

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 20-121/S009**

**PHARMACOLOGY REVIEW(S)**

**DIVISION OF PULMONARY DRUG PRODUCTS**  
**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**  
**Label Review**

**NDA:** 20-121, S-009

**Date of Submission:** 12/17/98

**Information to be Conveyed to Sponsor:** Yes (X), No ( )

**Reviewer:** Lawrence F. Sancilio, Ph.D.

**Date Review Completed:** 11/5/98

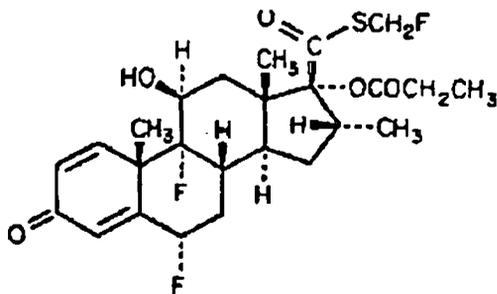
**Sponsor:** Glaxo Inc.  
5 Moore Drive  
Research Triangle Park, NC 27709

**Drug Name:** Fluticasone propionate

**Chemical Name:** S-fluoromethyl 6, 9 -difluoro-11 -hydroxy-16 - methyl-3-oxo- 17 - propionyloxyandrosta-1,4-diene-17 -carbothioate

**CAS No.** 80474-14-2

**Structure:**



**Molecular Weight and Formula:** 500.6 (C<sub>25</sub>H<sub>21</sub>F<sub>3</sub>O<sub>5</sub>S)

**Class:** Glucocorticoid

**Indication:** Management of non-allergic perennial allergic rhinitis in patients 4-11 years old and adults.

**Formulation:** Aqueous suspension of [redacted] microfine fluticasone propionate containing microcrystalline [redacted] carboxymethylcellulose sodium, dextrose, 0.02% benzalkonium chloride, polysorbate 80 and 0.25% w/w phenylethyl alcohol.

**Route of Administration and Maximum Daily Dose:** 200 mcg intranasally.

### Summary and Evaluation

This supplement of ND A20-121 is for fluticasone propionate to be administered by nasal inhalation as a spray for the management of perennial non-allergic rhinitis in patients 4-11 years old and in adults. The maximum human daily intranasal dose is 200-mcg day. This formulation of fluticasone propionate has already been approved for this indication in adults. The Pharmacology and Toxicology of fluticasone propionate have been studied in depth (see the review of the pharmacologic and toxicologic studies submitted in the original NDA and in NDA 20-770).

### Labeling Review

Changes are in **BOLD** and deletions are ~~strikeout~~.

***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg (approximately 20 times the maximum recommended daily intranasal dose in adults and approximately 10 times the maximum recommended daily intranasal dose in children on a mcg/m<sup>2</sup> basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults and approximately equivalent to the maximum recommended daily intranasal dose in children on a mcg/m<sup>2</sup> basis ) for 104 weeks.

Fluticasone propionate did not induce gene mutation.....

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses to 50 mcg/kg (approximately 2 times the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

***Pregnancy: Teratogenic Effects: Pregnancy Category C:*** Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively, (approximately equivalent to and 4 times, respectively, the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis) revealed.....

In the rabbit, fetal weight and cleft palate were observed at a subcutaneous dose of 4 mcg/kg [redacted] less than the maximum recommended daily intranasal dose in adults on a

mcg/m<sup>2</sup> basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 25 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) of fluticasone propionate.

Fluticasone propionate crossed the placenta following oral administration of 100 mcg/kg to rats and 300 mcg/kg to rabbits (approximately 4 and 25 times, respectively, the maximum recommended daily intranasal dose in adults on a mcg/m<sup>2</sup> basis)

**Nursing Mothers:** It is not known whether fluticasone propionate is excreted in human breast milk. [redacted] at a subcutaneous dose of 10 mcg/kg in rats [redacted] less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

**Overdosage:**

The oral and subcutaneous median lethal doses in mice and rats were > 1,000 mg/kg [redacted] > 20,000 and > 41,000 times, respectively, the maximum recommended daily intranasal dose in adults and [redacted] > 10,000 and > 20,000 times, respectively, the maximum recommended daily intranasal dose in children on a mg/m<sup>2</sup> basis).

