CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-762/S023

Trade Name: Nasonex®

Generic Name: mometasone furoate monohydrate

Sponsor: Schering Corporation

Approval Date: 12/15/2004

Indication: This supplemental new drug application provides clinical support for the use of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray, 50 mcg, for the treatment of nasal polyps in patients 18 years of age and older.

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APPLICATION NUMBER:

20-762/S023

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-762/S-023

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Attention: Ronald J. Garutti, M.D.
Group Vice President
Global Regulatory Affairs

Dear Dr. Garutti:

Please refer to your supplemental new drug application dated February 26, 2004, received February 26, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray, 50 mcg.

We acknowledge receipt of your submissions dated April 6 and 26, June 25, November 12, 19 and 30, and December 7 and 9, 2004.

This supplemental new drug application provides clinical support for the use of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray, 50 mcg, for the treatment of nasal polyps in patients 18 years of age and older.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions indicated in the enclosed labeling.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (immediate container and carton labels submitted November 19, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this/these submission(s) should be designated "FPL for approved supplement NDA 20-762/S-023." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 6 to 17 years until December 15, 2007.

We remind you that a waiver for pediatric studies for this application was granted for patients less than 6 years old, but denied for patients 6 to 17 years old, in our letter dated October 8, 2004.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered a required post-marketing study commitment. The status of these post-marketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric studies under PREA for the treatment of nasal polyps in pediatric patients ages 6 to 17.

   Final Report Submission: December 15, 2007

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric post-marketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

Submit clinical protocols to your IND for this product. Submit non-clinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these post-marketing study commitments must be prominently labeled "**Post-marketing Study Protocol**", "**Post-marketing Study Final Report**", or "**Post-marketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Pulmonary and Allergy Drug Products and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury

12/15/04 01:40:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-762/S023

LABELING

PRODUCT

INFORMATION

NASONEX®

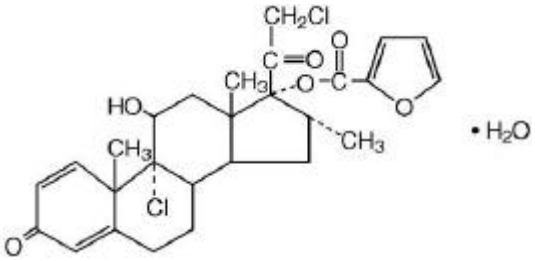
(mometasone furoate monohydrate)

Nasal Spray, 50 mcg*

FOR INTRANASAL USE ONLY

*calculated on the anhydrous basis

DESCRIPTION Mometasone furoate monohydrate, the active component of NASONEX Nasal Spray, 50 mcg, is an anti-inflammatory corticosteroid having the chemical name, 9,21-Dichloro-11ß,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2 furoate) monohydrate, and the following chemical structure:



Mometasone furoate monohydrate is a white powder, with an empirical formula of $C_{27}H_{30}Cl_2O_6 \bullet H_2O$, and a molecular weight of 539.45. It is practically insoluble in water; slightly soluble in methanol, ethanol, and isopropanol; soluble in acetone and chloroform; and freely soluble in tetrahydrofuran. Its partition coefficient between octanol and water is greater than 5000.

NASONEX Nasal Spray, 50 mcg is a metered-dose, manual pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mometasone furoate calculated on the anhydrous basis; in an aqueous medium containing glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, sodium citrate, citric acid, benzalkonium chloride, and polysorbate 80. The pH is between 4.3 and 4.9.

After initial priming (10 actuations), each actuation of the pump delivers a metered spray containing 100 mg of suspension containing mometasone furoate monohydrate equivalent to 50 mcg of mometasone furoate calculated on the

anhydrous basis. Each bottle of NASONEX Nasal Spray, 50 mcg provides 120 sprays.

CLINICAL PHARMACOLOGY NASONEX Nasal Spray, 50 mcg is a corticosteroid demonstrating anti-inflammatory properties. The precise mechanism of corticosteroid action on allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

In two clinical studies utilizing nasal antigen challenge, NASONEX Nasal Spray, 50 mcg decreased some markers of the early- and late-phase allergic response. These observations included decreases (vs placebo) in histamine and eosinophil cationic protein levels, and reductions (vs baseline) in eosinophils, neutrophils, and epithelial cell adhesion proteins. The clinical significance of these findings is not known.

The effect of NASONEX Nasal Spray, 50 mcg on nasal mucosa following 12 months of treatment was examined in 46 patients with allergic rhinitis. There was no evidence of atrophy and there was a marked reduction in intraepithelial eosinophilia and inflammatory cell infiltration (eg, eosinophils, lymphocytes, monocytes, neutrophils, and plasma cells).

