

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-121/S009

MEDICAL REVIEW(S)

141fik 62

OCT 21 1998

## MEDICAL OFFICER REVIEW

### Division of Pulmonary Drug Products (HFD-570)

Application #: 20-121	Application Type: NDA Efficacy Supplement
Sponsor: Glaxo Wellcome, Inc.	Product/Proprietary Name: FLONASE Nasal Spray
Principal Investigator: Not Applicable	USAN/Established Name: Fluticasone Propionate, 50 µg/actuation
Category of Drug: Corticosteroid	Route of Administration: Intranasal
Reviewer: Alexandra S. Worobec, M.D.	Review Date: 08/05/98, revised 09/16/98

#### SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
December 17, 1997	December 18, 1997	NDA 20-121, S-009	Efficacy Supplement
April 9, 1998	April 10, 1998	NDA 20-121, S-009	120-Day Safety Update

#### RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
November 20, 1991	NDA 20-121	NDA Application for FLONASE Nasal Spray
May 5, 1994	NDA 20-121	Medical Officer Review for NDA 20-121
October 31, 1997	NDA 20-121, S-005	Medical Officer Review for the Pediatric Efficacy Supplement to NDA 20-121 for the SAR/PAR indication in children 4-11 years of age.

**Overview of Application/Review:** This is an NDA Efficacy Supplement for FLONASE Nasal Spray (fluticasone propionate, 50 µg/actuation) administered once a day for the treatment of symptoms of NAPR (non-allergic perennial rhinitis, proposed nasal symptoms treated with FLONASE are to include: rhinorrhea, nasal obstruction, sneezing, and nasal itching) in adults and children 4 years of age and older. Three pivotal NAPR trials (2 trials conducted in adults age 12 years and older and one trial conducted in adults 25 years of age and older) were reviewed in order to determine efficacy in the treatment of NAPR symptoms in adults. One trial (FLTA 3010) consistently demonstrated statistically significantly greater decrease in NAPR symptoms throughout the entire treatment period of 6 months than did placebo. The other 2 trials showed similar numerical differences in symptom scores with a consistent trend in decreasing NAPR symptoms compared to placebo, but generally failed to achieve statistical significance. Of note, one of these 2 trials (FLN 350) was underpowered due to insufficient patient enrollment. In the studies that evaluated different doses of FLONASE Nasal Spray, no evidence of a clinical dose response was seen. In addition to the SAR and PAR studies previously reviewed for the approval of the original NDA for FLONASE Nasal Spray (NDA 20-121), 2 park studies to assess onset of action were performed and one of the 2 studies (FLN 444) consistently demonstrated an onset of action of 12 hours, whereas the other park study (FLN 445) demonstrated an onset of action at 12 hours which persisted till 23 hours after initial dosing (the end-of dosing interval). No outstanding safety concerns were seen with FLONASE Nasal Spray, with no significant increase in the incidence of nasal septal ulcers, nasal mucosal ulcers, nasal or oral candidiasis. Studies of adrenal response failed to demonstrate significant adrenal suppression at a dose of FP up to 200 µg bid given for 6 months (study FLNT 3010). Headache, epistaxis, throat irritation and upper respiratory infection (URI) were the most frequent AEs based on an ITT group population of 1191 patients treated with FP Nasal Spray. Based on a review of the data presented in the efficacy supplement submission to NDA 20-121, the medical reviewer recommends approval of FLONASE Nasal Spray in adults and children 4 years of age and older, for the treatment of nasal symptoms of NAPR (Adults (12 years and older): 200 µg qd or 100 µg bid, children 4-11 years: 100 µg qd).

**Outstanding Issues:** None

<b>Recommended Regulatory Action: Approvable</b>		<b>N drive location:</b>	
New Clinical Studies:	<u>NA</u> Clinical Hold	<u>NA</u>	Study May Proceed
NDAs:			
Efficacy/Label Supp.:	<u>NA</u> Approvable	<u>NA</u>	Not Approvable
Signed: Medical Reviewer:	[Redacted] /S/	Date:	<u>09/16/98</u>
Medical Team Leader:	[Redacted] /S/	Date:	<u>10/21/98</u>

cc: Original NDA 20-121/S-009  
 HFD-570 / Div file  
 HFD-570 / Workobec  
 HFD-570 / Himmel  
 HFD-570 / Hilfiker

APPEARS THIS WAY  
 ON ORIGINAL

**Medical Officer's Review**

NDA #: 20-121 Submission Date: December 17, 1997  
Medical Officer Review: 20-121 Filing Date: January 14, 1998  
Review Completed: August 5, 1998

- 1.2. Drug Name:
- 1.2.1. Generic Name: Fluticasone propionate aqueous nasal spray, 50 µg/actuation
- 1.2.2. Proposed Trade Name: FLONASE™ Nasal Spray
- 1.2.3. Chemical Name: S-fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyndrosta-1,4-diene-17β-carbothioate
- 1.3. Sponsor: Glaxo Wellcome, Inc.
- 1.4. Pharmacologic Category: Corticosteroid
- 1.5. Proposed Indication: Treatment of nasal symptoms due to non-allergic perennial rhinitis (NAPR)
- 1.6. Dosage form and route of administration: **Adults** 12 years of age and older: 2 Sprays (50 µg/actuation) in each nostril once a day or 1 spray (50µg/actuation) in each nostril twice a day. Total recommended dose: 200 µg qd.
- Children** 4-11 years of age: 1 Spray (50 µg/actuation) in each nostril once a day. Total recommended dose: 100 µg qd, with increase to 200 µg qd if poor relief of nasal symptoms of NAPR.
- 1.7. NDA Drug Classification: S-009
- 1.8. Related Drugs: NDA 20-121: FLONASE™ Nasal Spray (Fluticasone propionate nasal spray), Approved October 19, 1994 (for seasonal and perennial allergic rhinitis in adults and children age 12 years and older). Pediatric efficacy Supplement (S-005) to NDA 20-121 approved October 31, 1997 for treatment of SAR and PAR in children age 4-11 years of age.
- 1.9. Related Reviews: Chemistry review: None  
Pharmacology/Toxicology review: None  
Statistical review dated: 08/03/98  
Biopharmaceutics review dated: None

## 2.0. TABLE OF CONTENTS

3.0.	CONDUCT OF THE REVIEW.....	10
4.0.	CHEMISTRY, MANUFACTURING, AND CONTROLS.....	11
5.0.	ANIMAL PHARMACOLOGY/TOXICOLOGY.....	12
6.0.	CLINICAL BACKGROUND.....	12
	Relevant Human Experience.....	12
	Important Information from related INDs and NDAs.....	12
	Foreign Experience.....	14
	Human Pharmacology, pharmacokinetics, pharmacodynamics.....	14
	Directions for use.....	14
7.0.	DESCRIPTION OF CLINICAL DATA SOURCES.....	14
8.0.	CLINICAL STUDIES	
8.1.	<u>PERENNIAL NON-ALLERGIC RHINITIS (Pivotal Trial):</u> Protocol No. FLTA 3010: A double-blind, randomized, placebo-controlled study of the efficacy and safety of fluticasone propionate aqueous nasal spray vs. placebo followed by a 6 month open-label safety extension in subjects with perennial non-allergic rhinitis.	
	8.1.1. Objective.....	15
	8.1.2. Study Design.....	15
	8.1.3. Protocol.....	16
	8.1.3.1.a. Population.....	16
	8.1.3.1.b. Procedure.....	19
	8.1.3.2. Clinical Endpoints.....	26
	8.1.3.3. Statistical Analysis.....	26
	8.1.4. Results.....	28
	8.1.4.1. Patient Demographics.....	28
	8.1.4.2. Efficacy Endpoint Outcomes.....	32
	8.1.4.2.1. Nasal Cytology Studies.....	58
	8.1.4.3. Safety Analysis.....	58
	8.1.4.3.1. Demographics of the Exposed Population.....	59
	8.1.4.3.2. Duration of Patient Exposure/Patient Disposition.....	60
	8.1.4.4. Adverse Events.....	60
	8.1.4.4.1. Double-blind Treatment Period.....	60
	8.1.4.4.2. Open-label Treatment Period.....	61
	8.1.4.5. Adverse Event Stratification by Duration of Treatment.....	62
	8.1.4.6. Adverse Event Stratification by Demographics.....	63

8.1.4.7. Patient Discontinuation Due to Adverse Events.....	63
8.1.4.8. Serious Adverse Events.....	64
8.1.4.9. Laboratory Test Results.....	64
8.1.4.9.1. HPA-Axis Studies.....	66
8.1.4.10. Physical Examination.....	69
8.1.5. Reviewer's Conclusion of Study Results.....	71

**PERENNIAL NON-ALLERGIC RHINITIS (Pivotal 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.

8.2.1. Objectives.....	75
8.2.2. Study Design.....	75
8.2.3. Protocol.....	75
8.2.3.1.a. Population.....	75
8.2.3.1.b. Procedure.....	79
8.2.3.2. Clinical Endpoints.....	84
8.2.3.3. Statistical Analysis.....	85
8.2.4. Results.....	86
8.2.4.1. Patient Demographics.....	86
8.2.4.2. Efficacy Endpoint Outcomes.....	89
8.2.4.2. Nasal Cytology Studies.....	108
8.2.4.3. Safety Analysis.....	110
8.2.4.3.1. Demographics of the Exposed Population.....	110
8.2.4.3.2. Duration of Patient Exposure/Patient Disposition.....	110
8.2.4.4. Adverse Events.....	110
8.2.4.5. Adverse Event Stratification by Duration of Treatment.....	111
8.2.4.6. Adverse Event Stratification by Demographics.....	112
8.2.4.7. Patient Discontinuation Due to Adverse Events.....	112
8.2.4.8. Serious Adverse Events.....	112
8.2.4.9. Laboratory Test Results.....	112
8.2.4.9.1. A.M. Plasma Cortisol Studies.....	114
8.2.4.10. Physical Examination.....	115
8.2.5. Reviewer's Conclusion of Study Results.....	116

**PERENNIAL NON-ALLERGIC RHINITIS (Pivotal Trial):**

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

8.3.1. Objectives.....	119
8.3.2. Study Design.....	119

8.3.3. Protocol.....	119
8.3.3.1.a. Population.....	120
8.3.3.1.b. Procedure.....	123
8.3.3.2. Clinical Endpoints.....	128
8.3.3.3. Statistical Analysis.....	128
8.3.4. Results.....	130
8.3.4.1. Patient Demographics.....	130
8.3.4.2. Efficacy Endpoint Outcomes.....	134
8.3.4.2. Nasal Cytology Studies.....	149
8.3.4.3. Safety Analysis.....	150
8.3.4.3.1. Demographics of the Exposed Population.....	150
8.3.4.3.2. Duration of Patient Exposure/Patient Disposition.....	150
8.3.4.4. Adverse Events.....	150
8.3.4.5. Adverse Event Stratification by Duration of Treatment.....	152
8.3.4.6. Adverse Event Stratification by Demographics.....	152
8.3.4.7. Patient Discontinuation Due to Adverse Events.....	152
8.3.4.8. Serious Adverse Events.....	153
8.3.4.9. Laboratory Test Results.....	153
8.3.4.9.1. A.M. Plasma Cortisol Studies.....	154
8.3.4.10. Physical Examination.....	155
8.3.5. Reviewer's Conclusion of Study Results.....	157

**PERENNIAL ALLERGIC RHINITIS (Bridging Trial):**

8.4.

