= Day 61 (n, Δ in score ± SE)	63 -46.7 ± 9.9	59 -58.4 ± 9.9	59 -41.3 ± 7.4	65 -33.5 ± 9.0	0.884	0.686	0.165	0.589	0.130	0.190
Visit 6= Day 122 (n, Δ in score ± SE)	52 -65.1 ± 9.8	55 -70.0 ± 10	55 -55.5 ± 7.8	57 -60.3 ± 9.0	0.859	0.431	0.614	0.546	0.741	0.789
Visit 10= Day 183 (n, Δ in score ± SE)	51 -73.9 ± 11	55 -63.9 ± 11	55 -56.2 ± 8.8	53 -53.0 ± 9.8	0.175	0.151	0.090	0.988	0.727	0.729
Nasal Obstruction Score:										
Visit 4=Day 28 (n, mean score ± SE)	72 53.0 ± 3.0	68 44.3 ± 3.5	73 43.5 ± 3.2	76 38.7 ± 2.8	0.018	0.047	<0.001	0.660	0.284	0.126
Visit 5= Day 61 (n, Δ in score ± SE)	63 -14.9 ± 4.3	59 -19.5 ± 4.0	59 -12.0 ± 2.5	65 -6.7 ± 3.6	0.907	0.436	0.040	0.382	0.032	0.192
Visit 6= Day 122 (n, Δ in score ± SE)	52 -21.8 ± 3.9	55 -22.9 ± 4.1	55 -17.3 ± 3.1	57 -16.9 ± 3.8	0.771	0.332	0.309	0.503	0.463	0.938
Visit 10= Day 183 (n, Δ in score ± SE)	51 -25.3 ± 3.7	55 -23.0 ± 4.7	55 -18.3 ± 3.4	53 -16.5 ± 3.5	0.219	0.103	0.072	0.731	0.557	0.788
Postnasal Drip Score:										
Visit 4=Day 28 (n, mean score ± SE)	72 52.8 ± 3.4	68 45.9 ± 3.5	73 45.8 ± 3.4	76 44.8 ± 3.4	0.068	0.252	0.114	0.468	0.775	0.660
Visit 5= Day 61 (n, Δ in score ± SE)	63 -18.5 ± 3.4	59 -19.6 ± 3.6	59 -15.6 ± 3.3	65 -13.6 ± 3.9	0.628	0.589	0.237	0.973	0.497	0.511
Visit 6= Day 122 (n, Δ in score ± SE)	52 -22.5 ± 3.7	55 -25.1 ± 3.7	55 -19.0 ± 3.8	57 -23.7 ± 3.8	0.924	0.407	0.783	0.464	0.706	0.266
Visit 10= Day 183 (n, Δ in score ± SE)	51 -24.8 ± 4.3	55 -21.8 ± 4.5	55 -18.4 ± 3.6	53 -20.1 ± 3.8	0.300	0.190	0.399	0.821	0.849	0.675
Rhinorrhea Score:										
Visit 4=Day 28 (n, mean score ± SE)	72 44.2 ± 3.6	68 38.7 ± 3.3	73 39.5 ± 3.9	76 39.3 ± 3.1	0.107	0.690	0.077	0.213	0.912	0.171
Visit 5= Day 61 (n, Δ in score ± SE)	63 -13.3 ± 3.9	59 -19.3 ± 3.8	59 -13.8 ± 3.3	65 -13.2 ± 3.2	0.462	0.751	0.834	0.663	0.345	0.602
Visit 6= Day 122 (n, Δ in score ± SE)	52 -20.8 ± 4.0	55 -22.0 ± 4.0	55 -19.3 ± 3.1	57 -19.7 ± 3.5	0.960	0.894	0.607	0.936	0.638	0.692
Visit 10= Day 183 (n, Δ in score ± SE)	51 -23.8 ± 3.8	55 -19.1 ± 4.0	55 -19.5 ± 3.5	53 -16.5 ± 4.0	0.194	0.422	0.064	0.572	0.572	0.255

[1]FP=Fluticasone propionate. P-values at pre-treatment for the open-label period (day 28) were based on mean scores at baseline, and at subsequent visits p-values were based on mean absolute change from baseline using the F-test. No significant investigator by treatment interactions were observed.

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Table XXI.
(cy of Flonase Nasal Spray vs. Placebo: **Overall Patient Evaluation**
Open-label treatment period: Evaluable Patient Population
[NDA 20-121, S-009, 3:266]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. entering Open-Label Period	72	68	73	76						
Total # of Evaluable Pts.	66	66	71	68						
Patient Response to Treatment:										
At time of study entry					0.151	0.055	0.923	0.763	0.110	0.089
At time of completion of the open-label period:					0.423	0.601	0.289	0.962	0.936	0.981
Significant Improvement	33 (50%)	28 (42%)	32 (45%)	32 (47%)	NA	NA	NA	NA	NA	NA
Moderate Improvement	11 (17%)	15 (23%)	17 (24%)	20 (29%)	NA	NA	NA	NA	NA	NA
Mild Improvement	12 (18%)	15 (23%)	14 (20%)	9 (13%)	NA	NA	NA	NA	NA	NA
No change	9 (14%)	6 (9%)	7 (10%)	6 (9%)	NA	NA	NA	NA	NA	NA
Mildly Worse	1 (2%)	2 (3%)	1 (1%)	1 (1%)	NA	NA	NA	NA	NA	NA
Moderately Worse	0	0	0	0	NA	NA	NA	NA	NA	NA
...icantly	0	0	0	0	NA	NA	NA	NA	NA	NA

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

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Table XXII.

:acy of Flonase Nasal Spray vs. Placebo: **Overall Physician Evaluation**

:en-label treatment period: Evaluable Patient Population

[NDA 20-121, S-009, 3:267]

	TREATMENT GROUPS				P-value:					
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	Placebo vs. FP 50 µg bid	Placebo vs. FP 100 µg bid	Placebo vs. FP 200 µg bid	FP 50 µg bid vs. FP 100 µg bid	FP 50 µg bid vs. FP 200 µg bid	FP 100 µg bid vs. FP 200 µg bid
Total # Pts. entering Open-Label Period	72	68	73	76						
Total # of Evaluable Pts.	65	65	70	66						
Patient Response to Treatment:										
At time of study entry					0.122	0.093	0.880	0.809	0.110	0.090
At time of completion of the open-label period:					0.761	0.665	0.680	0.940	0.699	0.345
Significant Improvement	26 (40%)	25 (38%)	29 (41%)	29 (44%)	NA	NA	NA	NA	NA	NA
Moderate Improvement	17 (26%)	19 (29%)	21 (30%)	19 (29%)	NA	NA	NA	NA	NA	NA
Mild Improvement	14 (22%)	13 (20%)	9 (13%)	13 (20%)	NA	NA	NA	NA	NA	NA
No change	8 (12%)	6 (9%)	10 (14%)	4 (6%)	NA	NA	NA	NA	NA	NA
Mildly Worse	0	2 (3%)	1 (1%)	1 (2%)	NA	NA	NA	NA	NA	NA
Moderately Worse	0	0	0	0	NA	NA	NA	NA	NA	NA
Significantly Worse	0	0	0	0	NA	NA	NA	NA	NA	NA

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

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Analysis of Duration of Effect:

Analysis of the end-of-dosing interval efficacy (or duration of drug effect) was not readily evaluable as reflective but no instantaneous nasal symptom scores were quantified by patients. Nonetheless, information provided by the patient diary scores indicate that no significant difference was seen between the a.m. and p.m. symptom scores (total and individual NAPR scores) throughout the double-blind treatment period. Thus, at least for bid dosing, FP Nasal Spray appeared to have adequate efficacy in decreasing nasal symptoms when used twice a day and effects did not appear to wane significantly over the 12 hour period.

Analysis of Onset of Efficacy:

Formal analysis of the onset of efficacy of the 3 FP doses vs. placebo was not performed by the sponsor in FLTA 3010.

8.1.4.2.1. Nasal Cytology Studies

Nasal cytology studies were conducted in order to assess the proportion of patients enrolled in FLTA 3010 that might have NARES (non-allergic rhinitis with eosinophilia), a disorder different in etiology from perennial non-allergic rhinitis. Prevalence of eosinophils in nasal secretions was assessed at Visit 2 (baseline of the double-blind treatment period) and Visit 4 (day 28 of the double-blind treatment period). Based on these [redacted] studies; at baseline, the majority of patients enrolled into the 4 treatment groups did not have evidence of nasal eosinophilia (91% of placebo group patients, 87% of FP 50 μg bid patients, 93% of FP 100 μg bid patients, and 90% of FP 200 μg bid patients) [NDA 20-121, S-009, 3:129], which would be consistent with lack of a supporting clinical finding for NARES. Furthermore, the percentage of nasal smears with eosinophils decreased in each of the 4 active treatment groups by week 4 but did not change in the placebo group (91% of placebo group patients, 97% of FP 50 μg bid patients, 99% of FP 100 μg bid patients, and 96% of FP 200 μg bid patients) [NDA 20-121, S-009, 3:129].

8.1.4.3. Safety Analysis

Safety analysis for study FLTA 3010 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, and changes in physical examination (especially with regard to oropharyngeal and nasal exams) pre-and post-treatment in patients randomized into the study and 'exposed' to study medication (the intent-to-treat population) [NDA 20-121, S-009, 3:24]. In this trial, the safety evaluable population was the same as the ITT population. Safety analyses in this study were performed separately for the double-blind and the open-label periods. Eight hundred and thirty seven (837) patients comprised the intent-to-treat population (n=210 for the placebo group, n= 208 for the FP 50 μg bid group, n=211 for the FP 100 μg bid group, and n=208 for the FP 200 μg bid group). Conversely, for

the open label portion of FLTA 3010, 289 patients were randomized into the study and 223 or 77% of patients completed the entire 6 month safety extension. The breakdown of patients by double-blind treatment groups from which patients were enrolled into the open-label period was as follows: placebo group: 72 patients, FP 50 μg bid group: 68 patients, FP 100 μg bid group: 73 patients, and FP 200 μg bid group: 76 patients.