**RECOMMENDATIONS**

This NDA is for fluticasone propionate to be administered intranasally by inhalation for the treatment of non-allergic rhinitis in children and adults. From a preclinical standpoint, this NDA supplement is approvable.

The proposed changes in the label for the preclinical areas are recommended.

[redacted] /S/

Lawrence F. Sancilio, Ph.D.  
Pharmacologist/Toxicologist

[redacted] /S/

NOV, 5, 1998

- cc. /Division File, NDA 20-121 HFD-570
- /RMeyer, HFD-570
- /C.S.O., HFD-570
- /LFSancilio, HFD-570
- /JSun, HFD-570

Approved by J. Sun

**ATTACHMENT**

Drug: **Flonase 0.05%**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	Factor	mg/m <sup>2</sup>
Pediatric dose	4	0.2	1	0.2	16	0.0125	24	0.3
Adult dose	adult	0.2	1	0.2	50	0.004	37	0.148

	route	mg/kg/day	factor	mg/m <sup>2</sup>	Dose Ratio		Rounded Dose Ratio	
					Adults	Children		
<u>Carcinogenicity:</u>								
mouse	po	1	3	3	20.3	10.0	20	10
rat	po	0.057	6	0.342	2.3	1.1	2	1
rat	po		6	0	0.0	0.0	—	—
rat	po		6	0	0.0	0.0	—	—
hamster			4	0	0.0	0.0	—	—
extra			20	0	0.0	0.0	—	—
<u>Reproduction and Fertility:</u>								
mouse			3	0	0.0	0.0	—	—
rat	sc	0.05	6	0.3	2.0	1.0	2	1
extra			20	0	0.0	0.0	—	—
<u>Teratogenicity:</u>								
mouse	sc	0.045	3	0.135	0.9	0.5	1/1	1/2
mouse	po		3	0	0.0	0.0	—	—
mouse	po		3	0	0.0	0.0	—	—
mouse	sc		6	0	0.0	0.0	—	—
rat	sc	0.01	6	0.06	0.4	0.2	1/2	1/5
rat	sc	0.1	6	0.6	4.1	2.0	4	2
rabbit	po	0.3	12	3.6	24.3	12.0	25	10
rabbit	sc	0.004	12	0.048	0.3	0.2	1/3	1/6
<u>Overdosage:</u>								
mouse	po	1000	3	3000	20270.3	10000.0	20000	10000
rat	sc	1000	6	6000	40540.5	20000.0	41000	20000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-121/S009

STATISTICAL REVIEW(S)

Hilfiker, D

Statistical Review and Evaluation

NDA#: 20-121/S-009

AUG 3 1998

APPLICANT: Glaxo Wellcome Inc.

NAME OF DRUG: Flonase Nasal Spray

INDICATION: Perennial Nonallergic Rhinitis

DOCUMENTS REVIEW: Volumes 32.1, 32.3-33.31 dated December 17, 1997.  
Volumes dated February 4, 1998 and February 12, 1998.  
Datafiles were supplied in the December 17, 1997 and  
February 4, 1998 submissions.

This review pertains to three studies in nonallergic perennial rhinitis (NAPR) and two studies in perennial allergic rhinitis (PAR) where once a day dosing was used.

The medical officer for this submission is A. Worobec, MD (HFD-570) with whom this review was discussed.

**I. Background**

Flonase was approved for seasonal and perennial allergic rhinitis on October 19, 1994, and an efficacy supplement for the pediatric population (age 4 and above) for SAR and PAR was approved on October 31, 1997. The pilot drug division at that time concluded that they did not have adequate information for the NAPR indication. A 200mcg QD dose (two 50mcg sprays per nostril) was approved as the starting dose with the potential of decreasing the dosage to 100mcg QD. It was mentioned in the label that the 100mcg BID dose was also effective.