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

8.4.1. Objectives.....	160
8.4.2. Study Design.....	160
8.4.3. Protocol.....	160
8.4.3.1.a. Population.....	161
8.4.3.1.b. Procedure.....	164
8.4.3.2. Clinical Endpoints.....	168
8.4.3.3. Statistical Analysis.....	170
8.4.4. Results.....	171
8.4.4.1. Patient Demographics.....	171
8.4.4.2. Efficacy Endpoint Outcomes.....	174
8.4.4.2. Nasal Cytology Studies.....	183
8.4.4.3. Safety Analysis.....	184
8.4.5. Reviewer's Conclusion of Study Results.....	188

**PERENNIAL ALLERGIC RHINITIS (Bridging Trial):**

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

8.5.1. Objectives.....192

8.5.2. Study Design.....192

8.5.3. Protocol.....192

8.5.3.1.a. Population.....193

8.5.3.1.b. Procedure.....196

8.5.3.2. Clinical Endpoints.....200

8.5.3.3. Statistical Analysis.....202

8.5.4. Results.....203

8.5.4.1. Patient Demographics.....203

8.5.4.2. Efficacy Endpoint Outcomes.....207

8.5.4.2. Nasal Cytology Studies.....216

8.5.4.3. Safety Analysis.....217

8.5.5. Reviewer’s Conclusion of Study Results.....224

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

8.6.1. Protocol FLIP07: A dose-ranging, parallel-group study comparing FP Nasal Spray 50 µg, 100 µg, 200 µg, and 400 µg bid with placebo in perennial rhinitis.....226

8.6.2. Protocol FLNT43: A double-blind comparison of FP Nasal Spray 200 µg qd, FP Nasal Spray 200 µg bid, with BDP 200 µg bid, and with placebo aqueous nasal spray in the treatment of patients with perennial rhinitis.....227

8.6.3. Protocol FLIT11: A double-blind, parallel group study to assess the safety of long term use of FP Nasal Spray 200 µg bid compared with BDP 200 µg bid in the treatment of perennial rhinitis.....228

8.6.4. Protocol FLIT22: A parallel group comparison of FP Nasal Spray compared with placebo in patients with non-seasonal allergic rhinitis with symptoms all year round.....229

8.6.5. Protocol FLNP57: A double-blind, single-center, parallel group study to investigate the influence of FP Nasal Spray 200 µg given once daily, on nasal mucosal inflammation in PAR.....230

8.6.6. Protocol FLNP64: A double-blind, single-center, placebo-controlled, crossover study to investigate the effect of acute and chronic FP Nasal Spray 200 µg given once daily treatment on nasal responses to histamine in patients with PAR.....230

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

8.6.7. Protocol FLIT08: The long-term safety and efficacy of FP Nasal Spray 200 µg bid in the management of perennial rhinitis.....231

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

8.6.8. Protocol FLNT60: A double-blind comparison of FP Nasal Spray 100 µg qd, FP Nasal Spray 200 µg qd, and placebo qd in the treatment of perennial rhinitis in children aged 4-11 years.....232

8.6.9. Protocol FLNT61: A double-blind comparison of FP Nasal Spray 100 µg qd, FP Nasal Spray 100 µg bid, and BDP 200 µg bid in the treatment of perennial rhinitis in pediatric patients (aged 6-11 years).....233

8.7. ONSET OF ACTION

8.7.1. Protocol FLN444: A double-blind, randomized, placebo-controlled parallel group park study to compare the onset of action of fluticasone propionate (FP) aqueous nasal spray 200 µg qd vs. beclomethasone dipropionate aqueous nasal spray (BDP) 168 µg in patients with SAR.....235

8.7.2. Protocol FLN445: A double-blind, randomized, placebo-controlled parallel group park study to compare the onset of action of fluticasone propionate (FP) aqueous nasal spray 200 µg qd vs. beclomethasone dipropionate aqueous nasal spray (BDP) 168 µg in patients with SAR.....241

8.7.3. Summary of Onset of Action Data for SAR, PAR, and NAPR Studies Where This Endpoint was Evaluated.....246

8.7.4. Conclusion.....247

9.0. INTEGRATED SUMMARY OF EFFICACY.....250

10.0. INTEGRATED SUMMARY OF SAFETY.....256

11.0. DATA VERIFICATON (DSI AUDIT).....265

12.0. EXECUTIVE SUMMARY OF EFFICACY AND SAFETY.....265

    12.1. Reviewer's Recommendation for Approval.....265

13.0. Labeling Comments.....267

**APPEARS THIS WAY  
ON ORIGINAL**

### 3.0. CONDUCT OF THE REVIEW

The clinical review of the efficacy supplement to NDA 20-121 (FLONASE Aqueous Nasal Spray) was conducted using volumes 1-68 of the efficacy supplement submission [S-009-V1-V68], along with volumes 35.1-35.3 of an onset of action supplement to the NAPR efficacy supplement dated 01/30/98.

The 3 pivotal clinical studies for the NAPR indication consisted of studies FLTA 3010, FLN 310, and FLN 311, though study FLTA 3010 was clearly a better designed study, with greater patient enrollment than the other 2 NAPR studies. Two PAR studies (FLN 310 and FLN 311) were reviewed in order to make the determination that qd dosing with FLONASE Nasal Spray (FP Nasal Spray) was comparable to bid dosing in terms of efficacy. FP Nasal Spray is currently approved in children age 4-11 years of age and adults 12 years of age and older for the management of nasal symptoms of seasonal and perennial allergic rhinitis (SAR and PAR). This efficacy supplement is to extend the indication for FP Nasal Spray to non-allergic perennial rhinitis (NAPR) to adults 12 years and older and by the pediatric rule, extend approval of FP Nasal Spray for the NAPR indication in children 4-11 years of age.

Review of this efficacy supplement was conducted with pivotal trials reviewed first, followed by the two 'bridging' PAR studies, and the non-pivotal supportive studies. A summary of clinical trials reviewed in the NAPR efficacy supplement to NDA 20-121 is provided in Table I below.

Table I. Summary of Clinical Trials Reviewed in the NAPR Efficacy Supplement to NDA 20-121: FLONASE Aqueous Nasal Spray

STUDY	TREATMENT DURATION	TREATMENT ARMS:
<b>Pivotal NAPR</b>		
FLTA 3010	4 weeks	FP 50 µg bid, FP 100 µg bid, FP 200 µg bid, Placebo
FLN 350	4 weeks	FP 100 µg bid, FP 200 µg bid, Placebo
FLN 351	4 weeks	FP 100 µg bid, FP 200 µg bid, Placebo
<b>Bridging PAR</b>		
FLN 310	6 months	FP 100 µg bid, FP 200 µg qd, Placebo
FLN 311	6 months	FP 100 µg bid, FP 200 µg qd, BDP 168 µg bid, Placebo
<b>Controlled, Non-U.S. Perennial Rhinitis (PAR and/or NAPR) Trials</b>		
FLIP07	4 weeks	FP 50 µg bid, FP 100 µg bid, FP 200 µg bid, FP 400 µg bid
FLNT43	12 weeks	FP 200 µg qd, FP 200 µg bid, BDP 200 µg bid, Placebo
FLIT11	1 year	FP 200 µg bid, BDP 200 µg bid
FLIT22	1 year	FP 100 µg bid, Placebo
FLNP57	6 week	FP 200 µg qd, Placebo
FLNP64	4 weeks, followed by a 2 week washout period, followed by another 4 week treatment period (crossover)	FP 200 µg qd, Placebo
FLIT08	1 year (open label)	FP 200 µg bid
<b>Pediatric, Non-U.S. Perennial Rhinitis (PAR and NAPR) Trials</b>		
FLNT60	4 weeks	FP 100 µg qd, FP 200 µg qd, Placebo
FLNT61	12 weeks	FP 100 µg qd, FP 100 µg bid, FP 200 µg bid

Line listings were reviewed for all primary efficacy endpoints, demographic subgroups to verify accuracy with the study report data, and the efficacy results for the intent-to-treat population were compared to the efficacy evaluable population in order to evaluate any potential discrepancies. The safety review also consisted of a review of all adverse events by summary tables and line listings, along with review of the physical examination line listings. Particular importance was placed on ear, nose and throat findings such as nasal ulcerations, nasal septal perforations, and nasal/oral candidiasis. Other potential physical findings described with corticosteroid use such as glaucoma and cataracts were not specifically evaluated in any of the NAPR trials. Electrocardiographic (ECG) tracings were not performed in study patients and therefore not provided in this efficacy supplement. Laboratory tests were likewise reviewed, with special attention to trends in mean values post-treatment with FP Nasal Spray.

'Clinically significant' or 'outlier' changes were defined as falling outside the 'normal' range of values for the clinical parameter by a specified amount defined in the study report by the sponsor. In terms of laboratory testing, all 3 NAPR studies assessed adrenal function with a.m. plasma cortisol levels, and in addition FLTA 3010 assessed cortisol levels pre- and post-short Cortrosyn stimulation testing before, during and after completion of treatment with FP Nasal Spray at a dose of 200 µg bid.

Pertinent positive and negative safety and efficacy findings are discussed in the clinical study review, with the appropriate volumes indexed from the NDA [Submission Number-Volume of Submission-pages]. A focused integrated summary of efficacy and safety was provided for the 3 clinical studies reviewed in this efficacy supplement, along with an analysis of the onset of action of FP Nasal Spray. The medical reviewer's recommendations for approval are summarized in the Conclusion-'Executive summary of efficacy and safety' section (section 12.0.).

#### 4.0. CHEMISTRY, MANUFACTURING, AND CONTROLS

FLONASE Aqueous Nasal Spray is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. FP Nasal Spray also contains microcrystalline cellulose and [redacted] sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7. Use of FP Nasal Spray requires priming of the pump (before 1<sup>st</sup> use or after a period of non-use, i.e. > 1 week). After priming [redacted] actuations or until a fine spray appears, each actuation delivers 50 µg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each bottle of FP Nasal Spray provides 120 metered sprays.