Pharmacokinetics: ***Absorption:*** Mometasone furoate monohydrate administered as a nasal spray is virtually undetectable in plasma from adult and pediatric subjects despite the use of a sensitive assay with a lower quantitation limit (LOQ) of 50 pcg/mL.

Distribution: The *in vitro* protein binding for mometasone furoate was reported to be 98% to 99% in concentration range of 5 to 500 ng/mL.

Metabolism: Studies have shown that any portion of a mometasone furoate dose which is swallowed and absorbed undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. Upon *in vitro* incubation, one of the minor metabolites formed is 6ß-hydroxy-mometasone furoate. In human liver microsomes, the formation of the metabolite is regulated by

cytochrome P-450 3A4 (CYP3A4).

Elimination: Following intravenous administration, the effective plasma elimination half-life of mometasone furoate is 5.8 hours. Any absorbed drug is excreted as metabolites mostly via the bile, and to a limited extent, into the urine.

Special Populations: The effects of renal impairment, hepatic impairment, age, or gender on mometasone furoate pharmacokinetics have not been adequately investigated.

Pharmacodynamics: Four clinical pharmacology studies have been conducted in humans to assess the effect of NASONEX Nasal Spray, 50 mcg at various doses on adrenal function. In one study, daily doses of 200 and 400 mcg of NASONEX Nasal Spray, 50 mcg and 10 mg of prednisone were compared to placebo in 64 patients with allergic rhinitis. Adrenal function before and after 36 consecutive days of treatment was assessed by measuring plasma cortisol levels following a 6-hour Cortrosyn (ACTH) infusion and by measuring 24-hour urinary-free cortisol levels. NASONEX Nasal Spray, 50 mcg, at both the 200- and 400-mcg dose, was not associated with a statistically significant decrease in mean plasma cortisol levels post-Cortrosyn infusion or a statistically significant decrease in the 24-hour urinary-free cortisol levels compared to placebo. A statistically significant decrease in the mean plasma cortisol levels post-Cortrosyn infusion and 24-hour urinary-free cortisol levels was detected in the prednisone treatment group compared to placebo.

A second study assessed adrenal response to NASONEX Nasal Spray, 50 mcg (400 and 1600 mcg/day), prednisone (10 mg/day), and placebo, administered for 29 days in 48 male volunteers. The 24-hour plasma cortisol area under the curve (AUC_{0-24}), during and after an 8-hour Cortrosyn infusion and 24-hour urinary-free cortisol levels were determined at baseline and after 29 days of treatment. No statistically significant differences of adrenal function were observed with NASONEX Nasal Spray, 50 mcg compared to placebo.

A third study evaluated single, rising doses of NASONEX Nasal Spray, 50 mcg (1000, 2000, and 4000 mcg/day), orally administered mometasone furoate (2000, 4000, and 8000 mcg/day), orally administered dexamethasone (200, 400, and 800 mcg/day), and placebo (administered at the end of each series of doses) in

24 male volunteers. Dose administrations were separated by at least 72 hours. Determination of serial plasma cortisol levels at 8 AM and for the 24-hour period following each treatment were used to calculate the plasma cortisol area under the curve (AUC_{0-24}). In addition, 24-hour urinary-free cortisol levels were collected prior to initial treatment administration and during the period immediately following each dose. No statistically significant decreases in the plasma cortisol AUC, 8 AM cortisol levels, or 24-hour urinary-free cortisol levels were observed in volunteers treated with either NASONEX Nasal Spray, 50 mcg or oral mometasone, as compared with placebo treatment. Conversely, nearly all volunteers treated with the three doses of dexamethasone demonstrated abnormal 8 AM cortisol levels (defined as a cortisol level <10 mcg/dL), reduced 24-hour plasma AUC values, and decreased 24-hour urinary-free cortisol levels, as compared to placebo treatment.

In a fourth study, adrenal function was assessed in 213 patients with nasal polyps before and after 4 months of treatment with either NASONEX Nasal Spray, 50 mcg, (200 mcg once or twice daily) or placebo by measuring 24-hour urinary-free cortisol levels. NASONEX Nasal Spray, 50 mcg, at both doses (200 and 400 mcg/day), was not associated with statistically significant decreases in the 24-hour urinary-free cortisol levels compared to placebo.