The original datafiles for this submission contained patient diary data, whereas the submission reported the analyses of weekly means. This reviewer requested a set of derived data (weekly means including baseline means) for studies FLTA3010, FLN-350, and FLN-351, plus derived data from patient assessments for studies FLN-310 and FLN-311. In reviewing data analyses from SAS datafiles supplied with the submission, this reviewer was not able to duplicate the analyses of Studies FLN-351 and FLTA3010 in the submission. The sponsor provided new datafiles in their February 4, 1998 submission and corrected tables for studies FLN-351 and FLTA3010. This reviewer requested clinician assessments for Studies FLN-310 and FLN-311, which the sponsor provided in their February 12, 1998 submission.

Study FLN-350 was a very small study having about 23 per treatment group. Study FLN-351 had about 95 patients per treatment group, which was only slightly smaller than the

PAR studies that demonstrated efficacy for that indication. Study FLTA 3010 was a large study having over 200 patients per treatment group.

The sponsor is using the Points to Consider document on Clinical Development Programs for New Nasal Spray Formulations (January 1996) to extrapolate to QD dosing for NAPR from the efficacy of QD dosing in PAR studies FLN-310 and FLN-311. The NAPR studies only used BID dosing.

## **II. Study FLN-350**

### **A. Study Description and Method of Analysis**

This was a single center, double-blind, parallel group study comparing Flonase 100mcg BID, Flonase 200mcg BID and placebo with a 4 week treatment period preceded by a 4 to 14 day run-in period. Flonase will be frequently denoted by FP throughout this review.

The patient assessed nasal symptoms (nasal obstruction, rhinorrhea, postnasal drip, and sneezing) daily in the evening covering the whole day of treatment. They also rated their nasal obstruction in the morning (A.M. nasal obstruction) on awakening. These scores were assessed on a visual analog scale from 0 (absent) to 100 (most severe). A total nasal symptom score, TNSS, was formed by adding the evening scores of nasal obstruction, rhinorrhea and postnasal drip.

To enter the study the TNSS had to be at least 150 out of 300 possible points for at least 4 of the 7 consecutive days immediately preceding double-blind treatment, and, in addition, severity of at least two of the three symptoms making up TNSS had to be at least 40 out of 100 on those 4 days.

Weekly averages were found for each symptom and TNSS. The last 7 days of the run-in period was used to calculate the baseline score for each symptom.

Changes from baseline in patient weekly symptom scores and TNSS were analyzed by an analysis of variance with treatments as the only factor. The protocol and the statistical appendix mentioned that pairwise comparisons would be interpreted in the presence of a significant overall F-test.

The sponsor also obtained clinician symptom assessments at clinic visits. The analyses of these for the NAPR studies will not be discussed in this review because the patient symptom assessments are considered more relevant. Clinician assessments will be discussed in PAR studies FLN-310 and FLN-311.

The clinician completed an overall clinical evaluation of patient's response to therapy using the following scale: (3= significant improvement, 2= moderate improvement, 1= mild improvement, 0=no change, -1= mildly worse, -2=moderately worse, -3=

significantly worse). [The numeric values were assigned by the sponsor at the analysis stage.]

The protocol sized the study using overall clinical evaluation. The protocol stated that 35 to 40 patients per treatment group were needed to detect a difference of 0.87, with power=85% and a significance level of 0.05. The sponsor analyzed overall clinical evaluation using the Cochran-Mantel-Haenszel test. [The overall clinical evaluation will be discussed only for study FLN-350, because here they sized the study with respect to that parameter which gives that parameter more weight.]

### **B. Results**

There were 68 patients (23 on placebo, 23 on FP100mcg BID and 22 on FP200mcg BID) who were randomized into the study. Four patients (2 placebo, 1 FP100mcg BID, and 1 FP200mcg BID) withdrew prematurely. The treatment groups were comparable in demographic variables except for years of nonallergic rhinitis with higher percentages of patients having NAPR over 10 years in the placebo (70%) and FP200mcg BID (68%) groups than the FP100mcg BID group (30%).