8.1.4.3.1. Demographics of the Exposed Population

Demographics of the exposed population (which is the same as the ITT population) was presented in section 8.1.4.1 ('Patient Demographics') of the medical officer review of NDA 20-121, NAPR Efficacy Supplement. All 4 treatment groups were similar in terms of baseline characteristics with no statistically significant difference between any of the 4 treatment groups with regard to any particular demographic variable. Patient composition for this study is again provided in Table IV. below.

Table IV. Patient Demographics for the ITT Population-Double Blind Treatment Period [NDA 20-121, S-009, 3:118-120]:

Variable	Placebo (n=210)	FP 50 μg bid (n=208)	FP 100 μg bid (n=211)	FP 200 μg bid (n=208)	P-Value
Gender: (n, (%))					
Male	77 (37%)	66 (32%)	65 (31%)	62 (30%)	0.445
Female	133 (63%)	142 (68%)	146 (69%)	146 (70%)	
Race: (n, (%))					
Caucasian	205 (98%)	195 (94%)	194 (92%)	196 (94%)	0.329
Black	2 (<1%)	4 (2%)	9 (4%)	7 (3%)	
Asian	0	0	0	1 (<1%)	
Hispanic	3 (1%)	8 (4%)	7 (3%)	3 (1%)	
Other	0	1 (<1%)	1 (<1%)	1 (<1%0	
Age: (yrs)					
Mean ± SE	43.1 ± 1.0	42.7 ± 1.0	42.4 ± 1.0	40.6 ± 1.1	0.318
Median	43.2 43.6	41.3	42.7	39.4	
Range	12-79	14-86	12-76	12-74	
Weight: (lbs.)					
Mean ± SE	166.4 ± 2.9	166.9 ± 2.7	167.1 ± 3.1	159.3 ± 2.5	0.151
Median	157	162.5	164.5	152.0	
Range	86-319	96-294	84-340	100-290	
Height: (inches)					
Mean ± SE	66.9 ± 0.3	66.5 ± 0.3	66.5 ± 0.3	66.2 ± 0.3	0.267
Median	66.0	66.0	66.0	66.0	
Range	60-76	56-77	57-77	52-78	
Tobacco Use:					
Never Used	142 (68%)	142 (68%)	155 (73%)	139 (67%)	0.473
Former Use	67 (32%)	66 (32%)	66 (32%)	69 (33%)	
Current Use	1 (<1%)	0	0	0	
Medical History (at screening):					
Any abnormality	175 (83%)	167 (80%)	175 (83%)	170 (82%)	*NC
Ear, nose, & throat	21 (10%)	16 (8%)	14 (7%)	21 (10%)	
Respiratory	14 (7%)	35 (17%)	14 (7%)	14 (7%)	
% of Patients with ≥ 1 Concurrent Medication	167 (80%)	157 (75%)	175 (83%)	164 (79%)	*NC

P-value for gender, ethnic origin, and tobacco use based on the Chi-square test.
P-value for age, weight, and height based on the F-test. *NC=No comparison.

Reiterating the discussion in section 8.1.4.1., patient demographics for the open-label treatment period (which is not presented in tabular form in this review but referenced in Table 5E of the sponsor's submission) [NDA 20-121, S-009, 3:230-231] overall paralleled the demographics of the double-blind treatment period except that a slightly lower percentage of patients in this group never used tobacco [NDA 20-121, S-009, 3:231]. Importantly, in the open-label period, the number of patients enrolled from all 4 treatment groups in the double-blind period into the open-label were approximately equal for each respective treatment group.

8.1.4.3.2. Duration of Patient Exposure/Patient Disposition

Also reiterated in Section 8.1.4.1 of the NAPR Efficacy Supplement review, the extent of exposure to study medication of at least 2 weeks of double-blind treatment period for all 4 treatment groups combined was 798/837 patients or approximately 95% [NDA 20-121, S-009, 3:159]. A total of 39 patients completed 2 weeks or less of the double-blind treatment period.

For the open-label period of the study, 213 patients completed the open-label safety extension alone (where they received FP 200 μg bid) and a total of 76 patients completed both the double-blind portion of FLTA 3010 and the 6 month open label portion of FLTA 3010 (again, where they received a dose of FP 200 μg bid [NDA 20-121, S-009, 3:268].

8.1.4.4. Adverse Events (AE's)

8.1.4.4.1. Double-blind Treatment Period

The overall incidence of adverse events (AEs) were generally similar for all 4 treatment groups (44-54% range, highest in the FP 100 μg bid group). With regard to 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 headaches in the 3 FP treatment groups over placebo.

The most common AE for the 3 FP treatment groups was headache (incidence ≤ 16% for the 3 FP groups) followed by epistaxis (incidence ≤ 10% for the 3 FP groups), and throat irritation (incidence ≤ 10% for the 3 FP groups) (see Table XXIII). A dose response for the 3 treatment groups was not noted for any specific AE with the exception of a very subtle increase in the incidence of epistaxis with increasing dose (9% incidence in the FP 50 μg bid group, 10% incidence in the FP 100 μg bid group, and 11% incidence in the FP 200 μg bid group). Importantly, no significant increase in the incidence of viral respiratory infections (incidence ≤ 1% for the 3 FP groups compared with an incidence of 3% for placebo) or fungal skin infections (incidence < 1% for the 3 FP groups compared with an incidence of <1% for placebo) or sinusitis (incidence ≤ 3% for the 3 FP groups compared with an incidence of 3% for placebo) was noted in any of the 3 FP treatment groups compared to placebo combination during the double-blind treatment period [NDA 20-121, S-009, 3:160, 162, 165]. Likewise, no significant increase

in the incidence of nasal septal disorders was noted in either of the 4 treatment groups with treatment (incidence < 1% for all 4 groups).

In summary, the safety profile for period for FP nasal spray during the double-blind treatment period of FLTA 3010 was unremarkable, with no evidence of a significant increase in the incidence of AEs known to be associated with use of intranasal steroids, such as nasal septal ulcerations, oral or nasal candidiasis, glaucoma, and cataracts in the sponsor's AE database.

A summary of all reported adverse events for the 4 treatment groups during the double-blind treatment period (including placebo) presented in Table XXIII below.

Table XXIII. Adverse Event (AE) Frequency: More Common AEs (Incidence ≥ 3%) in Any Fluticasone Treatment Group for the Double-Blind Period (FLONASE Aqueous Nasal Spray), by Organ System and Preferred Term; ITT Population [NDA 20-121, S-009, 3:160-167]

BODY SYSTEM	Preferred Term	Placebo (n=210) n (%)	FP 50 µg bid (n=208) n (%)	FP 100 µg bid (n=211) n (%)	FP 200 µg bid (n=208) n (%)
All Systems	Any AE	92 (44%)	99 (48%)	114 (54%)	93 (45%)
ENT	Epistaxis	**11 (5%)**	**19 (9%)**	**22 (10%)**	**23 (11%)**
	Throat Irritation	**20 (10%)**	9 (4%)	**22 (10%)**	**19 (9%)**
	URI	**14 (7%)**	**10 (5%)**	**16 (8%)**	**11 (5%)**
	Nasal Irritation	5 (2%)	**10 (5%)**	5 (2%)	5 (2%)
	Sinusitis	6 (3%)	2 (<1%)	1 (<1%)	0
Neurology	Headaches	**17 (8%)**	**34 (16%)**	**27 (13%)**	**32 (15%)**
Gastrointestinal	Nausea and vomiting	4 (2%)	7 (3%)	6 (3%)	3 (1%)
	Diarrhea	2 (<1%)	6 (3%)	3 (1%)	3 (1%)
Lower Respiratory	Cough	7 (3%)	**13 (6%)**	**14 (7%)**	5 (2%)
	Viral Respiratory symptoms	3 (1%)	3 (1%)	8 (4%)	3 (1%)
Non-site specific	Viral Infections	6 (3%)	2 (<1%)	3 (1%)	3 (1%)
Musculoskeletal	Musculoskeletal pain	7 (3%)	4 (2%)	**10 (5%)**	4 (2%)

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

8.1.4.4.2. Open-Label Treatment Period

Similar to the double-blind treatment period, the qualitative distribution of AEs in the open-label treatment period consisted of headache as the most prevalent AE, followed by URI (this was AE was less prevalent in the double-blind period), and then epistaxis. A slightly higher overall incidence of AEs during this 6 month period was noted for the 4 treatment groups (range 57%-84%), with a slightly higher incidence noted for headache (range 12-24% for the 3 FP groups)—the most prevalent AE during the open-label period. The prevalence of epistaxis, throat irritation, URI, sinusitis (incidence 1-8% for the 3 FP groups compared with an incidence of 4% for placebo), cough, and menstruation abnormalities was also slightly higher during the open-label period.

For the open-label treatment period, no dose response was noted for any AE for the 3 different FP doses. In general, the highest incidence of AEs was noted to be present in patients who had previously been assigned during the double-blind

treatment period to the FP 50 μg bid and FP 100 μg bid treatment groups. A summary of all reported adverse events for the 4 treatment groups during the open-label treatment period (including placebo) presented in Table XXIV below.