Three clinical pharmacology studies have been conducted in pediatric patients to assess the effect of mometasone furoate nasal spray, on the adrenal function at daily doses of 50, 100, and 200 mcg vs placebo. In one study, adrenal function before and after 7 consecutive days of treatment was assessed in 48 pediatric patients with allergic rhinitis (ages 6 to 11 years) by measuring morning plasma cortisol and 24-hour urinary-free cortisol levels. Mometasone furoate nasal spray, at all three doses, was not associated with a statistically significant decrease in mean plasma cortisol levels or a statistically significant decrease in the 24-hour urinary-free cortisol levels compared to placebo. In the second study, adrenal function before and after 14 consecutive days of treatment was assessed in 48 pediatric patients (ages 3 to 5 years) with allergic rhinitis by measuring plasma cortisol levels following a 30-minute Cortrosyn infusion. Mometasone furoate nasal spray, 50 mcg, at all three doses (50, 100, and 200 mcg/day), was not associated

with a statistically significant decrease in mean plasma cortisol levels post-Cortrosyn infusion compared to placebo. All patients had a normal response to Cortrosyn. In the third study, adrenal function before and after up to 42 consecutive days of once-daily treatment was assessed in 52 patients with allergic rhinitis (ages 2 to 5 years), 28 of whom received mometasone furoate nasal spray, 50 mcg per nostril (total daily dose 100 mcg), by measuring morning plasma cortisol and 24-hour urinary-free cortisol levels. Mometasone furoate nasal spray was not associated with a statistically significant decrease in mean plasma cortisol levels or a statistically significant decrease in the 24-hour urinary-free cortisol levels compared to placebo.

Clinical Studies: ***Allergic Rhinitis.*** The efficacy and safety of NASONEX Nasal Spray, 50 mcg in the prophylaxis and treatment of seasonal allergic rhinitis and the treatment of perennial allergic rhinitis have been evaluated in 18 controlled trials, and one uncontrolled clinical trial, in approximately 3000 adults (ages 17 to 85 years) and adolescents (ages 12 to 16 years). This included 1757 males and 1453 females, including a total of 283 adolescents (182 boys and 101 girls) with seasonal allergic or perennial allergic rhinitis, treated with NASONEX Nasal Spray, 50 mcg at doses ranging from 50 to 800 mcg/day. The majority of patients were treated with 200 mcg/day. These trials evaluated the total nasal symptom scores that included stuffiness, rhinorrhea, itching, and sneezing. Patients treated with NASONEX Nasal Spray, 50 mcg, 200 mcg/day had a significant decrease in total nasal symptom scores compared to placebo-treated patients. No additional benefit was observed for mometasone furoate doses greater than 200 mcg/day. A total of 350 patients have been treated with NASONEX Nasal Spray, 50 mcg for 1 year or longer.

The efficacy and safety of NASONEX Nasal Spray, 50 mcg in the treatment of seasonal allergic and perennial allergic rhinitis in pediatric patients (ages 3 to 11 years) have been evaluated in four controlled trials. This included approximately 990 pediatric patients ages 3 to 11 years (606 males and 384 females) with seasonal allergic or perennial allergic rhinitis treated with mometasone furoate nasal spray at doses ranging from 25 to 200 mcg/day. Pediatric patients treated with NASONEX Nasal Spray, 50 mcg (100 mcg total daily dose, 374 patients) had a significant decrease in total nasal symptom (congestion, rhinorrhea, itching, and sneezing)

scores, compared to placebo-treated patients. No additional benefit was observed for the 200-mcg mometasone furoate total daily dose in pediatric patients (ages 3 to 11 years). A total of 163 pediatric patients have been treated for 1 year.

In patients with seasonal allergic rhinitis, NASONEX Nasal Spray, 50 mcg, demonstrated improvement in nasal symptoms (vs placebo) within 11 hours after the first dose based on one single-dose, parallel-group study of patients in an outdoor "park" setting (park study) and one environmental exposure unit (EEU) study, and within 2 days in two randomized, double-blind, placebo-controlled, parallel-group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1 to 2 weeks after initiation of dosing.

Prophylaxis of seasonal allergic rhinitis for patients 12 years of age and older with NASONEX Nasal Spray, 50 mcg, given at a dose of 200 mcg/day, was evaluated in two clinical studies in 284 patients. These studies were designed such that patients received 4 weeks of prophylaxis with NASONEX Nasal Spray, 50 mcg prior to the anticipated onset of the pollen season; however, some patients received only 2 to 3 weeks of prophylaxis. Patients receiving 2 to 4 weeks of prophylaxis with NASONEX Nasal Spray, 50 mcg demonstrated a statistically significantly smaller mean increase in total nasal symptom scores with onset of the pollen season as compared to placebo patients.

Nasal Polyps. Two studies were performed to evaluate the efficacy and safety of NASONEX Nasal Spray in the treatment of nasal polyps. These studies involved 664 patients with nasal polyps, 441 of whom received NASONEX Nasal spray. These studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in patients 18-86 years of age with bilateral nasal polyps. Patients were randomized to receive NASONEX Nasal Spray 200 mcg once daily, 200 mcg twice daily or placebo for a period of 4 months. The co-primary efficacy endpoints were 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of treatment as assessed by endoscopy. Efficacy was demonstrated in both studies at a dose of 200 mcg twice daily and in one study at a dose of 200 mcg once a day (see table below).