Of note, the drug lots for the 'to-be-marketed' FLONASE Aqueous Nasal Spray represent the same lots (i.e. formulation) used in the pivotal clinical trials in the original NDA for FP Nasal Spray (20-121), although the clinical trial pack of FLONASE bottles used in the 3 NAPR pivotal trials had a screw-on fitting to the

25 ml amber glass bottle, rather than a crimp-on fitting to a 20 ml amber glass bottle that was employed in the clinical trials in the original FLONASE NDA [FAX, Mrs. Alison Bowers, U.S. Regulatory Affairs, GlaxoWellcome, 04/02/98]. Studies undertaken on both types of nasal adapter were previously described in the amendment to IND [redacted] submitted on 02/28/91 and demonstrated that the distribution of droplet size within the spray and the pump performance and dose delivery were shown to be unaffected by these changes [FAX, Mrs. Alison Bowers, U.S. Regulatory Affairs, GlaxoWellcome, 04/10/98]. Further discussion on the issue of whether the currently 'marketed' drug product for FLONASE and that used in the NAPR clinical trials are the same was addressed with the reviewing chemist, Dr. Brian Rogers, and this issue was not felt to be of any significant concern. The formulation used in the placebo nasal spray for the NAPR trials (as in the SAR and PAR trials) was shown to have identical contents of excipients, but no active drug substance.

#### 5.0. ANIMAL PHARMACOLOGY/TOXICOLOGY

Animal pharmacology/toxicology was previously reviewed during approval of the original NDA for FP Nasal Spray (20-121) and will not be further discussed in this efficacy supplement review. No new information pertaining to preclinical pharmacology has been submitted to the Agency since approval of NDA 20-121.

Environmental assessment of FP Nasal Spray indicated that no environmental impact was anticipated, hence no alternatives to manufacturing practices were recommended by the Agency.

#### 6.0. CLINICAL BACKGROUND

##### Relevant Human Experience

Three adequate and well-controlled efficacy and safety phase III clinical trials were reviewed by the Agency as a basis for approval of FLONASE Aqueous Nasal Spray for the non-allergic perennial rhinitis (NAPR) indication in adults and adolescents 12 years of age and older with NAPR. Using the pediatric rule and the rationale that FP Nasal Spray was approved in children age 4-11 years for the SAR and PAR indication at a dose of 100 µg qd to a maximum dose of 200 µg qd and the assumption that the pathophysiology of SAR and PAR are not significantly different from that of NAPR (which they are not) though the environmental triggers for each may differ, or that the mechanism of action of FLONASE should not differ in adults and children, extension of approval of FP Nasal Spray to children age 4-11 years with NAPR was recommended in this efficacy supplement (also see section 'Important Information from related INDs and NDAs' below).

##### Important Information from related INDs and NDAs

Clinical experience with FP Nasal Spray is extensive, both from clinical trials and from marketing experience. Clinical trial data supported FDA approval of FP

Nasal Spray (NDA 20-121) as a safe and effective therapy for the treatment of nasal symptoms of SAR and PAR in adults and adolescents 12 years of age and older on 10/19/94. FP Nasal Spray was more recently approved for the SAR/PAR indication in children aged 4-11 years as an efficacy supplement (S-005) to NDA 20-121 on 10/31/97. In the pediatric efficacy supplement, a total of 3 studies (FLN 320, FLN 321, and FLNT 52) examined efficacy for SAR at 2 doses of FP Nasal Spray: 100 µg qd and 200 µg qd. The data from these 3 doses, considered together, offered reasonable evidence of efficacy for both doses of FP Nasal Spray, with studies FLN 320 and FLNT52 more strongly supporting the FP 100 µg qd dose and the FLN 321 study supporting the 200 µg qd dose. Nonetheless, no study gave clear evidence of a reliable dose response for efficacy, nor was there a titration component (either upward for non-response or downward for good response) to any of these trials [Medical Officer Review, 20-121, S-005, p.72-73]. For PAR, 2 studies (FLNT 60 and FLNT 61) were submitted by the sponsor, but one study (FLNT 61) was underpowered, and demonstrated a large placebo response. Study FLNT 60 failed to demonstrate statistical significance on 2 of the 3 sponsor defined primary efficacy endpoints. Despite these problems in the pediatric PAR studies, using the pediatric rule, the Pulmonary Division was able to conclude efficacy based on well controlled adult data under circumstances where the disease processes and the response to the medications do not differ significantly between adults and children.

Given that the proposed doses of FP Nasal Spray 100 µg qd and 200 µg qd were shown to be effective in SAR in children age 4-11 years of age, and shown to be effective in SAR and PAR in adults, and given that the main difference between SAR and PAR is the type of allergen and the duration of symptoms (but not pathophysiology), and given the modest support of efficacy coming from study FLNT 60, it is reasonable to conclude efficacy of FP Nasal Spray 100 µg qd and 200 µg qd for PAR in children 4-11 years of age [Medical Officer Review, 20-121, S-005, p.73-74]. This conclusion was felt to be particularly appropriate, as the Division has seen other instances where reasonably designed and conducted trials in allergic rhinitis have failed in children with a regimen that later, based on other data, was shown to be efficacious.

A total of 13 pivotal, randomized, double-blind, vehicle-controlled, parallel group studies were conducted in the U.S. in adults and children (4 years of age and older) with SAR and PAR (the original NDA). Based on 6 clinical trials, there were no significant differences between FP regimens whether administered as a single daily dose of 200 µg qd (2, 50 µg sprays in each nostril) or as 100 µg bid (1, 50 µg spray in each nostril). Furthermore, a clear dose response could not be identified in clinical trials. In one trial, 200 µg qd was slightly more effective than 50 µg qd during the 1<sup>st</sup> few days (i.e. 3 days) of treatment but thereafter, no difference was seen. The recommended dose in adults in the FLONASE label was given as either 200 µg qd or 100 µg bid. The recommended dose in children 4-11 years of age was given as 100 µg qd or if no clinical response in SAR/PAR symptoms was seen, an increase to 200 µg qd. Once adequate control is achieved,

the labeling recommends decreasing the dosage in children age 4-11 years to 100 µg qd. FP Nasal Spray was first marketed worldwide in 1991 (in the U.K., for SAR in adults) and has been marketed in the U.S. since 1995.

#### Foreign Experience

FP Nasal Spray is currently marketed in a large number of countries (75+) outside of the U.S. There have been no withdrawals of approval in foreign markets for FP Nasal Spray for any reason.

#### Human Pharmacology, pharmacokinetics, pharmacodynamics

Human pharmacology, PK and PD data were previously reviewed during approval of NDA 20-121. No new data were submitted by the sponsor to this efficacy supplement and additional data in special populations has not been performed. Hence, there are no new changes to this section of the label for FP Nasal Spray.

#### Directions for use

FLONASE Nasal Spray is currently indicated for the relief of nasal symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older and in children age 4-11 years of age. Symptoms treated effectively include rhinorrhea, nasal obstruction, sneezing, and nasal itching.

The recommended dose of FP Nasal Spray in adults and adolescents 12 years of age and older is 200 µg qd (2 sprays (50 µg/spray) in each nostril once a day) or alternatively 100 µg bid (1 spray (50 µg/spray) in each nostril twice a day). The recommended dose of FP Nasal Spray in children 4-11 years of age is 100 µg qd (1 spray (50 µg/spray) in each nostril once a day) with reservation to treatment with FP 200 µg qd (2, 50 µg sprays in each nostril once daily or 1, 50 µg spray in each nostril twice a day) in patients not responding to FP 100 µg qd. Once adequate control is achieved, the labeling recommends decreasing the dosage in children age 4-11 years to 100 µg qd [NDA 20-121, S-009, 1:15].

### 7.0. DESCRIPTION OF CLINICAL DATA SOURCES

The clinical data sources for the NAPR efficacy supplement to NDA 20-121 comprised the efficacy and safety data NDA 20-121, the 3 pivotal NAPR studies to NDA 20-121 and the wealth of post-marketing safety data.

Aside from the pivotal clinical trials FLTA 3010, FLN 350, and FLN 351, with bridging to the PAR studies FLN 310 and FLN 311, and a number of supportive controlled, non-U.S. perennial rhinitis trials (PAR and NAPR: FLIP07, FLNT43, FLIT11, FLIT22, FLNP57, FLNP64, FLTI08, FLNT60, and FLNT61) no additional human clinical studies of safety or efficacy for FP Nasal Spray were reviewed for the approval of this application.

## 8.0. CLINICAL STUDIES:

### NON-ALLERGIC PERENNIAL RHINITIS (Pivotal Trial):

- 8.1. Protocol No. FLTA 3010: A double-blind, randomized, placebo-controlled study of the efficacy and safety of fluticasone propionate aqueous nasal spray vs. placebo followed by a 6 month open-label safety extension in subjects with perennial non-allergic rhinitis.

Principal Investigator: None, multi-center study.

Participating Centers: 39 U.S. centers (for double-blind portion of study), 32 of these 39 centers participated in the open-label portion of the study (safety extension).

#### 8.1.1. Objective

The primary objective of this study was to investigate the safety and efficacy of a 4 week course of 3 different doses of fluticasone propionate (FP) nasal spray (50 µg bid, 100 µg bid, and 200 µg bid) vs. placebo nasal spray for the treatment of symptoms of perennial non-allergic rhinitis (NAPR).

A secondary objective was to evaluate long-term safety with the maximum dose of FP that could be expected to be used for treatment of NAPR, 200 µg bid via a 6 month open-label safety extension of FLTA 3010.

#### 8.1.2. Study Design

The study was a phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group, with 7-14 day placebo lead-in, safety and efficacy study of fluticasone propionate nasal spray (FP) 50 µg bid, vs. 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 6 month safety extension during which all patients received fluticasone propionate nasal spray at a dose of 200 µg bid [NDA 20-121, S-009, 3:47, 4:14].

The study consisted of 4 patient visits for the double-blind portion of the study: a screening visit (visit 1, day -7 to -14), visit 2 or 'the first day of the double-blind treatment period' (baseline visit, day 0), visit 3 (day 14 ± 2 days), and visit 4 (day 28 ± 2 days), the last day of the double-treatment period. Patients were evaluated in clinic from between 6:30 a.m.-9:30 a.m. for each study visit [NDA 20-121, S-009, 4:25]. The duration of the study for a given patient was approximately 4 weeks.

The open-label portion of the study consisted of visits 5 and 6 (day 61 and day 122 ± 7 days after visit 4), and visit 10 (day 183 ± days after visit 4, really

this visit should have been designated visit 7 as visit 7, 8, and 9 were eliminated in an amendment to the protocol (noted by but not changed by the sponsor, protocol amendment no. 3) [NDA 20-121, S-009, 3:51]. A flow chart of FLTA 3010 is provided in Appendix I (attached) [NDA 20-121, S-009, 3:107].