Table XXIV. Adverse Event (AE) Frequency:
More Common AEs (Incidence ≥ 3%) in Any Fluticasone Treatment Group for the Open-label Period (FLONASE Aqueous Nasal Spray), by Organ System and Preferred Term; ITT Population [NDA 20-121, S-009, 3:269-276]

BODY SYSTEM	Preferred Term	Double-blind: Placebo, followed by FP 200 μg bid (n=72) n (%)	Double-blind: FP 50 μg bid, followed by FP 200 μg bid (n=68) n (%)	Double-blind: FP 100 μg bid, followed by FP 200 μg bid (n=73) n (%)	Double-blind: FP 200 μg bid, followed by FP 200 μg bid (n=76) n (%)
All Systems	Any AE	42 (58%)	52 (76%)	61 (84%)	43 (57%)
ENT	Epistaxis	7 (10%)	9 (13%)	15 (21%)	10 (13%)
	Throat irritation	2 (3%)	7 (10%)	7 (10%)	5 (7%)
	URI	10 (14%)	7 (10%)	10 (14%)	8 (11%)
	Nasal irritation	2 (3%)	3 (4%)	3 (4%)	2 (3%)
	Ear signs and symptoms	5 (2%)	10 (5%)	5 (2%)	5 (2%)
	Sinusitis/sinus infection	4 (6%)	3 (4%)	2 (3%)	3 (4%)
	Sinusitis	3 (4%)	4 (6%)	6 (8%)	1 (1%)
	Blood in nasal mucosa	5 (7%)	3 (4%)	2 (3%)	2 (3%)
	Dryness of nose	3 (4%)	0	3 (4%)	5 (7%)
	Nasal congestion/blockage	1 (1%)	2 (3%)	4 (5%)	2 (3%)
	Ear signs and symptoms	2 (3%)	2 (3%)	3 (4%)	1 (1%)
	Pharyngitis/throat infection	0	1 (1%)	4 (5%)	0
Neurology	Headache	11 (15%)	16 (24%)	9 (12%)	10 (13%)
Gastrointestinal	Nausea and vomiting	1 (1%)	2 (3%)	6 (8%)	5 (7%)
	Diarrhea	0	1 (1%)	3 (4%)	3 (4%)
Lower Respiratory	Cough	3 (4%)	6 (9%)	9 (12%)	2 (3%)
	Viral Respiratory Infections	0	2 (3%)	5 (7%)	3 (4%)
	Bronchitis	0	1 (1%)	3 (4%)	1 (1%)
Non-site specific	Temp. regulation disturbance	3 (4%)	2 (3%)	3 (4%)	0
	Viral Infections	2 (3%)	0	0	3 (4%)
Musculoskeletal	Musculoskeletal pain	3 (4%)	3 (4%)	4 (5%)	0
Reproduction	Menstruation symptoms	0	3 (6%)	1 (2%)	2 (4%)

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

Reviewer's Note: Display of AE data for the open-label period, though included in this review of FLTA 3010, is somewhat misleading, as patients essentially received FP 200 μg bid for the majority of the study period during which AEs were evaluated. Hence, the AE frequencies presented in this table reflect more the AE frequency associated with the FP 200 μg bid dose than any of the other 2 FP doses.

8.1.4.5. Adverse Event Stratification by Duration of Treatment

Although adverse event stratification by duration of treatment was not performed by the sponsor, comparison can be made between the incidence of AEs in the 4 week double-blind treatment period and the 6 month safety extension (the

long-term safety follow-up) for FLTA 3010. No outstanding differences were noted between short-term use of FP Nasal Spray at either of the 3 doses or long-term use of FP Nasal Spray at 200 μg bid, although in general a small increase in the prevalence of most AEs recorded during the study (including the more prevalent AEs, such as: headache, epistaxis, and throat irritation), occurred with long-term treatment. Previous treatment with either of the 3 different doses of FP did not appear to impact significantly on the incidence of drug-related AEs. No marked change in the incidence of infections (bacterial, viral, fungal, sinusitis) occurred with long-term FP therapy during the open-label period at a dose of 200 μg bid [NDA 20-121, S-009, 3:160-167, 269-276].

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

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

8.1.4.7. Patient Discontinuation due to Adverse Events

A total of 18 patients discontinued treatment prematurely during the double-blind treatment period due to adverse events (6 in the placebo group, 6 in the FP 50 μg bid group, 3 in the FP 100 μg bid group, and 3 in the FP 200 μg bid group) [NDA 20-121, S-009, 3:188-191]. The most common AE which led to discontinuation of treatment was headache (6 patients), followed by epistaxis (4 patients). In general, the reasons for discontinuation of treatment in all 4 treatment groups were secondary to events that could be attributed to rhinitis symptoms (e.g. cough, sore throat, nasal burning, rhinitis symptoms). One patient in the placebo treatment group withdrew from the study due to sinusitis which began 10 days into the study (patient 11206) [NDA 20-121, S-009, 3:188].

Adverse events leading to study withdrawal during the double-blind period were considered drug-related by the investigator in 2 placebo group patients (reasons: unusual taste after study medication, pruritis of hands), 4 FP 50 μg bid group patients (reasons: headache, epistaxis in 2 patients, and exacerbation of cough/fatigue), 1 FP 100 μg bid group patient (reason: pain in body, headache), and 2 FP 200 μg bid group patients (reasons: epistaxis in both) [NDA 20-121, S-009, 3:82-83]. None of the patients who withdrew during the double-blind period experienced a serious AE.

For the open-label treatment period, 13 patients withdrew from the study for drug-related AEs (out of a total of 18 withdrawals) [NDA 20-121, S-009, 3:279-285]. The most common reason for study withdrawal was epistaxis (6 patients), followed by nasal burning/soreness (2 patients). Other events which led to study termination included: headache, sinusitis (1 patient, #11343), and nasal septal abrasion. One patient (#13298) withdrew from the study because of nasal septal ulcers, which were felt by the investigator to be 'probably' related to treatment with FP 200μg bid [NDA 20-121, S-009, 3:84, 171-184].

8.1.4.8. Serious Adverse Events and Death

[1]Serious AEs were reported for 3 patients during the double-blind period in FLTA 3010 (1 placebo group patient and 2 FP 100 μg bid group patients). None of the serious AEs were considered to be related to study medication (anxiety-patient #13239, death due to coronary atherosclerosis-patient # 12863, and intestinal obstruction-patient # 12252) [NDA 20-121, S-009, 3:82, 186-187]. Four (4) patients during the open-label period experienced serious AEs, again not felt to be related to study medication (patient # 12241: chronic cystitis, patient # 13371: chest pain/pain in arms, patient # 13444: ruptured ectopic pregnancy, patient # 12405: cholecystectomy) [NDA 20-121, S-009, 3:82, 286-287].

8.1.4.9. Laboratory Test Results

Laboratory tests performed during visit 1 (pre-randomization), visit 4 (completion of double-blind treatment), and visit 10 of the study (completion of the 6 month open-label safety extension) and which consisted of a complete blood count with differential count, blood chemistries, liver function tests (SGOT, SGPT, alkaline phosphatase, total protein, albumin, and total bilirubin), urinalysis, and serum pregnancy test (for all women) did not reveal any unexpected abnormalities in FP treated patients, as compared with placebo treated patients. The effects of the 4 treatments on laboratory parameters were analyzed (with the exception of serum pregnancy tests) using the change from baseline for the study visit, shift tables, and a tabulation of outlier values for individual patients [NDA 20-121, S-009, 3:85, 192-193, 194-206]. The sponsor's criteria for an abnormal laboratory value was a value outside the limits of normal for that parameter, based on Glaxo Wellcome definitions of clinically significant abnormal values [NDA 20-121, S-009, 3:192-193]. Summary tables for each laboratory value were computed using the designation of abnormally 'low' and 'high' values, based on the definitions of each respective lab value, as determined by Glaxo Wellcome [NDA 20-121, S-009, 3:198-199]. Statistical comparisons were not attempted by the sponsor with regard to analysis of laboratory abnormalities.

Summary tables for each laboratory value computed using the designation of abnormally 'low' and 'high' values, based on the definitions of each respective laboratory value, as determined by Glaxo Wellcome did not reveal any significant changes post-randomization during the double-blind treatment period (see Table 30 in the NAPR submission, NDA 20-121, S-009, 3:198-199].

Analysis of laboratory tests by shift tables (comparison between baseline and visit 4) failed to reveal any significant differences between the 4 treatment groups during the double-blind treatment period [NDA 20-121, S-009, 3:85, 194-197]. The majority of patients had laboratory tests within normal range at screening and

[1] 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.

remained within the normal range throughout the double-blind treatment period.

In general, shifts in laboratory test results were minor and showed no trends or dose response relationships. Similar to the double-blind period, no significant shifts in laboratory values were noted during the open-label period [NDA 20-121, S-009, 3:85, 293-296].

An evaluation of individual outliers (defined as marked abnormalities in laboratory parameters, based on a lower/higher cutoff limit for normal values for the given laboratory parameter, as determined by the sponsor) for each laboratory test showed no obvious difference in the number of patients with outliers between the 4 treatment groups during the double-blind treatment period or during the open-label treatment period [NDA 20-121, S-009, 3:85, 198-206]. These data are summarized in Tables 31 and 27E of the study report for FLTA3010 [NDA 20-121, S-009, 3:85, 200-206, 299-301]. A minimal increase in the number cases of hyperglycemia in patients treated with FP over those treated with placebo was seen in all 3 FP treatment groups (1 patient in the placebo group, 2 patients in the FP 50 μg bid group, 3 patients in the FP 100 μg bid group, and 3 patients in the FP 200 μg bid group) [NDA 20-121, S-009, 3:85, 198] but was not higher with long-term treatment with FP Nasal Spray than in those with short-term treatment (noted in the open label extension: 3 patients with hyperglycemia out of a total of n=289 patients (~1% incidence)) [NDA 20-121, S-009, 3:85, 297]. Of note, shift tables for laboratory values did not detect a significant shift to abnormally high glucose values in the 3 FP treatment groups, as compared with placebo or in the open-label treatment groups [NDA 20-121, S-009, 3:200-206].