Table 1 shows the weekly mean changes from baseline and p-values comparing treatments for TNSS, nasal obstruction, and A.M. nasal obstruction. The results for the other symptoms are not given because they were not significantly different from placebo at any week. Some suggestion of efficacy was seen for the TNSS at Day 1-7, Day 8-14, and Day 15-21. [None of these are significant by the sponsor's criteria that the overall F-test had to be significant to declare the pairwise comparisons significant.] If the criterion that the overall F-test must be significant to test pairwise comparisons is used, then only the Day 1-7 nasal obstruction comparison of placebo and FP100mcg BID is significant.

The sponsor found a significant difference in overall clinical evaluation favoring FP100mcg BID over placebo ( $p=0.004$ ) but not for FP200mcg BID ( $p=0.150$ ).

### **C. Reviewer's Comments**

This study has failed to demonstrate efficacy in patient's rated TNSS, which is the usual primary variable in rhinitis studies. It did show effectiveness in overall clinical evaluation, although only the lower dose was significant.

The study was sized too small for symptom scores. It is interesting to note that such a small study could show effectiveness for FP100mcg BID for overall clinical evaluation but, even then, it was too small since effectiveness for FP200mcg BID was not demonstrated.

### **III. Study FLN-351**

#### **A. Study Design and Method of Analysis**

This study was similar to study FLN-350 with the following important differences: It was a larger multicenter (12 centers) study and, as such, the ANOVA for patient rated symptoms included factors for treatment, center and treatment by center interaction. The sponsor sized this study using TNSS. [The protocol stated that sneezing would be included in TNSS but the sponsor's analyses used the same definition as Study FLN-350.] To enter the study the patient's revised TNSS had to be at least 150 out of 400 possible points for at least 4 of the 7 consecutive days immediately preceding double-blind treatment, and, in addition, severity of at least one of the four symptoms making up revised TNSS had to be at least 50 out of 100 on those 4 days.

#### **B. Results**

There were 286 patients (93 on placebo, 98 on FP100mcg BID and 95 on FP200mcg BID) who were randomized into the study. Twelve patients (5 placebo, 4 FP100mcg BID, and 3 FP200mcg BID) withdrew prematurely. The treatment groups were comparable in demographic variables.

Table 2 shows the weekly mean changes from baseline and p-values comparing treatments for TNSS, nasal obstruction, and A.M. nasal obstruction. The results for the other symptoms are not given because they were not significantly different from placebo at any week. Using the sponsor's rule that the overall F-test must be significant to declare the pairwise p-values significant, then only at Day 15-21 was the FP200mcg BID dose significantly different from placebo for TNSS. [The pairwise p-values were significant at other times for this dose, but the overall p-value was not significant.] For nasal obstruction both doses of FP were significant at Day 8-14, Day 15-21 and Day 22-28. For A.M. nasal obstruction, FP100mcg BID was significantly better than placebo at Day 8-14 and Day 22-28. The FP200mcg BID dose was significant at all 4 treatment weeks.

#### **C. Reviewer's Comments**

This study failed to demonstrate efficacy for TNSS, the primary efficacy variable. Effectiveness at only one of four weeks after adjusting for multiple treatment doses is not adequate evidence of effectiveness for TNSS in NAPR patients. However the study did demonstrate efficacy for nasal obstruction.

### **IV. Study FLTA3010**

#### **A. Study Design and Method of Analysis**

This study was similar to study FLN-350 with the following important differences:

The sponsor dropped the requirement that two of the three symptoms making up TNSS had to be 40 or more on the 4 days of baseline. Symptoms were measured in the A.M. as well as the P.M., covering the whole night and whole day, respectively. This study included a FP50mcg BID group in addition to the other treatments. The large sample size of this study should provide adequate power to detect differences from placebo if such differences exist.

## **B. Results**

Table 3 presents the treatment means and p-values comparing treatment means with placebo for TNSS, both A.M. and P.M. All doses of Flonase were significantly different from placebo. (The overall p-value comparing all treatments was always significant and therefore it is justifiable to do pairwise comparisons.) No dose response is apparent for TNSS. Effectiveness was generally seen in all components of TNSS and sneezing.