### 8.1.3. Protocol

8.1.3.1.a. Population: Male or female patients,  $\geq 12$  years of age, with NAPR defined by the inclusion criteria listed below [NDA 20-121, S-009, 3:52, 4:19].

- (I) **Inclusion Criteria** [NDA 20-121, S-009, 3:49, 52-53, 4:19-20, 25]:
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) presence of a negative skin test at screening to a comprehensive panel of seasonal and perennial allergens via the [ ] 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.  $< 180$  U/mL for adults, and  $< 120$  U/mL for patients  $< 15$  years of age),
    - (d) written or verbal confirmation of the presence of continuous symptoms of NAPR for at least 1 year.
  2. A morning (a.m.) plasma cortisol level of at least  $5 \mu\text{g/dL}$  on screening. If the a.m. plasma cortisol level was found to be  $> 40 \mu\text{g/dL}$ , 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 0) would need to meet the entry criteria of: a patient-rated total nasal symptom score (TNSS) of  $\geq 150$  points out of a maximum total of 300 points, based on a visual analog rating scale for the p.m. 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 12 hours, i.e. were to be scored reflectively by patients).

4. Sexually active females or females of childbearing potential were expected to use an effective form of birth control throughout the study.

**Reviewer's Notes: 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.**

- (II) Exclusion Criteria [NDA 20-121, S-009, 3:53-55, 4:20-22]:
1. Physical obstruction of the nares, as defined by septal deviation ( $\geq 50\%$  obstruction by physical exam) or nasal polyps that could obstruct delivery of the nasal spray.
  2. History of previous nasal or sinus surgery or nasal septal perforation.
  3. Presence of any disease state which could place the patient at significant risk through study participation or could affect the analysis of response to therapy if the disease exacerbated during the study, as determined by the clinical investigator: i.e. corticosteroid-dependent asthma, immunologic compromise, perennial and active SAR, rhinitis medicamentosa or reported chronic use of nasal decongestants, malignancy, clinically significant cardiovascular, hepatic, neurologic, endocrine, (or other major systemic disease which would make interpretation of the protocol results difficult).
  4. Clinical laboratory abnormalities that would confirm the diagnosis of the concurrent diseases listed above (in (3)).
  5. Patients refusing to complete the visit 2 pharmacoeconomic survey.
  6. History of hypersensitivity reactions to any intranasal, inhaled, or systemic corticosteroid therapy.
  7. The use (regular or prn) of other prescription or OTC drugs that could affect the course of rhinitis for at least 72 hours prior to screening (visit 1) and throughout the double-blind treatment period. Specific criteria regarding restricted and concurrent medication use is summarized in Section (III) below.
  8. Concurrent bacterial or viral infection (e.g. URI) that could confound analysis of efficacy. Patients with sinusitis would be excluded from the study based on sinus radiograph ( ) results.
  9. Use of any investigational new drug within 30 days prior to the screening visit.
  10. Patients with intolerable symptoms that would make participation in the study unbearable.

11. Concurrent use of cigarettes, cigars, pipes or marijuana.
12. History of previous enrollment in a NAPR study with fluticasone propionate aqueous nasal spray.
13. Females who are pregnant, lactating, or not using a medically acceptable form of birth control.

**Reviewer's Note: The clinical criteria (e.g. specific radiographic findings, additional reliance on culture results) for defining 'sinusitis' were not discussed in the study report but were discussed in the study protocol as: 'presence of mucosal thickening > 6 mm or an air fluid level or opacification' [NDA 20-121, S-009, 4:21].**

**(III). Concurrent Medication Restrictions [NDA 20-121, S-009, 3:54, 4:21-22]:**

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

<u>Medication</u>	<u>Time Discontinued Prior to Visit 1 (Screening visit)</u>
1. Antihistamines	≥ 72 hours
2. Astemizole	≥ 12 weeks (90 days)
3. Loratadine	≥ 1 week
4. Anticholinergics	≥ 72 hours
5. Decongestants	≥ 72 hours
6. Nasal saline sprays	≥ 72 hours
7. Sinus medications (not defined)	≥ 72 hours
8. Expectorants (not defined)	≥ 72 hours
9. Cold/cough preparations (not defined)	≥ 72 hours
10. β-blockers	≥ 72 hours
11. Rauwolfia compounds	≥ 72 hours
12. Intranasal cromolyn	≥ 2 weeks
13. Intranasal, inhaled, or systemic corticosteroids	≥ 1 month
14. Hyposensitization therapy	≥ 5 years

For the open-label period, patients were allowed to take concurrent rhinitis medications, with the exception of any intranasal products (not specified in protocol). Patients were likewise allowed use of topical hydrocortisone (1% or less) prior to and for the duration of the double-blind and open-label extension.

**Reviewer's Note: The medication exclusion criteria and concomitant wash-out periods are probably acceptable but not well-defined in terms of specific medication classes or products which comprise the different categories of restricted medications or the specific time periods that would be required for washout. For example, there is no mention of depot (I.M. or I.V.) corticosteroids. Furthermore, classes of drugs such as: decongestants, expectorants, sinus medications, cold/cough preparations,  $\beta$ -blockers, 'rauwolfia' compounds (e.g. reserpine) could have been classified in greater detail by the sponsor.**

#### 8.1.3.1.b. Procedure

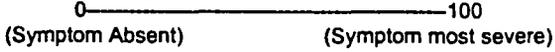
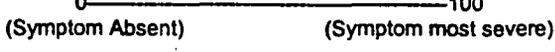
(I) Screening Visit (Visit 1) [NDA 20-121, S-009, 3:48, 4:24]:

A complete medical history and physical examination (to include ear and nasal exam, comprised of: an evaluation of the nasal septum, nasal polyps, the degree of enlargement of nasal turbinates, the appearance of the mucosa, and the quantity, consistency, and color of nasal secretions and examination of the ear for clinical evidence of infections, perforations, scarring, and calcific deposits) [NDA 20-121, S-009, 3:57] and an evaluation for oral or nasal candidiasis (with cultures obtained if there was clinical evidence of candidiasis in order to confirm the diagnosis) [NDA 20-121, S-009, 3:60]) was performed at the screening visit. In addition, laboratory evaluation (to include a.m. plasma cortisol levels along with routine blood chemistry, hematology, total IgE, urinalysis and tests to rule out pregnancy), sinus radiography (using ) and confirmation of the patient's allergen hypersensitivity with skin prick testing was performed on all potential patients at the screening visit (at all study sites).

The purpose of the screening visit (visit 1) was to determine if prospective patients met the requisite inclusion/exclusion criteria to qualify for entry into the 1-2 week run-in period of the study, to be subsequently followed by the 4 week double-blind treatment period. Patients likewise underwent a physician-rated nasal symptom assessment during screening which was used to determine if patients had NAPR symptoms sufficiently severe in order to qualify for study entry (see study inclusion criteria, section 8.1.3.1.a.(I)).

Diary cards for nasal symptom recording were issued to patients during the run-in period and patients were instructed in their completion. Specifically, patients were to subjectively rate the following 4 nasal symptoms reflectively over the previous 12 hours on their diary cards: (1) rhinorrhea, (2) nasal obstruction, (3) postnasal drip, and (4) sneezing using the visual analog scale shown in Figure 1 below, which ranged from a score of 0 (=absent symptoms) to 100 (most severe symptoms) in the a.m. (on awakening) and in the p.m. (at the end of each day) [NDA 20-121, S-009, 3:49].

Figure 1: Subjective NAPR symptom rating scale:

NAPR Symptoms	Visual Analog Scale
Rhinorrhea	
Nasal obstruction	
Postnasal drip	
Sneezing	

The physician would then measure the distance (in millimeters) from the 0 score to the mark made by the patient and record the symptom severity number on the case report form (CRF). Beginning with visit 1, patients were instructed not to take any medications aside from study drug for treatment of rhinitis symptoms throughout the double-blind treatment period.

**Reviewer's Note:** The total nasal symptom score (TNSS) was calculated by summing the individual reflective symptom scores for nasal obstruction, rhinorrhea, and postnasal drip. Symptom severity was rated each day during the double-blind treatment period; during the open-label safety extension, nasal symptoms were assessed only during each of the 7 days preceding scheduled visits.

In addition to patient-rated symptoms (which were recorded twice daily by all patients during the double-blind period), physician-rated nasal symptoms were also obtained at each clinic visit and these were based on the nasal examination and physician's observation of the patient. Again, these symptom scores (which were quantified for each individual symptom) were based on a visual analog scale of 0-100. The physician assessed rhinorrhea, nasal obstruction, and postnasal drip but not sneezing [NDA 20-121, S-009, 3:24, 58]. Nasal symptoms were evaluated individually and a TNSS was calculated by summing the individual scores for rhinorrhea, nasal obstruction, and postnasal drip. These evaluations were performed at each clinic visit during the double-blind treatment period (Day 14 and Day 28) and every 2 months during the open-label safety extension [NDA 20-121, S-009, 3:24].

**Reviewer's Note:** A single-blind placebo lead-in was used to reduce the number of 'placebo responders' in the double-blind period of the study. Furthermore, a specific acceptable time frame prior to medication dosing which patients were to record symptoms was not specified in the protocol. Discussion with Mrs. Alison Bowers of Glaxo Wellcome, U.S. Regulatory

Affairs indicated that patients and clinicians were required to record all nasal symptoms and overall condition of NAPR in the a.m. prior to dosing with study medication [Telephone Conversation, Mrs. Alison Bowers, Glaxo Wellcome, U.S. Regulatory Affairs, 01/14/98]. Similarly, for the patient-self rated p.m. symptom scores, these were recorded immediately prior to dosing with medication, although a pre-specified time was not afforded in the protocol nor available in any specific documents [NDA 20-121, S-009, 4:25, 50].

In order to qualify for enrollment into the double-blind portion of the study, patients were to be sufficiently symptomatic for at least 4 of the 7 days immediately preceding the 1<sup>st</sup> day of double-blind treatment assignment (of the run-in period) as defined by a p.m. total nasal symptom score (TNSS=composite score of rhinorrhea, nasal obstruction, and postnasal drip (sneezing excluded)) of at least 150 out of a maximum score of 300 [NDA 20-121, S-009, 3:49]. In other words, the a.m. TNSS was not used as a qualifying endpoint for patient enrollment into the double-blind portion of the study.

(II) Visit 2 (Day 0, 1<sup>st</sup> day of double-blind study medication) [NDA 20-121, S-009, 3:49, 4:25]:

After completion of the single-blind placebo lead-in portion of the study, patients underwent re-evaluation of NAPR symptomatology via review of the patient symptom diary and assessment of compliance with study medication for the lead-in period at study visit 2. Adverse events and concurrent medication assessments were reviewed by the investigator.