Review of the individual patient listings for significant laboratory test abnormalities during the double-blind treatment period showed that indeed a slightly greater number of patients in the 3 FP treatment groups had developed hyperglycemia with FP treatment as compared to placebo treatment (1 patient in the placebo group, 2 patients in the FP 50 μg bid group, 2 patients in the FP 100 μg bid group, and 3 patients in the FP 200 μg bid group) [NDA 20-121, S-009, 3:85, 195, 293-294]. Of note, increase in blood glucose in these patients was noted to more commonly occur in those patients with already elevated baseline glucose levels. Likewise in the 3 FP treatments, elevation of serum bilirubin was seen in 3 patients total (patient # 16313: FP 100 μg bid, patient # 13389: FP 100 μg bid, and patient # 11566: FP 200 μg bid) compared with 2 patients in the placebo group (patients # 16477 and 11448). The change (increase) in serum bilirubin was generally less than 1.5 mg/dL across all treatment groups though more remarkable in the active FP treatments, and was noted to occur predominantly in patients with a baseline elevated serum bilirubin level [NDA 20-121, S-009, 3:200-206].

During the open-label treatment period, again the 2 predominant laboratory test outlier abnormalities consisted of hyperglycemia (3 patients total: # 12028, 12545, and 12986) and increase in serum bilirubin (3 patients: #11119, 12089, and 12329) [NDA 20-121, S-009, 3:299-301]. Increase in these 2 laboratory parameters during the open-label period occurred in patients with baseline

elevated serum glucose and bilirubin. Hence, laboratory outlier results were similar to one-another for the double-blind and open-label periods of FLTA 3010. Importantly, both the double-blind and open-label treatment periods, no laboratory test result met the definition of an adverse event, although 1 patient (# 13452) was withdrawn from the double-blind treatment period because of an abnormal SGPT (ALT) which was elevated on screening to 104 U/L but continued to increase to a value of 280 U/L by day 3 of the study [NDA 20-121, S-009, 3:85].

8.1.4.9.1. HPA-Axis Studies

Adrenal function was evaluated in FLTA 3010 by measurement of both: (1) a.m. plasma cortisol levels at baseline, post-4 weeks, and post-6 months of treatment with study drug (or at early patient discontinuation) and (2) Cortrosyn-stimulation testing with 250 μg cosyntropin and measurement of plasma cortisol levels 30 or 60 minutes after administration of cosyntropin; post-4 weeks and post-6 months of treatment with study drug. Baseline Cortrosyn-stimulation testing at the start of the double-blind treatment period was not performed.

A.M. plasma cortisol measurements (pre- and post-treatment) for the double-blind and open-label periods were presented in the FLTA 3010 submission as individual patient line listings and as a list of patient outliers [NDA 20-121, S-009, 3:207-216, 302-306, 12:1-8]. Results for Cortrosyn-stimulation testing were presented in tabular form for Visit 4 (post-4 weeks of treatment with study drug) and for Visit 10 (post-6 months of treatment with FP 200 μg bid) in which the number and percentage of patients with abnormal adrenal response were tallied (a normal adrenal response to Cortrosyn defined as: a baseline plasma cortisol level > 5 μg/dL, with a 30' post-stimulation increase of ≥ 7 μg/dL and a post-stimulation cortisol level of ≥ 18 μg/dL [NDA 20-121, S-009, 3:60]. If a 60' test period was used, the criterion for a normal response in plasma cortisol level, was an approximate doubling of the a.m. plasma cortisol value). [NDA 20-121, S-009, 3:307-308]. Means of a.m. plasma cortisol levels (with statistical analysis) were not performed in this study.

For the a.m. plasma cortisol measurements during the double-blind treatment period, a total of 11 patients (2 patient in the placebo group, 3 patients each in the FP 50 μg bid group, FP 100 μg bid group, and FP 200 μg bid group) [NDA 20-121, S-009, 3:86] had plasma cortisol levels < 5 μg/dL prior to and/or during the double-blind treatment period. Of these 11 patients (out of a total of 789 patients who had a.m. plasma cortisol levels measured), 1 placebo patient had a decrease in a.m. plasma cortisol with placebo treatment, 3 FP 50 μg bid group patients had a decrease in a.m. plasma cortisol with FP treatment, 3 FP 100 μg bid group patients had a decrease in a.m. plasma cortisol with FP treatment, and 2 FP 200 μg bid group patients patient had a decrease in a.m. plasma cortisol with FP treatment where the post-treatment a.m. plasma cortisol was ≤ 5 μg/dL, respectively [NDA 20-121, S-009, 3:86]. If less stringent and more clinically relevant criteria of: a post-treatment a.m. plasma cortisol ≤ 5 μg/dL and/or decrease in post-treatment a.m. plamsa cortisol < 7 μg/dL (from baseline) were used as criteria for defining 'abnormal' adrenal function, a greater number of

patients in all 4 treatment arms had evidence of adrenal suppression, including the placebo treatment arm. Namely, by these criteria, 5 placebo patients had lower a.m. plasma cortisol levels post- double-blind period treatment, 5 FP 50 μg bid group patients had lower a.m. plasma cortisol levels post- double-blind period treatment, 4 FP 100 μg bid group patients had lower a.m. plasma cortisol levels post- double-blind period treatment, and 6 FP 200 μg bid group patients had lower a.m. plasma cortisol levels post- double-blind period treatment [NDA 20-121, S-009, 3:207-215]. No dose response was noted for the different doses of FP with respect to suppression of a.m. plasma cortisol levels during the double-blind treatment period.

For the open-label period, interestingly, no patient (at either Visit 4, the baseline visit for the open-label period or Visit 10, the 6 month follow-up visit) had an a.m. plasma cortisol level ≤ 5 μg/dL [NDA 20-121, S-009, 3:87]. If the less stringent but more clinically relevant criteria of: a post-treatment a.m. plasma cortisol < 5 μg/dL and/or decrease in post-treatment a.m. plasma cortisol < 7 μg/dL (from baseline) were used to assess adrenal function for the open-label treatment period, then 4 patients originally in the placebo group had lower a.m. plasma cortisol levels post- open-label treatment, 6 patients originally in the FP 50 μg bid group had lower a.m. plasma cortisol levels post- open-label treatment, 9 patients originally in the FP 100 μg bid group had lower a.m. plasma cortisol levels post- open-label treatment, and 2 patients originally in the FP 200 μg bid group had lower a.m. plasma cortisol levels post- open-label treatment [NDA 20-121, S-009, 3:302-306]. Importantly, all of these patients were receiving FP 200 μg bid during the open-label treatment. Thus, it appears that despite the fact that no patient in the open-label portion of the study was found to have an a.m. plasma cortisol level < 5, long-term treatment with FP 200 μg bid nonetheless, did increase the number of patients who exhibited a numerical decrease in their a.m. plasma cortisol level—a finding which would be suggestive of blunting of the adrenal response.

Results for Cortrosyn-stimulation testing which was at the end of the double-blind period and end of the open-label period is presented in Table XXV below with line listing of these patients provided in Table 30E of the NAPR supplement [NDA 20-121, S-009, 3:307-308, 309-316].

Table XXV. Cortrosyn-Stimulation Testing: Plasma Cortisol Abnormalities at baseline (Visit 4) and post-6 months of treatment (Visit 10) with Study Drug (FLONASE Aqueous Nasal Spray); ITT Population [NDA 20-121, S-009, 3:307-308]

	Placebo Visit 4, n=69 Visit 10, n=55 n (%)	FP 50 µg bid Visit 4, n=68 Visit 10, n=53 n (%)	FP 100 µg bid Visit 4, n=69 Visit 10, n=61 n (%)	FP 200 µg bid Visit 4, n=73 Visit 10, n=53 n (%)	Total Patients Visit 4, n=279 Visit 10, n=222 n (%)
Patients with low baseline cortisol (≤ 5 µg/dL)					
Visit 4	0 (0%)	0 (0%)	1 (1%)	2 (3%)	3 (1%)
Visit 10	1 (2%)	0 (0%)	1 (2%)	0 (0%)	2 (1%)
Patients with Post-Cortrosyn stimulation Δ in cortisol < 7 µg/dL					
Visit 4	**6 (9%)**	**8 (12%)**	**8 (12%)**	**5 (7%)**	**27 (10%)**
Visit 10	**3 (5%)**	**11 (21%)**	**17 (28%)**	**8 (15%)**	**39 (18%)**
Patients with Post-Cortrosyn stimulation cortisol < 18 µg/dL					
Visit 4	4 (6%)	2 (3%)	2 (3%)	3 (4%)	11 (4%)
Visit 10	0 (0%)	2 (4%)	4 (7%)	1 (2%)	7 (3%)
Patients with Post-Cortrosyn stimulation Δ in cortisol < 7 µg/dL and cortisol < 18 µg/dL					
Visit 4	3 (4%)	2 (3%)	2 (3%)	1 (1%)	8 (3%)
Visit 10	0 (0%)	1 (2%)	3 (5%)	1 (2%)	5 (2%)

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

According to the sponsor's a priori criteria for definition of an abnormal response to Cortrosyn-stimulation testing, a total of 27 patients at Visit 4 (6 placebo, 8 FP 50 µg bid patients, 8 FP 100 µg bid patients, and 5 FP 200 µg bid patients) had a change in post-Cortrosyn stimulation plasma cortisol levels < 7 µg/dL. At Visit 10, 39 patients (3 previous placebo, 11 previous FP 50 µg bid patients, 17 previous FP 100 µg bid patients, and 8 previous FP 200 µg bid patients), all of whom had been receiving FP 200 µg bid during the open-label period, had a change in post-Cortrosyn stimulation plasma cortisol levels < 7 µg/dL [NDA 20-121, S-009, 3:88]. Importantly, 11 patients had a decrease (negative change) in post-Cortrosyn stimulation cortisol levels which might indicate either sample mislabeling or blunting of the adrenal response after 6 months of treatment with FP 200 µg bid.