## **C. Reviewer's Comments**

The sponsor mentioned that multivariate methods would be used to analyze the three nasal symptoms. The sponsor did not provide any multivariate analysis. This reviewer thinks that the analysis of TNSS is a meaningful way to create a univariate analysis from the three different symptoms.

This study has adequately demonstrated efficacy for both FP100mcg BID and FP200mcg BID. Although FP50mcg BID was, also, shown to be effective in this study, confirmatory evidence would be needed to approve that dose.

## **V. PAR Studies**

These studies were reviewed by the Pilot Drug Division when Flonase was approved for PAR. That division found both FP100mcg BID and FP200mcg QD effective and approved a QD dosing for Flonase for the treatment of PAR. This review will focus on a few issues that were not adequately discussed in the review of the PAR studies, in particular, analyses that address the issue of comparability of BID and QD dosing of Flonase. Patients rated A.M. nasal obstruction at the end of dosing interval for both dosing regimens. Clinician-rated symptoms at weeks 4, 12 and 24 are at end of dosing interval because only on those days did the protocol specify that the patient was not to take the morning dose because pre-dose assessments were made of A.M. plasma cortisol after which an ACTH Stimulation test was performed. [The protocol did not adequately specify that clinician's assessments were pre-dose. This reviewer assumes that they were pre-dose.] This review will not discuss the results for beclomethasone, which was included in Study FLN-311. TNSS in these studies also included sneezing.

Tables 4 and 5 present the p-values comparing treatments for patient-rated A.M. nasal obstruction and clinician-rated TNSS in Study FLN-310 and FLN-311, respectively. The p-values of on-treatment comparisons with placebo come from an analysis of variance on

changes from baseline with treatments and investigators as factors and baseline as covariate. These analyses show both treatments were effective at the end of dosing interval with a suggestion that FP100mcg BID was slightly more effective. Significantly more efficacy for FP100mcg BID over FP200mcg QD was only seen at the early weeks for A.M. nasal obstruction. [This reviewer duplicated the sponsor's analyses.]

**VI. Overall Comments**

Study FLTA3010 showed both FP100mcg BID and FP200mcg BID to be effective doses in all symptoms and TNSS in NAPR patients. Study FLN-351 showed effectiveness in nasal obstruction and A.M. nasal obstruction, but not TNSS.

The analyses of patient-rated A.M. nasal obstruction and clinician-rated TNSS at Weeks 4, 12, and 24 show that both FP100mcg BID and FP200mcg QD show end of dosing interval efficacy in PAR patients with slightly more efficacy for the BID dose.

These studies show that the nonallergic perennial rhinitis indication can be added to the label with the same dosage recommendation as perennial allergic rhinitis.

**/S/**  
James Gebert, Ph.D.  
Mathematical Statistician

Concur: Dr. Wilson **/S/** 7/21/98  
Dr. Nevius **/S/** 8/31/98

This review contains 6 pages of text and 5 pages of tables.

CC:

- Archival NDA 20-121/S-009
- HFD-570
- HFD-570/Dr. Worobec
- HFD-570/Mr. Hilfiker ✓
- HFD-715/Div. File, Chron
- HFD-715/Dr. Gebert
- HFD-715/Dr. Wilson