A repeat nasal/oropharyngeal and ear examination was performed (along with evaluation for oral or nasal candidiasis) and a physician-rated nasal symptom assessment was completed. Nasal cytology using collection of nasal mucosal cells via the [redacted] was performed at this visit in order to identify patients with non-allergic rhinitis eosinophilic syndrome (NARES) [NDA 20-121, S-009, 3:56]. The relative numbers of eosinophils using this technique were assessed using the 5-point scale summarized in Figure 2 [NDA 20-121, S-009, 3:57, 4:51]:

Figure 2: Nasal Cytology Scale

0	=No eosinophils
1	=Few, scattered eosinophils
2	=Moderate #, small clumps of eosinophils
3	=Large clumps of eosinophils, not covering entire field
4	=Clumps of eosinophils covering the entire field

**Reviewer's Note:** The nasal cytology scale employed a quasi-subjective rating system that was used by the investigating physician to broadly quantify the degree of eosinophilia in participating patients' nasal secretions.

In addition, a pharmacoeconomic survey was completed by participating patients on visit 2 of the study, although results were not discussed in the sponsor's efficacy supplement, per se. [NDA 20-121, S-009, 4:59- 63].

Study enrollable patients were given new diary cards to record twice daily nasal symptoms and study medication usage (the latter, for assessment of compliance), and randomized to 1 of 4 study medication groups according to a computer generated code. Patients were then administered the 1<sup>st</sup> dose of study medication in the clinic (hence the 1<sup>st</sup> dose of study medication was administered in the a.m.). The 4 treatment groups were as follows [NDA 20-121, S-009, 3:55, 4:33]:

Double Blind Treatment Groups:	
STUDY GROUPS	DOSING
(1) Fluticasone propionate nasal spray 50 µg bid (12.5 µg/actuation)	2 sprays bid (q a.m. and p.m.)
(2) Fluticasone propionate nasal spray 100 µg bid (25 µg/actuation)	2 sprays bid (q a.m. and p.m.)
(3) Fluticasone propionate nasal spray 200 µg bid (50 µg/actuation)	2 sprays bid (q a.m. and p.m.)
(4) Placebo	2 sprays bid (q a.m. and p.m.)

Blinding of the 4 study medications were such that bottles were identical in appearance (25 mL amber glass bottles of 200 sprays/bottle fitted with a white pump and dust cover) but differed in the concentration of FP in each bottle [NDA 20-121, S-009, 3:45, 46].

As per clarification by Mrs. Alison Bowers of Glaxo Wellcome, U.S. Regulatory Affairs [Teleconference, 03/29/98, Mrs. Alison Bowers of Glaxo Wellcome, U.S. Regulatory Affairs and FAX, 04/02/98, Mrs. Alison Bowers of Glaxo Wellcome, U.S. Regulatory Affairs, p. 1-2 and FAX, 04/10/98, Mrs. Alison Bowers of Glaxo Wellcome, U.S. Regulatory Affairs, p. 3], clinical trial bottles for study FLTA 3010 (and also study FLN 350 and 351) consisted of [redacted] amber glass bottles similar in appearance to the Beconase™ bottles but differing in that they had a screw top and were not crimped. The specification used during assembly and labeling of these bottles included inspection to make sure that active and placebo bottles matched, especially with regard to the color of the dust cap. The clinical trial pack was 'very similar' to the market pack of FLONASE™ Nasal Spray except that the pump had a screw-on fitting to the 25 ml amber glass bottle, resembling the Beconase AQ Nasal Spray pack, rather than a crimp-on fitting to a 20 ml amber glass bottle. Minor changes to the nasal adapter had been shown in in-vitro testing not to alter the orifice or overall size of the nozzle of the nasal adapter. The distribution of droplet size within the spray and the pump performance and dose delivery were shown to be unaffected by these changes (for more information, please refer to the CMC section of the Medical Officer Review for NDA 20-121, S-009). Importantly, the bottles used

in this study (FLTA 3010) were also used in all other FLONASE clinical studies (both in the original NDA and in this NAPR supplement).

Patients in each group were instructed to take medication administered as the same number of sprays (2 sprays) in each nostril, morning and evening, after recording the severity of nasal symptoms. Patients were dispensed with a 2 week supply of study medication and instructed to return in  $14 \pm 2$  days to clinic, having withheld their a.m. dose of study medication prior to clinic evaluation.

(III) Visit 3 (Day  $14 \pm 2$  days) [NDA 20-121, S-009, 3:50, 4:26]:

During visit 3 of the study, NAPR symptoms were again assessed by the investigator (the physician-rated TNSS) and patient diaries were collected, with new diaries assigned. Again, AEs and concurrent medication use was assessed by the investigator. A follow-up nasal/oropharyngeal and ear examination was performed (along with evaluation for oral or nasal candidiasis but with no nasal cytology performed at this visit). Another pharmacoeconomic survey was administered to patients during visit 3. Patients were given a new batch (2 week supply) of study medication with instructions to return to clinic for reassessment in  $14 \pm 2$  days.

(IV) Visit 4 (Day  $28 \pm 2$  days, last day of the double-blind treatment period and day 0/baseline visit of open label extension) [NDA 20-121, S-009, 3:50, 4:26]:

During visit 4 of the study, patients underwent repeat physical examination (including the nasal/oropharyngeal and ear examination, evaluation for oral or nasal candidiasis, and nasal cytology), repeat laboratory testing (including a.m. plasma cortisol levels and serum IgE levels), along with a review of NAPR symptoms and concomitant medications by the investigator. Patient-rated and physician-rated overall evaluation of response to therapy was performed on this last visit of the double-blind treatment period. Another pharmacoeconomic survey was completed by patients.

Patients with no protocol violations and no clinically significant (as determined by the investigator) laboratory tests during the 4 week double-blind treatment period who were willing to participate in the 6 month open-label safety extension of study FLTA 3010, underwent Cortrosyn-stimulation testing on visit 4 (the 1<sup>st</sup> Cortrosyn stimulation test performed in this study) and were dispensed open-label study medication (FP 200  $\mu\text{g}$  bid), with the 1<sup>st</sup> dose administered in the clinic on visit 4. Again, these patients were required to have fulfilled the same inclusion/exclusion criteria as previously delineated for the screening visit in order to be enrolled in the open-label safety extension [NDA 20-121, S-009, 3:53-55].

(V) Open-label safety extension (Visit 4, 5, 6, and 10 (no visits 7, 8, or 9 per protocol) [NDA 20-121, S-009, 3:50-55, 4:27-28]:

APPEARS THIS WAY  
ON ORIGINAL

The first 288 patients who qualified for enrollment into the open-label safety extension and who were willing to participate in this 6 month safety extension were continued in the open-label extension of the study. These patients were given new diary cards, and open-label study medication which consisted of sufficient medication for the time interval between visit 4 and 5 (3 bottles of FP in the 50 µg/actuation strength) to be taken at a dose of FP 200 µg bid. Patients were instructed to use 2 sprays of study medication bid, in the a.m. and p.m. In addition, patients were instructed to record on their diary cards study medication usage and adverse events. Importantly, however, TNSS were assessed by patients only during each of the 7 days (i.e. 1 week) immediately preceding scheduled study visits and not daily (as had been previously done for the double-blind period) for the entire open-label period [NDA 20-121, S-009, 3:51]; as the primary objective of the open-label extension was safety monitoring and not assessment of efficacy. In addition to patient-rated total nasal symptoms, at visit 4 and 10 (or at the time of early patient discontinuation), patients subjectively rated their overall response to treatment during the double-blind treatment period (visit 4) or open-label treatment period (visit 10) using the 7-point ordinal scale summarized in Figure 3 below [NDA 20-121, S-009, 3:58]:

Figure 3: Patient-self Rated Overall Response to Therapy Evaluation Using An Ordinal Scale

Significant Improvement
Moderate improvement
Mild improvement
No change
Mildly worse
Moderately worse
Significantly worse

APPEARS THIS WAY  
ON ORIGINAL

Physicians were likewise asked to rate patients' overall response to therapy using the same scale as the overall patient evaluation for visits 4 and 10 (or at the time of early patient discontinuation), albeit with the addition of a 'not evaluable' category to the ordinal scale (see Figure 4 below):

Figure 4: Physician's Ordinal Rating of Patients' Overall Response to Therapy Evaluation Scale [NDA 20-121, S-009, 3:58, 4:50]:

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

APPEARS THIS WAY  
ON ORIGINAL

At study visits 5 and 6 (Day  $61 \pm 7$  days and day  $122 \pm 7$  days, respectively, post-visit 4), patients' symptoms were re-assessed by the investigator (physician-rated TNSS), and a follow-up nasal/oropharyngeal and ear examination was performed prior to administration of the a.m. dose of FP Nasal Spray in the clinic. Adverse events, concurrent medication assessments and study drug compliance was assessed. Again, new diary cards and study medication was dispensed for use till visit 10.

Visit 10 (day  $183 \pm 7$  days post-visit 4) constituted the final study visit of the open-label extension (and indeed the final visit for the entire study). Consequently, more extensive patient follow-up was performed during this visit, consisting of: a repeat physical exam (with follow-up nasal/oropharyngeal and ear examination), clinical laboratory tests (including a.m. plasma cortisol and Cosyntropin testing), patient-rated and physician-rated overall evaluation of response to therapy, AE and concomitant medication assessments. Any unresolved AE or abnormalities in laboratory data considered 'possibly' related to study medication by the investigator at the final study visit required further follow-up visits by protocol [NDA 20-121, S-009, 3:51-52].

(VI) Collection of pollen counts:

For the purposes of this study, which was to assess the therapeutic response of non-allergic perennial rhinitis patients, pollen counts were not collected on a daily basis by the sponsor, nor recorded in a log.

(VII) Safety evaluations [NDA 20-121, S-009, 3:58-60, 64, 4:47-49]:

In addition to the review of all adverse events (AEs) by the investigator, performance of routine laboratory tests, and physical examination performed at each clinic visit (with an emphasis in detecting potential adverse side effects associated with corticosteroid treatment), short (30-60') Cortrosyn stimulation testing to evaluate the response of the adrenal axis to stress was performed using the standard dose of cosyntropin (250  $\mu$ g) administered either I.V. or I.M. at visits 4 and 10, to those patients participating in the open-label extension of the study. Measurement of a.m. plasma cortisol and Cortrosyn-stimulation testing was performed prior to dosing with a.m. study medication.

A normal response to Cortrosyn stimulation testing was defined as a baseline plasma cortisol level  $> 5 \mu$ g/dL, with a 30' post-stimulation increase of  $\geq 7 \mu$ g/dL and a post-stimulation cortisol level of  $\geq 18 \mu$ g/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.