Regarding the prevalence of post-Cortrosyn stimulation cortisol levels < 18 µg/dL in all 4 treatment groups, at Visit 4, 11 patients total (4 placebo, 2 FP 50 µg bid patients, 2 FP 100 µg bid patients, and 3 FP 200 µg bid patients) had post-Cortrosyn stimulation plasma cortisol levels < 18 µg/dL. At Visit 10, 7 patients (2 previous FP 50 µg bid patients, 4 previous FP 100 µg bid patients, and 1 previous FP 200 µg bid patient), again, all of whom had been receiving FP 200 µg bid

during the open-label period, had post-Cortrosyn stimulation plasma cortisol levels < 18 μg/dL [NDA 20-121, S-009, 3:88].

In terms of both laboratory abnormalities, 8 patients at Visit 4 and 5 patients at Visit 10 had both a post-stimulation change in plasma cortisol < 7 μg/dL and a post-Cortrosyn stimulation value < 18 μg/dL. Only 1 patient (# 11560) had both abnormalities at both Visit 4 and 10. One patient previously in the FP 50 μg bid group, 3 patients previously in the FP 100 μg bid group, and 1 patient previously in the FP 200 μg bid group had both abnormalities at Visit 10 [NDA 20-121, S-009, 3:31, 89]. Means of the change in plasma cortisol levels post-treatment with FP 200 μg bid were not performed by the sponsor and only outlier values and their % of the total patient population were presented in FLTA 3010.

Thus, in summary, the Cortrosyn stimulation testing showed that only a small proportion of those patients randomized into the open-label portion of the did develop blunting of adrenal response on FP Nasal Spray. Because all patients were randomized at Visit 4 to the FP 200 μg bid dose, it is difficult if not altogether impossible to speculate as to whether there may have been a dose response with FP Nasal Spray with regard to adrenal suppression during this 6 month period.

Hence, overall, the likelihood of adrenal suppression, while very small, was not likely to be significant for most patients compared to placebo treatment post-4 weeks of therapy with study drug. Furthermore, adrenal suppression was seen in patients receiving all 3 doses of FP nasal spray and was noted to be more prevalent by Visit 10 in FP treated patients.

Reviewer' Note: Since a placebo control group was not included in the long-term safety extension study, comparison of the different treatment groups via statistical analysis (i.e. determination of p-values) could not be performed in order to assess the potential significance of these outlier values on adrenal response. Nonetheless, it appears that in rare patients blunting of the adrenal axis may occur with longer-term use of FP Nasal Spray (i.e. up to 6 months of treatment). A placebo group was included for the initial 4 week double-blind period—and here one can conclude that little difference (in terms of % of patient outliers) was noted between the placebo treatment and the 3 active comparators. Furthermore, a dose response of FP treatment on adrenal suppression was not seen.

8.1.4.10. Physical Examination (including ENT exam)

Evaluation of change in the physical examination of patients during the double-blind and open-label periods revealed no significant trends in physical findings and only minor changes on exam. For the double-blind treatment period, only 15 patients had minor changes in physical exam and for the open-label period, only 22 patients had minor changes in physical exam (Tables 33, 31 E and 32 E of the sponsor's submission) [NDA 20-121, S-009, 3:89, 218, 317-319]. A very slightly greater incidence of ENT changes (not classified in table) was noted

in the FP 100 and 200 μg bid groups (3 and 4% of patients), as compared to placebo treatment (0 % of patients), and the FP 50 μg bid group (0 % of patients) [NDA 20-121, S-009, 3:317]. In particular, for the double-blind treatment period no significant change in nasal obstruction by nasal polyps (by those patients who had them) was seen in the FP treated patients, compared to placebo at the 3 different doses of FP Nasal Spray [NDA 20-121, S-009, 3:122] and although a slight decrease in nasal turbinate enlargement (specifically, moderate turbinate enlargement) was noted at Visits 3 and 4 of the double-blind treatment period, this change was seen in all 4 treatment groups, including placebo treatment [NDA 20-121, S-009, 3:123].

With respect to infections, in particular, sinusitis, for the open-label patients, 1 patient previously treated with FP 100 μg bid was diagnosed with acute sinusitis by physical examination which was not further elaborated upon in the sponsor's submission (# 12031) [NDA 20-121, S-009, 3:318]. No patients in the double-blind treatment period were diagnosed with sinusitis on physical examination. Four additional cases of sinusitis were detected in patients at baseline by X-ray studies (1 placebo patient # 13374, [NDA 20-121, S-009, 8:137], 1 patient on FP 50 μg bid (# 13233) [NDA 20-121, S-009, 8:147], and 2 patients on FP 200 μg bid (# 11435 and 169, respectively) [NDA 20-121, S-009, 8:161, 169]. Aside from these reports, no notable increase in the incidence of viral, bacterial, or fungal infections was seen in FP Nasal Spray treated patients.

Evaluation of the ear, nose, and throat (ENT exam) to rule out nasal or oral candidiasis or nasal septal ulcerations and/or perforations was performed at every clinic visit [NDA 20-121, S-009, 9:83-182] and results of these examinations revealed that a total of 4 patients (1 patient in the placebo group at Visit 4 (# 13069) [NDA 20-121, S-009, 9:104], 2 patients in the FP 50 μg bid group at Visit 3 (# 12466 and 12472) [NDA 20-121, S-009, 9:124], and 1 patient in the FP 200 μg bid group at Visit 4 (# 11496) [NDA 20-121, S-009, 9:162]) developed oral candidiasis during treatment with study drug [NDA 20-121, S-009, 3:89]. Culture results for all 4 of these patients, however, were reported as negative by the sponsor. One additional patient in the FP 200 μg bid group (# 11963) was noted to develop oropharyngeal candidiasis on clinical exam, however this was not confirmed by a [redacted] [NDA 20-121, S-009, 9:104]. During the open-label period, respectively, 2 patients had clinical evidence of oral candidiasis (# 13298 at Visit 5 and #13062 at Visit 6) drug [NDA 20-121, S-009, 3:89]. No cases of nasal candidiasis were reported in either of the 4 treatment groups during the double-blind or open-label treatment periods of FLTA 3010. Clinical evaluation for presence of nasal septal ulcers or perforations revealed a case of nasal septal perforation after 15 days of treatment with FP 100 μg bid (patient # 12849) [NDA 20-121, S-009, 9:68] and a case of bilateral superficial nasal ulceration in the anterior nares at visit 4 in a patient treated with FP 200 μg bid (patient # 12312) [NDA 20-121, S-009, 8:69]. No new perforations were reported in the eardrums of any patients in FLTA 3010 for both the double-blind and open-label treatment periods [NDA 20-121, S-009, 8:171-287] nor were any cases of

serous otitis media reported during the double-blind treatment period [NDA 20-121, S-009, 3:128].

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

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

(2) A summary table of all efficacy parameters, studied in patients age 12 years and older is presented below and shows that for all primary efficacy endpoints and the majority of secondary efficacy endpoints all 3 doses of FLONASE Aqueous Nasal Spray demonstrated statistically significant efficacy compared to placebo treatment. In this study, the FP 50 μg bid and FP 100 μg bid doses of FLONASE Aqueous Nasal Spray showed numerically greater efficacy for most clinical endpoints than did the FP 200 μg bid dose but these differences were not statistically significant. In general, FLONASE Aqueous Nasal Spray (at all 3 doses) demonstrated greatest efficacy in decreasing the NAPR symptoms of nasal obstruction over that of rhinorrhea, postnasal drip, or sneezing. Results of the open-label portion of the study show that FLONASE Aqueous Nasal Spray continued to decrease NAPR symptoms up to 6 months of treatment, although only the FP 200 μg bid dose was studied—a dose which is higher than the proposed 'to-be-marketed' dose of FLONASE Aqueous Nasal Spray.

Results that Support Approval:

The results for all efficacy endpoints are summarized below and demonstrate statistical significance of all 3 doses of FLONASE Aqueous Nasal Spray in decreasing NAPR symptoms per the primary efficacy variable measurements: (1) change from baseline in patient-rated p.m. total nasal symptom score and (2) the overall patient evaluation (of response to treatment). With regard to secondary efficacy endpoints, a numerical decrease in symptom scores was demonstrable for almost all secondary efficacy endpoints with FP Nasal Spray treatment at each of the 3 different doses but some of these were not found to be statistically significant differences, when compared with placebo (see Summary Table). A dose response was not demonstrable for either the primary or secondary efficacy variables.

Results that do not Support Approval:

As discussed above, a number of time points for the secondary efficacy endpoints failed to demonstrate statistical significance of FP treatment over placebo, namely: (1) several time points in the change from baseline

in patient-rated average a.m. and p.m. postnasal drip scores, (2) several time points in the change from baseline in patient-rated average a.m. and p.m. rhinorrhea scores, (3) several time points in the change from baseline in patient-rated average a.m. and p.m. sneezing scores, (4) the Day 14 change from baseline in physician-rated TNSS, (5) several time points in the change from baseline in physician-rated postnasal drip score, (6) several time points in the change from baseline in physician-rated rhinorrhea score, and (7) the FP 50 µg bid and FP 100 µg bid treatment groups for the overall physician evaluation.