**APPEARS THIS WAY  
ON ORIGINAL**

Table 1  
Study FLN-350  
Mean changes from baseline

	Placebo		FP100 BID		FP200 BID		P-Value		
	N	Mean	N	Mean	N	Mean	Overall	P vs FP100	P vs FP200
<b>TNSS</b>									
Baseline	23	205.4	23	204.6	22	205.5	0.996	0.938	0.997
Day 1-7	23	-23.1	23	-56.3	22	-38.7	0.104	0.034	0.317
Day 8-14	23	-39.9	23	-86.6	22	-71.6	0.075	0.026	0.131
Day 15-21	22	-57.3	23	-109	22	-74.0	0.090	0.033	0.491
Day 22-28	22	-69.5	23	-108	21	-81.0	0.279	0.121	0.648
<b>Nasal Obstruction</b>									
Baseline	23	68.1	23	67.1	22	66.9	0.977	0.867	0.843
Day 1-7	23	-5.8	23	-24.1	22	-11.3	0.011	0.003	0.372
Day 8-14	23	-13.0	23	-30.7	22	-22.0	0.068	0.021	0.237
Day 15-21	22	-18.9	23	-36.7	22	-23.0	0.094	0.039	0.640
Day 22-28	22	-23.9	23	-36.5	21	-28.1	0.315	0.137	0.626
<b>A.M. Nasal Obstruction</b>									
Baseline	23	70.3	23	66.6	22	71.6	0.702	0.546	0.836
Day 1-7	23	-3.4	23	-17.3	22	-13.6	0.073	0.027	0.107
Day 8-14	23	-11.8	23	-28.0	22	-24.3	0.104	0.043	0.119
Day 15-21	22	-16.9	23	-31.1	22	-27.2	0.263	0.114	0.252
Day 22-28	22	-23.5	23	-32.4	21	-32.0	0.524	0.311	0.344

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ON ORIGINAL

Table 2  
Study FLN-351  
Mean changes from baseline

	Placebo		FP100 BID		FP200 BID		P-Value		
	N	Mean	N	Mean	N	Mean	Overall	P vs FP100	P vs FP200
<b>TNSS</b>									
Baseline	92	181.4	98	181.7	95	185.1	0.751	0.935	0.492
Day 1-7	92	-33.7	98	-35.1	94	-44.1	0.309	0.824	0.157
Day 8-14	92	-45.6	98	-58.7	94	-64.9	0.053	0.095	0.018
Day 15-21	89	-52.2	97	-63.0	94	-75.0	0.038	0.185	0.011
Day 22-28	88	-61.2	95	-70.8	92	-80.2	0.138	0.266	0.047
<b>Nasal Obstruction</b>									
Baseline	92	58.4	98	62.7	95	59.9	0.315	0.134	0.583
Day 1-7	92	-9.8	98	-14.6	94	-15.9	0.061	0.066	0.027
Day 8-14	92	-12.8	98	-21.6	94	-21.4	0.004	0.003	0.006
Day 15-21	89	-14.8	97	-22.2	94	-24.6	0.013	0.024	0.005
Day 22-28	88	-16.9	95	-25.4	92	-26.3	0.014	0.013	0.010
<b>A.M. Nasal Obstruction</b>									
Baseline	92	62.6	98	64.4	95	65.3	0.639	0.516	0.356
Day 1-7	92	-7.1	98	-10.1	94	-14.0	0.030	0.204	0.008
Day 8-14	92	-10.4	98	-18.3	94	-20.8	0.002	0.008	<0.001
Day 15-21	90	-13.2	97	-18.6	94	-25.6	0.002	0.089	<0.001
Day 22-28	88	-14.9	95	-22.2	92	-27.2	0.005	0.039	0.001

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 3**  
**Mean Changes from baseline and p-values compared to placebo**

**Study FLTA3010**

TNSS PM	Placebo		FP 50mcg BID		FP 100mcg BID		FP200mcg BID		P- Values <sup>1</sup>			
	N	Mean	N	Mean	N	Mean	N	Mean	P Vs FP 50	P Vs FP 100	P Vs FP 200	
Baseline	210	203.9	208	207.6	211	207.4	208	203.6	0.283	0.321	0.943	
Day 1-7	210	-36.1	204	-54.9	207	-52.7	205	-48.3	<0.001	0.001	0.021	
Day 8-14	208	-51.6	201	-75.2	204	-73.1	204	-71.4	<0.001	<0.001	0.002	
Day 15-21	203	-60.1	192	-82.4	201	-78.1	202	-81.3	<0.001	0.005	0.001	
Day 22-28	203	-64.2	191	-90.8	197	-87.2	198	-87.8	<0.001	<0.001	<0.001	
<b>TNSS AM</b>												
Baseline	210	197.6	208	205.2	211	202.6	208	198.1	0.077	0.264	0.855	
Day 1-7	210	-31.7	204	-56.3	207	-51.2	205	-48.2	<0.001	<0.001	0.003	
Day 8-14	208	-47.1	200	-74.5	204	-67.9	204	-66.8	<0.001	0.001	0.002	
Day 15-21	203	-54.9	192	-81.0	201	-75.4	200	-75.4	<0.001	0.003	0.003	
Day 22-28	203	-57.1	191	-88.7	197	-84.3	198	-82.0	<0.001	<0.001	<0.001	

<sup>1</sup> P-values are from an Analysis of Variance with factors treatment, investigators and their interaction.