Likewise a.m. plasma cortisol levels were measured at screening (visit 1), post-4 weeks of double-blind treatment (week 4), and at the end of the open-label study extension (week 10) or at the time of patient discontinuation, whichever time period preceded the other [NDA 20-121, S-009, 3:60]. Of note, the a.m. plasma cortisol level (at screening and all other study visits when drawn)

was obtained between 6:30 a.m. and 9:30 a.m. An a.m. cortisol level of at least 5 µg/dL was required for study entry [NDA 20-121, S-009, 4:47].

**Reviewer's Note: Patients were instructed to fast overnight (~ 8 hours) for all clinical laboratory tests, including Cortrosyn-stimulation testing. The time of collection of specimens for the Cortrosyn-stimulation testing was recorded on the case report forms (CRFs) [FAX, 04/02/98, Mrs. Alison Bowers, U.S. Regulatory Affairs, Glaxo Wellcome, p. 2]**

#### 8.1.3.2. Clinical Endpoints:

The following primary and secondary efficacy variables were assessed in this NAPR study:

##### Primary Efficacy Variables [NDA 20-121, S-009, 3:63-64, 4:30]:

- (1) The change from baseline (defined as Visit 1) in the patient-rated average p.m. reflective TNSS (=sum of rhinorrhea, nasal obstruction, and postnasal drip) for each week of the double-blind period.
- (2) The change from baseline in the patient-rated overall evaluation of response to therapy for the double-blind treatment.

**Reviewer's Note: Given a symptom score range of 0-100 for any individual NAPR symptom, patients could achieve a TNSS ranging from 0-300. The primary comparison of interest (FP 100 µg bid vs. placebo) was not specified by the sponsor in either the study protocol or study report.**

##### Secondary Efficacy Variables [NDA 20-121, S-009, 3:63]:

- (1) Average patient-rated individual symptom scores for both the a.m. and p.m. (summarized by each study week),
- (2) Physician-rated improvement in nasal symptoms (both TNSS and the nasal individual symptoms) at baseline and all subsequent individual clinic visits,
- (3) Physician-rated evaluation of patients' overall response to therapy for the double-blind treatment period.

**Reviewer's Note: The change from baseline (defined as Visit 1) in the patient-rated average a.m. reflective TNSS (=sum of rhinorrhea, nasal obstruction, and postnasal drip) for each week of the the double-blind period was included by the medical officer as a secondary efficacy endpoint.**

#### 8.1.3.1. Statistical Analysis [NDA 20-121, S-009, 3:63, 4:29-31]

A minimum sample size of 160 patients per treatment arm (or 640 patients total) was calculated in order to detect a treatment difference of at least 20 points in the patient-rated TNSS symptom score, between placebo and the 3 FP treatment groups, based on a 2-sided  $\alpha=0.05$ , a power of 80%, and an estimated

standard deviation of 65 points for the TNSS. This estimated sample size was based on results from NAPR study FLN-351 [NDA 20-121, S-009, 3:62, 4:29].

The patient-rated and physician-rated overall response to therapy was tabulated, and the Cochran-Mantel-Haenszel test was used to detect statistically significant differences between treatment groups [NDA 20-121, S-009, 3:63].

The primary efficacy variable and all secondary efficacy variables were analyzed for intent-to-treat patients (patients who were exposed to double-blind medication with baseline and post-baseline symptom assessments) [NDA 20-121, S-009, 4:30]. An 'evaluable' efficacy population (i.e. all patients who had no major protocol violations as determined by the investigator(s)) was used to support results for the primary efficacy variable in the intent-to-treat population. Safety analyses were based on the intent-to-treat population who underwent evaluation for adverse event occurrence, clinical laboratory tests (including tests to assess adrenal function), vital signs, physical examination, and 12-lead ECG. The open-label safety population consisted of those patients who continued in the 1 year open-label safety extension) [NDA 20-121, S-009, 4:30].

Missing symptom scores used to generate a total symptom score were handled by not replacing ('imputing') a particular missing score and with no last observation carried forward. In the case of missing diary card values, means were computed from the available data for that time period (i.e. week) [FAX, 04/02/98, Mrs. Alison Bowers, GlaxoWellcome, U.S. Regulatory Affairs, p. 2].

The primary and secondary variables were analyzed using 2-way analysis of variance (ANOVA), which used the F-test to assess statistically significant differences between treatment groups with regard to changes in mean weekly scores or mean scores per visit from baseline. Subsequent pairwise comparisons were interpreted in the presence of all significant overall tests. Of note, multivariate analyses were not employed as originally stated in the protocol because of the sponsor's difficulty in interpreting the complicated interrelationships among the different measures within the scope of clinical significance [NDA 20-121, S-009, 3:62, Reference: Statistical Review, Dr. James Gebert, HFD-715, 03/98, p. 5].

Data collected during the open-label extension were analyzed by assessing the change from baseline (defined as Visit 4 or the last day of the double-blind treatment period) in total symptom scores and individual symptoms and were summarized and tested using the paired t-test [NDA 20-121, S-009, 4:31]. Subgroup analysis by age, gender, race, weight, severity of symptoms, or other demographic characteristics was not performed by the sponsor for either the primary or secondary efficacy variables.

The safety assessment of adrenal response was presented as a tabulation of the frequency of change in a.m. plasma cortisol levels from Visit 1 to Visit 4 according to 'normal' and 'abnormal' categories (as previously defined in section 8.1.3.1.b. (VII)). Responses of the different treatment groups were compared using a chi-square test [NDA 20-121, S-009, 4:32]. Results of Cortrosyn stimulation testing was presented not as mean change from baseline but rather as the frequency of abnormal plasma cortisol concentration and abnormal post-

stimulation change from baseline, as tabulated by treatment group and visit [NDA 20-121, S-009, 4:32].

#### 8.1.4. Results

##### 8.1.4.1. Patient Demographics

(A) A total of 837 patients with a history of NAPR (and a negative skin test to all allergens relevant to the geographic area of each study site) were randomized into the study. Two hundred and ten (210) patients were randomized to placebo, 208 were assigned to FP 50 µg bid, 211 were assigned to FP 100 µg bid, and 208 were assigned to FP 200 µg bid [NDA 20-121, S-009, 3:23] and these patients comprised the intent-to-treat population (ITT). Seven hundred and seventy nine patients (779, or 93% of all patients randomized into the double-blind portion of the study) completed the double-blind portion of the study and 58 patients withdrew from the study prior to study completion. For the open-label portion of the study, a total of 289 patients were enrolled (at 32 study sites), all or whom received FP 200 µg bid. Two hundred and twenty three (223) or 77% of all patients randomized into the open-label portion of the study completed the open-label safety extension and 66 patients withdrew from the study.

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

Table II. Patient Disposition [NDA 20-121, S-009, 3:23, 66]

PATIENT DISPOSITION	DOUBLE-BLIND TREATMENT PERIOD				OPEN-LABEL PERIOD
	Placebo	FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	FP 200 µg bid
Enrolled Patients	210	208	211	208	289
Intent-to-Treat	210	208	211	208	289
Safety Evaluable (same as ITT)	210	208	211	208	289
Completed Study	189	188	196	196	223

(B) As discussed above, a total of 58 patients withdrew from the double-blind portion of the study prior to study completion, leaving 779 patients who completed the entire double-blind portion of the study. No overwhelming reason for early discontinuation was noted in the double-blind portion of the study and the highest incidence (3%) of discontinuation was noted in the placebo and FP 50 µg bid groups, due to 'adverse events' [NDA 20-121, S-009, 3:66]. For the open-label period, out of the 289 patients enrolled, 66 (23%) discontinued treatment prematurely. The most common reason for early discontinuation during the open-label period either was due to adverse events (18 patients discontinued=6% of total) or due to 'other reasons' (defined as, e.g.: withdrawal of consent, protocol violation, patient moved away) in which case a total of 17 patients for the 4 treatment groups combined (6% of total) discontinued treatment. This data is summarized in Table III. [NDA 20-121, S-009, 3:66].

Table III. Number and Percentage (%) of Randomized Patients Who Discontinued the Study with Reasons for Discontinuation, ITT Population [NDA 20-121, S-009, 3:66]:

	DOUBLE-BLIND TREATMENT PERIOD				OPEN-LABEL PERIOD
	Placebo	FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	FP 200 µg bid
Number Enrolled	210	208	211	208	289
Number (%) Withdrawn	11 (5%)	20 (9%)	15 (7%)	12 (6%)	66 (23%)
<b>Reason for Discontinuation:</b>					
Adverse event	6 (3%)	6 (3%)	3 (1%)	3 (1%)	18 (6%)
Failed to Meet Entrance Criteria	2 (1%)	5 (2%)	5 (2%)	3 (1%)	1 (<1%)
Failed to Return	0 (0%)	2 (1%)	3 (1%)	4 (2%)	19 (7%)
Lack of Efficacy	1 (<1%)	2 (1%)	3 (1%)	0 (0%)	11 (4%)
*Other	2 (1%)	5 (2%)	1 (<1%)	2 (1%)	17 (6%)
<b>ALL REASONS</b>	<b>11 (5%)</b>	<b>20 (9%)</b>	<b>15 (7%)</b>	<b>12 (6%)</b>	<b>66 (23%)</b>

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

**Reviewer's Note:** With the exception of the open-label period, the total % of patient discontinuation was less than 10% of the total number of patients randomized into the study. The overall discontinuation rate for all 4 treatment arms was approximately 7%, which represents a reasonable rate of premature patient discontinuation for the double-blind period. Overall, the reasons for early patient discontinuation were deemed acceptable by the medical reviewer.

(C) Pooled demographic data with regard to patient characteristics in the intent-to-treat population (ITT) for the double-blind treatment period are summarized in Table IV. below:

APPEARS THIS WAY  
ON ORIGINAL

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
<b>Gender: (n, (%))</b>					
Male	77 (37%)	66 (32%)	65 (31%)	62 (30%)	0.445
Female	133 (63%)	142 (68%)	146 (69%)	146 (70%)	
<b>Race: (n, (%))</b>					
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%)	
<b>Age: (yrs)</b>					
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	
<b>Weight: (lbs.)</b>					
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	
<b>Height: (inches)</b>					
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	
<b>Tobacco Use:</b>					
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	
<b>Medical History (at screening):</b>					
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%)	
<b>% of Patients with ≥ 1 Concurrent Medication</b>					
	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.