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

EFFICACY VARIABLE	Statistically Significant Response (as compared with placebo) Yes/No
Primary Efficacy Variable	
1. Δ from baseline in patient-rated average p.m. reflective TNSS:	**Yes:** FP 50, 100, and 200 µg bid: Week 1-4
2. Overall Patient Evaluation	**Yes:** FP 50, 100, and 200 µg bid
Secondary Efficacy Variables	
1. Δ from baseline in patient-rated average a.m. reflective [1]TNSS:	**Yes:** FP 50, 100, and 200 µg bid: Week 1-4
2. Δ from baseline in patient-rated average a.m. and p.m. nasal obstruction score	**Yes:** FP 50, 100, and 200 µg bid: Week 1-4
3. Δ from baseline in patient-rated average a.m. and p.m. postnasal drip score	**Yes:** FP 50 and 100 µg bid: Week 1-4 FP 200 µg bid: Week 2-4, Week 1: a.m. **No:** FP 200 µg bid: Week 1, p.m.
4. Δ from baseline in patient-rated average a.m. and p.m. rhinorrhea score	**Yes:** FP 50 and 100 µg bid: Week 1-4. FP 200 µg bid: Week 2, 4, Week 3: p.m. **No:** FP 200 µg bid: Week 1, Week 3: a.m.
5. Δ from baseline in patient-rated average a.m. and p.m. sneezing score	**Yes:** FP 50 µg bid: Week 1-4 FP 100 µg bid: Week 1-2, Week 3: p.m., Week 4: p.m. FP 200 µg bid: Week 1, Week 2-4: p.m. **No:** FP 200 µg bid: Week 2-4: a.m.
6. Δ from baseline in Physician-rated TNSS	**Yes:** FP 50 and 100 µg bid: Day 14 and 28. FP 200 µg bid: Day 28 **No:** FP 200 µg bid: Day 14
7. Δ from baseline in Physician-rated nasal obstruction score	**Yes:** FP 50, 100, and 200 µg bid: Day 14 and 28
8. Δ from baseline in Physician-rated postnasal drip score	**Yes:** FP 50 µg bid: Day 28 **No:** FP 50 µg bid: Day 14, FP 100 and 200 µg bid: Day 14 and Day 28
9. Δ from baseline in Physician-rated rhinorrhea score	**Yes:** FP 50 µg bid: Day 14 and 28 FP 100 µg bid: Day 14 FP 200 µg bid: Day 28 **No:** FP 100 µg bid: Day 28 FP 200 µg bid: Day 14
10. Overall Physician Evaluation	**Yes:** FP 200 µg bid **No:** FP 50 and 100 µg bid

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

Other Results:

FLONASE Aqueous Nasal Spray demonstrated adequate duration of efficacy over an approximately 12 hour time period, as assessed by patient-rated 'reflective' NAPR symptom scores recorded twice daily in a patient diary. Since the study treatments were not dosed once daily (qd), no comment can be made from this study alone as to the duration of effect after once daily dosing. Onset of action was not evaluated in this study.

Safety:

Overall, FP Nasal Spray was safe and well-tolerated given twice a day, at a dose of either 50 μg bid, 100 μg bid, or 200 μg bid. No serious adverse events occurred in patients treated with FP Nasal Spray at either of the 3 different doses, and the 1 death that did occur (at FP 100 μg bid) was not related to study treatment. With long-term use, for treatment groups (including placebo), headache was the most common adverse event, followed by URI, epistaxis, and throat irritation. No significant increase in oropharyngeal candidiasis or nasal septal ulcerations/perforations were seen in patient treated with FP Nasal Spray, compared with placebo. Although there was no placebo group for the open-label extension comparison, at least a small number of patients receiving FP 200 μg bid for up to 6 months did demonstrate laboratory evidence of mild blunting of the adrenal response, as evaluated by a.m. plasma cortisol levels and Cortrosyn stimulation testing. Short-term treatment (i.e. ≤ 4 weeks) with FP Nasal Spray at either of the 3 doses did no show a large numerical difference in patient adrenal response outliers, compared with placebo treatment.

Summary:

Based on the results of this NAPR trial, FP Nasal Spray given at a dose of 50 μg bid, 100 μg bid, and 200 μg bid demonstrated adequate evidence of efficacy and safety at compared with placebo comparators, fexofenadine HCl and pseudoephedrine HCl, for the treatment of NAPR symptoms in adults and children 12 years of age and older. Based on the numerical differences in symptom scores for NAPR, an appropriate starting dose of FP Nasal Spray for this indication would be 100 μg bid or 200 μg qd (once daily regimen), with titration to 50 μg bid (or 100 μg qd, as a once daily regimen).

APPENDIX I: STUDY FLOW-CHART FOR NAPR STUDY FLTA 3010
[NDA 20-121, S-009, 3:107]

Figure 2: Overall Time and Event Schedule

	Screen	Double-Blind Treatment Period			Open-Label Safety Extension			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 10[b]	Early Subject Discontinuation
	Study Day -14 to -7	Study Day 0 ± 0	Study Day 14 ± 2	Study Day 28 ± 2/E0[a]	Study Day E61 ± 7	Study Day E122 ± 7	Study Day E183 ± 7	
Informed Consent	X							
Medical History	X							
Physical Examination	X			X			X	X
Skin Testing	X							
Sinus Radiography	X							
Concurrent Medication Assessment	X	X	X	X	X	X	X	X
Clinical Laboratory Tests	X			X			X	X
AM Plasma Cortisol	X			X			X	X
Pregnancy Test (all females)	X			X			X	X
Nasal & Ear Examination	X	X	X	X	X	X	X	X
Clinician-Rated Nasal Symptoms Assessment	X	X	X	X	X	X	X	X
Diary Cards Dispensed	X	X	X	X	X	X		
Pharmacoeconomic Survey		X	X	X				X[c]
Adverse Events		X	X	X	X	X	X	X
Nasal Cytology		X		X				X[c]
Medication Dispensed		X	X	X	X	X		
Medication Compliance Assessment			X	X	X	X	X	X
Cosyntropin Stimulation				X			X	X[d]
Patient-Rated and Clinician-Rated Overall Evaluations				X			X	X

a Visit 4 was the final double-blind visit AND the baseline visit for patients continuing into the open-label safety extension.
b Protocol Amendment No. 3 reduced the open-label safety extension from 1 year to 6 months; Visits 7, 8, and 9 were eliminated.
c During double-blind treatment period only.
d During open-label safety extension only.

Summary of Patient-Rated Symptom Scores[1]
A.M. Symptoms - Mean Absolute Change From Baseline

	Placebo n Mean(SE)	FP50 BID [2] n Mean(SE)	FP100 BID [2] n Mean(SE)	FP200 BID [2] n Mean(SE)	Over-all	Pla vs 50[3]	Pla vs 100[3]	Pla vs 200[3]	50 vs 100[3]	50 vs 200[3]	100 vs 200[3]
Total Patients at Screening	210	208	211	208							
Total Nasal Symptom Score[4]											
Day -6 - 0[5]	210 197.6(3.7)	208 205.2(3.4)	211 202.6(3.6)	208 198.1(3.4)	0.252	0.077	0.264	0.855	0.510	0.113	0.352
Day 1 - 7	210 -31.7(3.9)	204 -56.3(4.2)	207 -51.2(4.1)	205 -48.2(3.9)	<0.001	<0.001	<0.001	0.003	0.358	0.131	0.552
Day 8 - 14	208 -47.1(4.7)	200 -74.5(5.1)	204 -67.9(5.1)	204 -66.8(4.5)	<0.001	<0.001	0.001	0.002	0.322	0.249	0.870
Day 15 - 21	203 -54.9(4.8)	192 -81.0(5.4)	201 -75.4(5.3)	200 -75.4(4.7)	<0.001	<0.001	0.003	0.003	0.409	0.377	0.952
Day 22 - 28	203 -57.1(5.3)	191 -88.7(5.4)	197 -84.3(5.6)	198 -82.0(5.2)	<0.001	<0.001	<0.001	<0.001	0.520	0.268	0.641
Nasal Obstruction											
Day -6 - 0[5]	210 69.5(1.6)	208 73.8(1.4)	211 70.7(1.6)	208 70.3(1.5)	0.216	0.052	0.599	0.770	0.154	0.099	0.816
Day 1 - 7	210 -8.9(1.5)	204 -19.8(1.6)	207 -17.3(1.6)	205 -16.8(1.5)	<0.001	<0.001	<0.001	<0.001	0.276	0.154	0.733
Day 8 - 14	208 -15.0(1.7)	200 -26.6(1.9)	204 -23.7(1.9)	204 -23.7(1.7)	<0.001	<0.001	<0.001	<0.001	0.281	0.292	0.980
Day 15 - 21	203 -16.8(1.8)	192 -28.5(2.2)	201 -25.6(2.0)	200 -27.1(1.8)	<0.001	<0.001	0.001	<0.001	0.287	0.604	0.582
Day 22 - 28	203 -17.6(2.0)	191 -30.7(2.1)	197 -27.9(2.1)	198 -29.7(1.9)	<0.001	<0.001	<0.001	<0.001	0.339	0.666	0.596
Postnasal Drip											
Day -6 - 0[5]	210 70.7(1.6)	208 72.2(1.4)	211 71.0(1.4)	208 70.3(1.4)	0.783	0.455	0.936	0.807	0.504	0.322	0.745
Day 1 - 7	210 -11.3(1.5)	204 -18.2(1.6)	207 -15.6(1.6)	205 -16.8(1.5)	0.011	0.002	0.047	0.011	0.241	0.544	0.572
Day 8 - 14	208 -16.9(1.8)	200 -23.7(1.9)	204 -22.3(2.0)	204 -23.1(1.8)	0.031	0.008	0.037	0.015	0.569	0.816	0.735
Day 15 - 21	203 -19.6(1.9)	192 -26.4(2.0)	201 -24.9(2.0)	200 -25.4(1.8)	0.051	0.011	0.046	0.034	0.559	0.650	0.895
Day 22 - 28	203 -20.2(2.0)	191 -28.9(2.0)	197 -29.0(2.1)	198 -27.4(2.1)	0.004	0.002	0.002	0.016	0.993	0.483	0.474
Rhinorrhea											
Day -6 - 0[5]	210 57.4(1.9)	208 59.3(1.9)	211 61.0(1.8)	208 57.6(1.8)	0.308	0.236	0.090	0.732	0.615	0.399	0.177
Day 1 - 7	210 -11.2(1.5)	204 -18.4(1.6)	207 -17.9(1.6)	205 -14.6(1.6)	<0.001	<0.001	<0.001	0.089	0.780	0.062	0.110
Day 8 - 14	208 -14.9(1.9)	200 -24.3(1.8)	204 -21.9(1.9)	204 -20.1(1.7)	<0.001	<0.001	0.003	0.026	0.309	0.081	0.463
Day 15 - 21	203 -18.3(1.8)	192 -25.9(2.0)	201 -24.9(2.0)	200 -22.9(1.8)	0.008	0.002	0.006	0.060	0.667	0.197	0.383
Day 22 - 28	203 -19.2(2.0)	191 -29.1(2.1)	197 -27.3(2.0)	198 -24.8(1.9)	<0.001	<0.001	0.001	0.031	0.431	0.071	0.305
Sneezing											
Day -6 - 0[5]	210 27.1(1.9)	208 28.6(1.9)	211 29.1(1.9)	208 25.4(1.7)	0.477	0.450	0.379	0.627	0.905	0.216	0.173
Day 1 - 7	210 -4.5(1.2)	204 -10.5(1.3)	207 -9.4(1.3)	205 -8.4(1.2)	0.003	<0.001	0.003	0.023	0.536	0.208	0.519
Day 8 - 14	208 -7.7(1.4)	200 -13.6(1.6)	204 -11.6(1.5)	204 -11.4(1.4)	0.027	0.003	0.048	0.068	0.322	0.253	0.879
Day 15 - 21	203 -9.2(1.5)	192 -14.2(1.7)	201 -13.0(1.5)	200 -12.1(1.5)	0.097	0.017	0.062	0.176	0.583	0.293	0.611
Day 22 - 28	203 -9.2(1.6)	191 -15.8(1.7)	197 -13.9(1.6)	198 -12.1(1.6)	0.022	0.003	0.034	0.219	0.383	0.080	0.376