**APPEARS THIS WAY  
ON ORIGINAL**

Table 4  
Study FLN-310  
Treatment Means and p-values comparing treatments

	Placebo		FP100 BID		FP200 QD		P-Value		
	N	Mean	N	Mean	N	Mean	P vs FP100 BID	P vs FP200 QD	FP100 BID vs FP200 QD
<b>Clinician-rated TNSS</b>									
Baseline	113	211.6	121	215.8	128	209.4	0.542	0.635	0.266
Week 4	104	170.8	116	127.1	122	133.9	<0.001	<0.001	0.550
Week 12	98	147.1	102	114.5	113	116.2	0.004	0.003	0.999
Week 24	91	143.0	96	95.6	108	103.5	<0.001	<0.001	0.756
<b>Patient-rated A.M. Nasal Obstruction</b>									
Baseline	111	69.8	120	71.6	127	67.6	0.303	0.380	0.050
Week 1	109	68.2	119	60.5	127	61.8	<0.001	0.012	0.008
Week 2	107	66.1	117	55.2	126	57.5	<0.001	<0.001	0.011
Week 4	104	61.7	113	51.3	121	54.6	<0.001	0.028	0.009
Week 6	102	62.4	109	48.1	118	52.9	<0.001	<0.001	0.005
Week 8	100	61.3	109	49.6	117	49.7	<0.001	<0.001	0.489
Week 10	100	59.2	107	47.1	116	47.8	<0.001	<0.001	0.469
Week 12	97	55.9	105	47.4	113	47.5	0.001	0.007	0.561
Week 16	95	53.9	103	42.7	113	44.9	<0.001	0.004	0.209
Week 20	94	54.2	98	43.5	112	43.8	<0.001	0.001	0.685
Week 24	94	52.8	99	42.3	110	43.1	<0.001	0.002	0.556

APPEARS THIS WAY  
ON ORIGINAL

Table 5  
Study FLN-311  
Treatment Means and p-values comparing treatments

	Placebo		FP100 BID		FP200 QD		P-Value		
	N	Mean	N	Mean	N	Mean	P vs FP100 BID	P vs FP200 QD	FP100 BID vs FP200 QD
<b>Clinician-rated TNSS</b>									
Baseline	111	190.0	116	192.6	118	193.1	0.839	0.845	0.993
Week 4	107	163.9	111	133.9	117	134.2	<0.001	<0.001	0.928
Week 12	91	143.6	101	108.2	108	120.9	<0.001	0.007	0.243
Week 24	81	128.3	91	94.4	102	105.4	<0.001	0.009	0.340
<b>Patient-rated A.M. Nasal Obstruction</b>									
Baseline	112	66.9	117	66.5	118	68.5	0.737	0.499	0.306
Week 1	112	64.1	116	60.1	116	62.9	0.033	0.154	0.470
Week 2	108	62.2	114	56.7	116	57.9	0.015	0.008	0.833
Week 4	108	60.5	111	54.4	115	54.1	0.008	<0.001	0.460
Week 6	104	57.4	109	49.7	116	54.4	0.002	0.087	0.147
Week 8	98	56.0	104	48.8	116	51.5	0.010	0.043	0.532
Week 10	92	54.3	103	47.2	114	50.7	0.007	0.076	0.312
Week 12	91	53.5	99	46.3	110	48.0	0.009	0.018	0.740
Week 16	91	52.2	98	45.2	108	46.3	0.023	0.018	0.967
Week 20	90	51.1	96	43.2	105	45.4	0.007	0.024	0.602
Week 24	85	50.9	94	42.8	103	44.9	0.006	0.012	0.734

APPEARS THIS WAY  
ON ORIGINAL