**Reviewer's Note: Overall, the 4 treatment groups were well balanced in comparison to one another from a demographic standpoint. No statistically significant differences for any of the parameters evaluated were noted amongst the 4 treatment groups. The majority of study patients were Caucasian (> 90% of total). Approximately twice as many female patients as male patients were enrolled in the study but surprisingly this numerical difference was not found to be statistically significant. The majority of patients did not use tobacco (> 2/3 of total) during the double-blind period of the study. With the exception of a higher prevalence of underlying respiratory disorders in the FP 50 µg bid group (not specified or categorized in the study report) [NDA 20-121, S-009, 3:120], all 4 treatment groups had a similar prevalence of medical disorders that would fall under the category of 'allergic disease'. Furthermore, the majority of patients (80-83%) in each treatment group had concurrent medical conditions at the time of**

randomization and a majority were using a concurrent medication (one that was allowed per study exclusion criteria) at the time of randomization. For all 4 treatment groups, the most commonly used classes of medications included: NSAIDs, acetaminophen, aspirin, alka-seltzer, estrogens (female patients), oral contraceptive pills (female patients), multivitamins, antidepressants, and thyroid preparations) [NDA 20-121, S-009, 3:131-148].

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.

(D) Patient distribution by disease severity at screening (Day -6 to Day 0) in the ITT population, as assessed by patient self-rated total nasal symptom scores (TNSS) and the individual nasal symptoms of nasal obstruction, postnasal drip, rhinorrhea, and sneezing, for the a.m. and p.m. separately; failed to reveal a statistically significant difference in TNSS and the respective individual nasal symptoms between the 4 treatment groups [NDA 20-121, S-009, 3:149-154]. Nonetheless, for the a.m. and p.m. and individual nasal symptoms at screening, the FP 50 µg bid group and FP 100 µg bid groups numerically had slightly higher symptom scores (TNSS=205.2 ± 3.4 (standard error (SE)) and 202.6 ± 3.6 (SE)) than the other 2 treatment groups (TNSS=197.6 ± 3.7 (SE), placebo group and 198.1 ± 3.4 (SE), FP 200 µg bid) [NDA 20-121, S-009, 3:149-150, 152-154].

#### (E) Patient Validity

Patients diary data were invalidated in study FLTA 3010 if patients failed to meet the minimal requirement for compliance (defined as ≥ 80% use or 45 doses out of a total of 56 doses bid of study medication of study medication taken during the double-blind period) during each week of the double-blind period of the study. Forty eight (48) patients (7 treated with placebo, 17 treated with FP 50 µg bid, 14 treated with FP 100 µg bid, and 10 treated with FP 200 µg bid) of the 789 patients randomized to 1 of the 4 treatment groups had data invalidated for at least 1 of the 4 weeks of the double-blind treatment period for reasons of incomplete efficacy data [FAX, 04/10/98, Mrs. Alison Bowers, U.S. Regulatory Affairs, Glaxo Wellcome, p. 5-7]. All patients listed as withdrawals for FLTA 3010 (see Table 3 of the sponsor's NAPR submission [NDA 20-121, S-009, 3:112-116]) also had diary data that was invalidated for efficacy analysis with the exception of 4 patients in the group, and 2 patients in the FP 200 µg bid group, respectively, who were withdrawn from the study after they had contributed ≥ 22 days of diary data and hence were included in the efficacy analysis [FAX,

04/10/98, Ms. Alison Bowers, U.S. Regulatory Affairs, Glaxo Wellcome, p. 2-3].

A summary of invalidated patients and the reasons for invalidation are summarized in Attachment 1 of a FAX provided by the sponsor on 04/10/98 [FAX, 04/10/98, Mrs. Alison Bowers, U.S. Regulatory Affairs, Glaxo Wellcome, p. 5-7].

**Reviewer's Note: Criteria for invalidation of patient data (insufficient number of diary recordings) was somewhat less stringent to those seen in rhinitis trials but overall deemed reasonable by the medical reviewer. Additionally, patients were altogether withdrawn from the study if they failed to return for clinic visits, failed to meet entrance criteria, withdrew consent, left for reasons of an adverse event. These criteria were comparable to that of other rhinitis studies. Hence, overall, the criteria for excluding patients from efficacy analysis were appropriate and consistent with other rhinitis trials.**

**(F) Duration of Study Medication Exposure**

The extent of exposure to study medication of at least 2 weeks of double-blind treatment period for all 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].

**(G) Patient Compliance [NDA 20-121, S-009, 3:66, 117]**

Assessment of patient compliance with double-blind medication was determined by diary card data in which patients recorded all doses of study medication taken and the time of dosing. The number of patients who reported that they took at least 80% of scheduled medication was tabulated by treatment group and study week [NDA 20-121, S-009, 3:117 (Table 4)]. Based on these data, at least 94% of patients (range 94-97%) in each treatment group (for the 4 groups) were ≥ 80% compliant in taking study medication during Weeks 1 and 2 of the study and ≥ 97% of patients in each treatment group were ≥ 80% compliant during Weeks 3 and 4 of the study.

For the open-label safety extension, between 82% and 91% of patients reported they had been ≥ 80% compliant with study medication during the week preceding Week 4. Reported compliance remained high at study Visits 5 and 6, with ≥ 87% of patients reporting that they took ≥ 80% of their study medication.

**8.1.4.2. Efficacy Endpoint Outcomes**

**(I) Primary Efficacy Variables:**

All efficacy analyses in this review were based on the intent-to-treat (ITT) 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). The primary efficacy variables consisted of: (1) the change from baseline (defined as Visit 1) in the patient-rated average p.m. reflective TNSS (=sum of rhinorrhea, nasal obstruction, and postnasal drip) for each week of the double-blind period (4 weeks total) where the primary comparison of interest (though not explicitly specified in the study protocol) was the FP 100 µg bid treatment group (the proposed dose of FP for the NAPR indication) vs. placebo and (2) the change from baseline in the patient-rated overall evaluation of response to therapy for the double-blind treatment; where the primary comparison of interest was the FP 100 µg bid treatment group vs. placebo [NDA 20-121, S-009, 3:63, 4:30].

For the change from baseline in the patient-rated average p.m. reflective TNSS for each week of the double-blind treatment period, all 3 doses of FP nasal spray demonstrated statistically significantly greater efficacy in decreasing total nasal symptoms from baseline, compared to placebo treatment (Table V). Furthermore, as previously noted, all 4 treatment groups were reasonably balanced with respect to overall NAPR symptom scores (the TNSS) at the time of pre-treatment with study medication (range in TNSS scores: [redacted] [NDA 20-121, S-009, 3:154 (Table 17 in efficacy supplement or Table V. in this medical officer review)]).

Interestingly, for the change in p.m. TNSS from the baseline efficacy endpoint, the FP 50 µg bid treatment group showed the greatest degree of change in patient self-rated symptoms with a mean maximum decrease in TNSS of -90.8 points by week 4 of treatment, as compared with placebo (mean -64.2 point decrease) [NDA 20-121, S-009, 3:153-154 (Table 17 in efficacy supplement or Table V. in this medical officer review)]. For all 3 active FP treatments, efficacy was seen by week 1 of treatment and this efficacy (mean decrease in TNSS) became progressively greater by week 4 of treatment. No statistically significant differences between the 3 active treatments were noted at any of the time points during the double-blind treatment period, nor did any of the p-values in which comparisons were performed between the 3 active treatment groups approach statistical significance.

Review of the individual patient self-rated p.m. nasal symptom scores of nasal obstruction, postnasal drip, and rhinorrhea (secondary efficacy endpoints discussed later in the review) which comprised the TNSS for the double-blind treatment period, revealed that each individual nasal symptom contributed approximately equally to the TNSS, although for all 4 treatment groups, the postnasal drip score (range pre-treatment: [redacted]) followed by the nasal obstruction score (range pre-treatment: [redacted]) contributed slightly more to the determination of the total nasal symptom score (TNSS) than did the rhinorrhea score (range pre-treatment: [redacted]) [NDA 20-121, S-009, 3:153-154 (Table 17 in efficacy supplement or Table V. in this medical officer review)]. The sneezing score (which was not tallied in the TNSS) was the least severe symptom score

with a pre-treatment range of [redacted] for the 4 treatment groups [NDA 20-121, S-009, 3:154].

For the primary efficacy endpoint of change from baseline in the patient-rated overall evaluation of response to therapy for the double-blind treatment period, again all 3 active FP treatment groups demonstrated a statistically significant response to treatment for the double-blind period (4 weeks duration) compared to placebo ( $p \leq 0.011$ ) [NDA 20-121, S-009, 3:157 (Table 20 in efficacy supplement or Table VI. in this medical officer review)]. Interestingly, a significant placebo response (~ 30% decrease in the TNSS score by week 4 of treatment or ~ 15% of these patients noted 'significant improvement' with placebo treatment) was noted in the placebo group. A greater proportion of patients in the FP 200  $\mu\text{g}$  bid group demonstrated 'significant improvement' as compared with the other 2 doses of active FP (and placebo) and a lower proportion of patients in the FP 200  $\mu\text{g}$  bid group demonstrated 'no change' in response, as compared with the FP 50 and 100  $\mu\text{g}$  bid groups. Overall, however, no statistically significant difference in treatment response was noted between the 3 FP treatment groups ( $p \geq 0.356$ ) [NDA 20-121, S-009, 3:157 (Table 20 in efficacy supplement or Table VI. in this medical officer review)]. Daily p.m. symptom scores which could be used to assess onset of action of FP were not provided as data in this efficacy supplement. Additionally, a subgroup analysis of the 2 primary efficacy variables was not performed in this study.

**Reviewer's Note:** For the 2 primary efficacy endpoints discussed above, review of evaluable patients for the double-blind treatment period, indicates that relatively few patients were classified as 'unevaluable' for any of the 4 treatment groups. As previously discussed in section 8.1.4.1. 'Patient Demographics', a reasonable number of patients in all 4 treatment groups completed the double-blind treatment. A total of 58 patients withdrew sometime during the double-blind treatment period, leaving 779 (or 93% of the total ITT population) patients who completed the 4 week trial.

Based on review of the primary efficacy endpoint data, the FP 50  $\mu\text{g}$  bid treatment demonstrated slightly greater efficacy for the change from pre-treatment in the patient self-rated p.m. total nasal symptom score (TNSS for each of the 4 weeks of treatment, although the differences between all 3 active treatments were very small with small variability in symptom scores in all 4 treatment arms. For the primary efficacy endpoint of patient self-rated response to treatment, the FP 100  $\mu\text{g}$  bid and FP 200  $\mu\text{g}$  bid groups afforded slightly greater overall improvement in symptoms, as compared with either the FP 50  $\mu\text{g}$  bid or placebo treatments (again, the numerical differences between the 3 treatment groups were small). Thus, overall, for the 2 primary efficacy endpoints, no dose response was clearly discernible between the 3 active treatment groups.