[1] Symptom scores are based on visual analogue scale from 0 (absent) to 100 (most severe).
[2] FP50 = Fluticasone Propionate 50mcg twice daily
FP100 = Fluticasone Propionate 100mcg twice daily
FP200 = Fluticasone Propionate 200mcg twice daily
[3] P-values at pre-treatment are based on mean scores at baseline, and at subsequent visits p-values are based on mean absolute change from baseline using the F-test. The following linear model was fitted: mean change = trmt invid invid*trmt. No significant investigator by treatment interactions were observed.
[4] Total Nasal Symptom Score = Nasal Obstruction + Postnasal Drip + Rhinorrhea
[5] Days -6 through 0 represent the pre-treatment period.

Summary of Patient-Rated Symptom Scores[1]
P.M. Symptoms - Mean Absolute Change From Baseline

	Placebo n Mean(SE)	FP50 BID [2] n Mean(SE)	FP100 BID [2] n Mean(SE)	FP200 BID [2] n Mean(SE)	Over-all	Pla vs 50[3]	Pla vs 100[3]	Pla vs 200[3]	50 vs 100[3]	50 vs 200[3]	100 vs 200[3]
Total Patients at Screening	210	208	211	208							
Total Nasal Symptom Score[4]											
Day -6 - 0[5]	210 203.9(2.9)	208 207.6(3.0)	211 207.4(3.2)	207 203.6(2.8)	0.573	0.283	0.321	0.943	0.931	0.317	0.359
Day 1 - 7	210 -36.1(3.6)	204 -54.9(4.0)	207 -52.7(4.0)	205 -48.3(3.9)	0.002	<0.001	0.001	0.021	0.708	0.212	0.380
Day 8 - 14	208 -51.6(4.6)	201 -75.2(4.8)	204 -73.1(5.0)	204 -71.4(4.5)	<0.001	<0.001	<0.001	0.002	0.744	0.571	0.809
Day 15 - 21	203 -60.1(4.3)	192 -82.4(5.2)	201 -78.1(5.1)	202 -81.3(4.7)	0.001	<0.001	0.005	0.001	0.479	0.776	0.667
Day 22 - 28	203 -64.2(4.8)	191 -90.8(5.2)	197 -87.2(5.3)	198 -87.8(5.0)	<0.001	<0.001	<0.001	<0.001	0.586	0.523	0.925
Nasal Obstruction											
Day -6 - 0[5]	210 68.2(1.4)	208 71.5(1.4)	211 68.7(1.6)	207 69.4(1.5)	0.474	0.140	0.808	0.578	0.216	0.359	0.753
Day 1 - 7	210 -10.2(1.3)	204 -18.3(1.5)	207 -16.8(1.6)	205 -16.6(1.5)	<0.001	<0.001	0.001	0.002	0.536	0.424	0.855
Day 8 - 14	208 -15.6(1.7)	201 -25.9(1.8)	204 -23.0(1.9)	204 -24.4(1.7)	<0.001	<0.001	0.002	<0.001	0.255	0.557	0.580
Day 15 - 21	203 -17.2(1.7)	192 -27.4(2.1)	201 -23.7(1.9)	202 -27.8(1.8)	<0.001	<0.001	0.017	<0.001	0.141	0.945	0.118
Day 22 - 28	203 -19.1(1.9)	191 -29.8(2.1)	197 -26.7(2.1)	198 -30.1(1.9)	<0.001	<0.001	0.007	<0.001	0.284	0.998	0.281
Postnasal Drip											
Day -6 - 0[5]	210 73.2(1.3)	208 72.7(1.4)	211 73.0(1.3)	207 71.8(1.3)	0.869	0.811	0.946	0.444	0.863	0.600	0.485
Day 1 - 7	210 -13.0(1.3)	204 -17.3(1.5)	207 -16.7(1.5)	205 -16.1(1.5)	0.152	0.038	0.063	0.131	0.819	0.568	0.731
Day 8 - 14	208 -18.5(1.7)	201 -23.7(1.8)	204 -24.1(1.9)	204 -24.0(1.8)	0.075	0.045	0.027	0.029	0.844	0.868	0.975
Day 15 - 21	203 -21.4(1.8)	192 -26.6(2.0)	201 -26.2(1.9)	202 -27.3(1.8)	0.089	0.047	0.054	0.024	0.929	0.812	0.740
Day 22 - 28	203 -23.0(1.9)	191 -29.5(2.0)	197 -30.3(2.0)	198 -29.3(2.0)	0.021	0.014	0.005	0.026	0.747	0.800	0.562
Rhinorrhea											
Day -6 - 0[5]	210 62.5(1.7)	208 63.4(1.8)	211 65.6(1.6)	207 62.4(1.7)	0.426	0.462	0.123	0.810	0.424	0.620	0.195
Day 1 - 7	210 -12.8(1.4)	204 -19.3(1.6)	207 -19.1(1.6)	205 -15.6(1.5)	0.003	0.001	0.002	0.153	0.884	0.073	0.098
Day 8 - 14	208 -17.2(1.8)	201 -25.6(1.9)	204 -26.0(1.9)	204 -23.0(1.7)	<0.001	<0.001	<0.001	0.014	0.946	0.280	0.249
Day 15 - 21	203 -21.2(1.6)	192 -28.4(2.0)	201 -28.2(1.9)	202 -26.1(1.8)	0.006	0.002	0.003	0.033	0.820	0.291	0.401
Day 22 - 28	203 -22.1(1.8)	191 -31.5(2.1)	197 -30.2(1.9)	198 -28.3(1.9)	<0.001	<0.001	0.001	0.014	0.523	0.149	0.417
Sneezing											
Day -6 - 0[5]	210 30.3(1.9)	208 31.5(1.9)	211 32.9(1.8)	207 29.8(1.7)	0.593	0.534	0.252	0.969	0.603	0.510	0.238
Day 1 - 7	210 -4.1(1.2)	204 -10.4(1.4)	207 -10.1(1.3)	205 -8.8(1.2)	<0.001	<0.001	<0.001	0.006	0.868	0.345	0.434
Day 8 - 14	208 -6.6(1.4)	201 -13.9(1.6)	204 -12.9(1.6)	204 -12.7(1.4)	0.001	<0.001	0.002	0.003	0.594	0.537	0.933
Day 15 - 21	203 -9.4(1.4)	192 -15.0(1.8)	201 -14.2(1.6)	202 -14.1(1.6)	0.032	0.008	0.022	0.027	0.689	0.633	0.939
Day 22 - 28	203 -9.6(1.6)	191 -17.1(1.8)	197 -15.5(1.6)	198 -15.3(1.6)	0.005	<0.001	0.008	0.012	0.455	0.374	0.887

[1] Symptom scores are based on visual analogue scale from 0 (absent) to 100 (most severe).
[2] FP50 BID = Fluticasone Propionate 50mcg twice daily
FP100 BID = Fluticasone Propionate 100mcg twice daily
FP200 BID = Fluticasone Propionate 200mcg twice daily
[3] P-values at pre-treatment are based on mean scores at baseline, and at subsequent visits p-values are based on mean absolute change from baseline using the F-test. The following linear model was fitted: mean change = trmt invid invid*trmt. No significant investigator by treatment interactions were observed.
[4] Total Nasal Symptom Score = Nasal Obstruction + Postnasal Drip + Rhinorrhea.
[5] Days -6 through 0 represent the pre-treatment period.

Summary of Clinician-Rated Symptom Scores[1]
Mean Absolute Change From Baseline

	Placebo n Mean(SE)	FP50 BID [2] n Mean(SE)	FP100 BID [2] n Mean(SE)	FP200 BID [2] n Mean(SE)	Over-all	Pla vs 50[3]	Pla vs 100[3]	Pla vs 200[3]	50 vs 100[3]	50 vs 200[3]	100 vs 200[3]
Total Subjects at Screening	210	208	211	208							
Total Nasal Symptom Scores[4]											
Baseline	210 193.8(3.3)	207 202.1(3.3)	210 200.2(3.3)	208 197.6(3.5)	0.273	0.073	0.116	0.367	0.820	0.372	0.503
Day 14	204 -48.9(5.0)	192 -71.0(5.4)	198 -68.6(5.1)	198 -59.6(5.2)	0.006	0.003	0.003	0.160	0.917	0.106	0.128
Day 28	199 -56.8(4.9)	187 -85.5(5.5)	196 -70.7(5.4)	194 -79.6(5.7)	<0.001	<0.001	0.040	0.002	0.039	0.334	0.268
Nasal Obstruction											
Baseline	210 64.3(1.6)	207 69.3(1.4)	210 67.3(1.4)	208 67.8(1.4)	0.067	0.011	0.125	0.049	0.302	0.555	0.658
Day 14	204 -14.7(1.9)	192 -25.3(2.1)	198 -20.2(1.9)	198 -21.7(2.1)	0.002	<0.001	0.040	0.012	0.094	0.217	0.655
Day 28	199 -16.4(2.0)	187 -29.3(2.0)	196 -22.6(2.0)	194 -28.0(2.2)	<0.001	<0.001	0.021	<0.001	0.013	0.626	0.043
Postnasal Drip											
Baseline	210 70.5(1.5)	207 70.6(1.6)	210 70.8(1.5)	208 69.4(1.5)	0.817	0.937	0.840	0.476	0.780	0.528	0.361
Day 14	204 -19.3(2.1)	192 -23.0(2.2)	198 -23.9(2.1)	198 -18.8(2.1)	0.146	0.264	0.087	0.739	0.567	0.151	0.043
Day 28	199 -22.0(2.0)	187 -27.5(2.2)	196 -24.7(2.1)	194 -25.9(2.3)	0.236	0.042	0.304	0.210	0.306	0.426	0.820
Rhinorrhea											
Baseline	210 59.0(1.9)	207 62.2(1.7)	210 62.1(1.7)	208 60.4(1.9)	0.470	0.210	0.152	0.514	0.863	0.546	0.436
Day 14	204 -14.8(2.2)	192 -22.8(2.3)	198 -24.4(2.1)	198 -19.0(2.2)	0.006	0.012	0.001	0.193	0.471	0.217	0.049
Day 28	199 -18.4(2.2)	187 -28.6(2.4)	196 -23.4(2.3)	194 -25.7(2.3)	0.009	<0.001	0.083	0.022	0.106	0.293	0.570

[1] Symptom scores are based on visual analogue scale from 0 (absent) to 100 (most severe).
[2] FP50 BID = Fluticasone Propionate 50mcg twice daily
FP100 BID = Fluticasone Propionate 100mcg twice daily
FP200 BID = Fluticasone Propionate 200mcg twice daily
[3] P-values at pre-treatment are based on mean scores at baseline, and at subsequent visits p-values are based on mean absolute change from baseline using the F-test. The following linear model was fitted: mean change = trmt invid invid*trmt. No significant investigator by treatment interactions were observed.
[4] Total Nasal Symptom Score = Nasal Obstruction + Postnasal Drip + Rhinorrhea.

Overall Clinician Evaluation
All Investigators

	Placebo	FP50 BID [1]	FP100 BID [1]	FP200 BID [1]	Overall	Pla vs 50[2]	Pla vs 100[2]	Pla vs 200[2]	50 vs 100[2]	50 vs 200[2]	100 vs 200[2]
Number of Patients at Baseline	210	208	211	208							
Number of Evaluable Patients	208	203	205	204							
Patient Response to Treatment[3]					0.027	0.074	0.223	<0.001	0.993	0.283	0.297
Significant Improvement	21 (10%)	33 (16%)	32 (16%)	36 (18%)							
Moderate Improvement	46 (22%)	52 (26%)	56 (27%)	54 (26%)							
Mild Improvement	58 (28%)	57 (28%)	57 (28%)	73 (36%)							
No Change	73 (35%)	48 (24%)	50 (24%)	33 (16%)							
Mildly Worse	7 (3%)	6 (3%)	5 (2%)	2 (<1%)							
Moderately Worse	1 (<1%)	5 (2%)	3 (1%)	5 (2%)							
Signficantly Worse	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)							

[1] FP50 BID = Fluticasone Propionate 50mcg twice daily
FP100 BID = Fluticasone Propionate 100mcg twice daily
FP200 BID = Fluticasone Propionate 200mcg twice daily
[2] P-values based on the Cochran-Mantel-Haenszel test controlling for investigator.
[3] Percentages are based on the number of evaluable patients.

NON-ALLERGIC PERENNIAL RHINITIS (Supportive Trial):

8.2. Protocol No. FLN 351: A double-blind, randomized, placebo-controlled study of the efficacy and safety of fluticasone propionate aqueous nasal spray bid vs. placebo for 4 weeks in patients with perennial non-allergic rhinitis.

Principal Investigator: None, multi-center study.

Participating Centers: 12 U.S. centers.

8.2.1 Objectives

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

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

8.2.2. Study Design

The study was a phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group, with a 4-14 day placebo lead-in, safety and efficacy study of fluticasone propionate nasal spray (FP) 100 μg bid, vs. fluticasone propionate nasal spray (FP) 200 μg bid, and vs. placebo nasal spray bid given for a duration of 28 days (4 weeks) for the treatment of NAPR in patients 12 years of age and older. The 4 week double-blind treatment period was followed by a post-treatment assessment at the day 36 visit [NDA 20-121, S-009, 21:17, 129, 133].

The study consisted of a total of 7 patient visits: a screening visit (visit 1, day -14 to 0), visit 1 or 'the first day of the double-blind treatment period' (baseline visit, day 1), visit 2 (day 8), visit 3 (day 15 ± 2 days), and visit 4 (day 22 ± 2 days), visit 5 (day 29, the last day of the double-treatment period), and visit 6 (day 36, the post-treatment follow-up visit) [NDA 20-121, S-009, 21:52, 129, 133]. Patients were evaluated in clinic from between 6:30 a.m.-9:30 a.m. for each study visit. The duration of the study for a given patient was approximately 4 weeks. A flow chart of FLN 351 is provided in Appendix I (attached) [NDA 20-121, S-009, 21:52, 130].

8.2.3. Protocol

8.2.3.1.a. Population: Male or female patients, ≥ 12 years of age, with NAPR defined by the inclusion criteria listed below [NDA 20-121, S-009, 21:20-21, 129, 133].

(I) Inclusion Criteria [NDA 20-121, S-009, 21:20-21, 133-134]:

1. Diagnosis of NAPR as defined by the following criteria:
   (a) appearance of the nasal mucosa consistent with a diagnosis of rhinitis (specific criteria for this diagnosis were not provided in the protocol).
   (b) evidence of a negative skin test at screening to a comprehensive panel of seasonal and perennial allergens via the [redacted] method (positive response defined as wheal diameter > 2 mm than the negative control) in order to fulfill the diagnosis of non-allergic perennial rhinitis (NAPR). Of note, in preparation for skin testing, patients were not to have used antihistamines for at least 72 hours, astemizole for at least 12 weeks prior to the skin test and loratadine for at least 7 days prior to the skin test,
   (c) total serum IgE levels within normal limits for the contract laboratory (i.e. < 250 IU/mL).

2. A morning (a.m.) plasma cortisol level of at least 5 µg/dL on screening. If the a.m. plasma cortisol level was found to be > 40 µg/dL, enrollment was allowed only if the patient was taking birth control pills or hormonal replacement therapy.

3. The patient's self-rated severity of disease at baseline (visit 1, day 1) would need to meet the entry criteria of: a patient-rated total nasal symptom score (TNSS=nasal obstruction, rhinorrhea, postnasal drip, and sneezing) of ≥ 150 points out of a maximum total of 400 points, based on a visual analog rating scale for the **daily** TNSS for at least 4 out of 7 consecutive days immediately prior to receiving double-blind study medication. (This score was supposed to represent symptoms throughout the previous 24 hours, i.e. were to be scored reflectively by patients in the p.m. prior to dosing with study medication). In addition, on those 4 days, severity of at least 1 of the 4 symptoms was to be at least 50 out of 100 possible points.

Reviewer's Notes: Similar to the pivotal NAPR study FLTA 3010, specific criteria for the diagnosis of rhinitis were not provided in terms of nasal mucosal appearance, as was not provided information regarding the diluent used for the negative control in skin testing, nor the specific allergens tested. In addition, in this study sneezing was included in the TNSS score for study entry (compared to FLTA 3010), changing the maximum total score to 400 and not 300 [NDA 20-121, S-009, 21:21, 134].