**Thus, based on these data for the primary efficacy variables, the recommended dose of fluticasone propionate nasal spray for NAPR symptoms would be 100 µg bid (or conversely 200 µg qd).**

**(II) Secondary Efficacy Variables:**

The secondary efficacy variables for study FLTA 3010 consisted of a number of clinical endpoints evaluated in the ITT or efficacy evaluable population: (1) the mean change from baseline (defined as the mean score for the study run-in period) in patient-rated individual symptom scores for both the a.m. and p.m. (summarized by each study week), (2) physician-rated improvement in nasal symptoms (both TNSS and the individual nasal symptoms) from baseline at all subsequent individual clinic visits, and (3) physician-rated evaluation of patients' overall response to therapy for the double-blind treatment period, along with (4) the change from baseline (defined as Visit 1) in the patient-rated average a.m. reflective TNSS (=sum of rhinorrhea, nasal obstruction, and postnasal drip) for each separate week of the double-blind period.

Review of efficacy for the latter endpoint (#4) revealed that again, all 3 active FP treatment groups demonstrated statistically significantly greater efficacy in decreasing the a.m. TNSS at each week post-treatment from the pre-treatment score, compared to placebo ( $p \leq 0.003$ ) [(Table 15 in efficacy supplement or Table VII. in this medical officer review), NDA 20-121, S-009, 3:150]. Again, the FP 50 µg bid group afforded a numerically slightly greater decrease in TNSS than the other 2 active FP groups, consistent with the change in p.m. TNSS data for FLTA 3010.

APPEARS THIS WAY  
ON ORIGINAL

Table V.  
 3f of Flonase Nasal Spray vs. Placebo: P.M. Total Nasal Symptom Score  
 Primary Efficacy Variable: Intent-to-Treat (ITT) for the Double-blind Treatment Period  
 NDA 20-121, S-009, 3:153]

	TREATMENT GROUPS				P-value:					
	Placebo	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						
<b>Total Nasal Symptom Score (TNSS): Composite of Rhinorrhea, Nasal Obstruction, Postnasal Drip</b>										
Pre-Treatment (day -6 to 0) (n, mean score ± SE)	210 203.9 ± 2.9	208 207.6 ± 3.0	211 207.4 ± 3.2	207 203.6 ± 2.8	0.283	0.321	0.943	0.931	0.317	0.359
Week 1 (day 1-7) (n, Δ in score ± SE)	210 -36.1 ± 3.6	204 -54.9 ± 4.0	207 -52.7 ± 4.0	205 -48.3 ± 3.9	<0.001	<0.001	<0.021	0.708	0.212	0.380
Week 2 (day 8-14) (n, Δ in score ± SE)	208 -51.6 ± 4.6	201 -75.2 ± 4.8	204 -73.1 ± 5.0	204 -71.4 ± 4.5	<0.001	<0.001	<0.002	0.744	0.571	0.809
Week 3 (day 15-21) (n, Δ in score ± SE)	203 -60.1 ± 4.3	192 -82.4 ± 5.2	201 -78.1 ± 5.1	202 -81.3 ± 4.7	<0.001	0.005	<0.001	0.479	0.776	0.667
Week 4 (day 22-28) (n, Δ in score ± SE)	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	0.586	0.523	0.925

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

APPEARS THIS WAY  
ON ORIGINAL

Table VI.  
 3f of Flonase Nasal Spray vs. Placebo: Overall Patient Evaluation  
 Primary Efficacy Variable: Intent-to-Treat (ITT) for the Double-blind Treatment Period  
 NDA 20-121, S-009, 3:157]

	TREATMENT GROUPS				P-value:					
	Placebo	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	206	204						
<b>Patient Response to Treatment</b>					0.008	0.011	<0.001	0.843	0.439	0.356
Significant Improvement	32 (15%)	45 (22%)	43 (21%)	47 (23%)	NA	NA	NA	NA	NA	NA
Moderate Improvement	36 (17%)	47 (23%)	51 (25%)	59 (29%)	NA	NA	NA	NA	NA	NA
Mild Improvement	58 (28%)	58 (29%)	66 (32%)	61 (30%)	NA	NA	NA	NA	NA	NA
No change	67 (32%)	41 (20%)	34 (17%)	29 (14%)	NA	NA	NA	NA	NA	NA
Mildly Worse	10 (5%)	2 (<1%)	5 (2%)	0	NA	NA	NA	NA	NA	NA
Moderately Worse	3 (1%)	8 (4%)	5 (2%)	6 (3%)	NA	NA	NA	NA	NA	NA
Significantly Worse	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	NA	NA	NA	NA	NA	NA

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

APPEARS THIS WAY  
ON ORIGINAL

Table VII.  
 31 of Flonase Nasal Spray vs. Placebo: A.M. Total Nasal Symptom Score  
 Secondary Efficacy Variable: ITT Patient Population for the Double-blind Treatment Period  
 NDA 20-121, S-009, 3:150]

	TREATMENT GROUPS				P-value:					
	Placebo	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						
<b>Total Nasal Symptom Score (TNSS): Composite of Rhinorrhea + Nasal Obstruction + Postnasal Drip</b>										
Pre-Treatment (day -6 to 0) (n, mean score ± SE)	210 197.6 ± 3.7	208 205.2 ± 3.4	211 202.6 ± 3.6	207 198.1 ± 3.4	0.077	0.264	0.855	0.510	0.113	0.352
Week 1 (day 1-7) (n, Δ in score ± SE)	210 -37.7 ± 3.9	204 -56.3 ± 4.2	207 -51.2 ± 4.1	205 -48.2 ± 3.9	<0.001	<0.001	0.003	0.358	0.131	0.552
Week 2 (day 8-14) (n, Δ in score ± SE)	208 -47.1 ± 4.7	200 -74.5 ± 5.1	204 -67.9 ± 5.1	204 -66.8 ± 4.5	<0.001	0.001	0.002	0.322	0.249	0.870
Week 3 (day 15-21) (n, Δ in score ± SE)	203 -54.9 ± 4.8	192 -81.0 ± 5.4	201 -75.4 ± 5.3	200 -75.4 ± 4.7	<0.001	0.003	0.003	0.409	0.377	0.952
Week 4 (day 22-28) (n, Δ in score ± SE)	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	0.520	0.268	0.641

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

APPEARS THIS WAY  
 ON ORIGINAL

Table VIII.  
 Efficacy of Flonase Nasal Spray vs. Placebo: Patient Self-Rated A.M and P.M. Nasal Obstruction 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	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						
<b>Nasal Obstruction Score</b>										
<b>Day -6 to 0 (Pre-treatment)</b> (n, mean score ± SE):										
A.M.	210 69.5 ± 1.6	208 73.8 ± 3.4	211 70.7 ± 1.6	208 70.3 ± 1.5	0.052	0.599	0.770	0.154	0.099	0.816
P.M.	210 68.2 ± 1.4	208 71.5 ± 1.4	211 68.7 ± 1.6	207 69.4 ± 1.5	0.140	0.808	0.578	0.216	0.359	0.753
<b>Day 1-7</b> (n, Δ in score ± SE):										
A.M.	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	0.276	0.154	0.733
P.M.	210 -10.2 ± 1.3	204 -18.3 ± 1.5	207 -16.8 ± 1.6	205 -16.6 ± 1.5	<0.001	<0.001	<0.002	0.536	0.424	0.855
<b>Day 14</b> (n, Δ in score ± SE):										
A.M.	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	0.281	0.292	0.980
P.M.	208 -15.6 ± 1.7	201 -25.9 ± 1.8	204 -23.0 ± 1.9	204 -24.4 ± 1.7	<0.001	<0.002	<0.001	0.255	0.557	0.580
<b>Day 15-21</b> (n, Δ in score ± SE):										
A.M.	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	0.287	0.604	0.582
P.M.	203 -17.2 ± 1.7	192 -27.4 ± 2.1	201 -23.7 ± 1.9	202 -27.8 ± 1.8	<0.001	<0.017	<0.001	0.141	0.845	0.118
<b>Day 22-28</b> (n, Δ in score ± SE):										
A.M.	203 -17.6 ± 2.0	191 -30.7 ± 2.1	197 -27.9 ± 2.1	198 -29.76 ± 1.9	<0.001	<0.001	<0.001	0.339	0.666	0.596
P.M.	203 -19.1 ± 1.9	191 -29.8 ± 2.1	197 -26.7 ± 2.1	198 -30.1 ± 1.9	<0.001	<0.007	<0.001	0.284	0.998	0.281

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.

APPEARS THIS WAY  
ON ORIGINAL

Table IX.  
 Efficacy of Flonase Nasal Spray vs. Placebo: Patient Self-Rated A.M and P.M. Postnasal Drip 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	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						
<b>Postnasal Drip Score</b>										
<b>Day -6 to 0 (Pre-treatment)</b> (n, mean score ± SE):										
A.M.	210 70.7 ± 1.6	208 72.2 ± 1.4	211 71.0 ± 1.4	208 70.3 ± 1.4	0.455	0.936	0.807	0.504	0.322	0.745
P.M.	210 73.2 ± 1.3	208 72.7 ± 1.4	211 68.7 ± 1.6	207 69.4 ± 1.5	0.811	0.946	0.444	0.863	0.600	0.485
<b>Day 1-7</b> (n, Δ in score ± SE):										
A.M.	210 -11.3 ± 1.5	204 -18.2 ± 1.6	207 -15.6 ± 1.6	205 -16.8 ± 1.5	0.002	0.047	0.011	0.241	0.544	0.572
P.M.	210 -13.0 ± 1.3	204 -17.3 ± 1.5	207 -16.7 ± 1.5	204 -16.1 ± 1.5	0.038	0.063	0.131	0.819	0.568	0.731
<b>Day 14</b> (n, Δ in score ± SE):										
A.M.	208 -16.9 ± 1.8	200 -23.7 ± 1.9	204 -22.3 ± 2.0	204 -23.1 ± 1.8	0.008	0.037	0.015	0.569	0.816	0.735
P.M.	208 -18.5 ± 1.7	201 -23.7 ± 1.8	204 -24.1 ± 1.9	56 -24.0 ± 1.8	0.045	0.027	0.029	0.844	0.868	0.975
<b>Day 15-21</b> (n, Δ in score ± SE):										
A.M.	203 -19.6 ± 1.9	192 -26.4 ± 2.0	201 -24.9 ± 2.0	200 -25.4 ± 1.8	0.011	0.046	0.034	0.559	0.650	0.895
P.M.	203 -21.4 ± 1.8	192 -26.6 ± 2.0	201 -26.2 ± 1.9	202 -27.3 ± 1.8	0.047	0.054	0.024	0.929	0.812	0.740
<b>Day 22-28</b> (n, Δ in score ± SE):										
A.M.	203 -20.2 ± 2.0	191 -28.9 ± 2.0	197 -29.0 ± 2.1	198 -27.4 ± 2.1	0.002	0.002	0.016	0.993	0.483	0.474
P.M.	203 -23.0 ± 1.9	191 -29.5 ± 1.0	197 -30.3 ± 2.0	198 -29.3 ± 2.0	0.014	0.005	0.026	0.747	0.800	0.562

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.

APPEARS THIS WAY  
ON ORIGINAL