Effect of Nasonex Nasal Spray in two randomized, placebo-controlled trials in patients with nasal polyps

	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value for Nasonex 200 mcg qd vs placebo	P value for Nasonex 200 mcg bid vs placebo
Study 1	N = 115	N= 122	N= 117		
Baseline bilateral polyp grade*	4.21	4.27	4.25		
Mean change from baseline in bilateral polyp grade	-1.15	-0.96	-0.50	<0.001	0.01
Baseline nasal congestion**	2.29	2.35	2.28		
Mean change from baseline in nasal congestion	-0.47	-0.61	-0.24	0.001	<0.001
Study 2	N = 102	N = 102	N = 106		
Baseline bilateral polyp grade*	4.00	4.10	4.17		
Mean change from baseline in bilateral polyp grade	-0.78	-0.96	-0.62	0.33	0.04
Baseline nasal congestion**	2.23	2.20	2.18		
Mean change from baseline in nasal congestion	-0.42	-0.66	-0.23	0.01	<0.001

* polyps in each nasal fossa were graded by the investigator based on endoscopic visualization, using a scale of 0-3 where 0 = no polyps; 1 = polyps in the middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate; 3 = polyps reaching to or below the border of the inferior turbinate, or polyps medial to the middle turbinate (score reflects sum of left and right nasal fossa grades).

** nasal congestion/obstruction was scored daily by the patient using a 0-3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms.

There were no clinically relevant differences in the effectiveness of NASONEX Nasal Spray, 50 mcg, in the studies evaluating treatment of nasal polyps across subgroups of patients defined by gender, age, or race.

INDICATIONS AND USAGE NASONEX Nasal Spray, 50 mcg is indicated for the treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis, in adults and pediatric patients 2 years of age and older. NASONEX Nasal Spray, 50 mcg is indicated for the prophylaxis of the nasal symptoms of seasonal allergic rhinitis in adult and adolescent patients 12 years and older. In patients with a known

seasonal allergen that precipitates nasal symptoms of seasonal allergic rhinitis, initiation of prophylaxis with NASONEX Nasal Spray, 50 mcg is recommended 2 to 4 weeks prior to the anticipated start of the pollen season. Safety and effectiveness of NASONEX Nasal Spray, 50 mcg in pediatric patients less than 2 years of age have not been established.

NASONEX Nasal Spray, 50 mcg, is indicated for the treatment of nasal polyps in ~~adult and adolescent~~ patients 18 years of age and older. Safety and effectiveness of NASONEX Nasal Spray, 50 mcg, for the treatment of nasal polyps in pediatric patients less than 18 years of age have not been established.

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal; ie, joint and/or muscular pain, lassitude, and depression. Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to topical corticosteroids, with careful monitoring for acute adrenal insufficiency in response to stress. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroid dosing may cause a severe exacerbation of their symptoms.

If recommended doses of intranasal corticosteroids are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, topical corticosteroids should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for

example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS General: Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see **PRECAUTIONS, Pediatric Use** section). In clinical studies with NASONEX Nasal Spray, 50 mcg, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, use of NASONEX Nasal Spray, 50 mcg should be discontinued and appropriate local or systemic therapy instituted, if needed.

Nasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infection of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of mometasone furoate monohydrate. Extremely rare instances of wheezing have been reported.

Rare instances of nasal septum perforation and increased intraocular pressure have also been reported following the intranasal application of aerosolized corticosteroids. As with any long-term topical treatment of the nasal cavity, patients using NASONEX Nasal Spray, 50 mcg over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

Glaucoma and cataract formation was evaluated in one controlled study of 12 weeks' duration and one uncontrolled study of 12 months' duration in patients treated with NASONEX Nasal Spray, 50 mcg at 200 mcg/day, using intraocular pressure measurements and slit lamp examination. No significant change from baseline was noted in the mean intraocular pressure measurements for the 141 NASONEX-treated patients in the 12-week study, as compared with 141 placebo-treated patients. No individual NASONEX-treated patient was noted to have developed a significant elevation in intraocular pressure or cataracts in this 12-week study. Likewise, no significant change from baseline was noted in the mean intraocular pressure measurements for the 139 NASONEX-treated patients in the 12-month study and again, no cataracts were detected in these patients. Nonetheless, nasal and inhaled corticosteroids have been associated with the development of glaucoma and/or cataracts. Therefore, close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

When nasal corticosteroids are used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, NASONEX Nasal Spray, 50 mcg should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with NASONEX Nasal Spray, 50 mcg should be given the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all intended or possible adverse effects. Patients should use NASONEX Nasal Spray, 50 mcg at regular intervals (see **DOSAGE AND ADMINISTRATION**) since its effectiveness depends on regular use. Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose based on one single-dose, parallel-group study of patients in an outdoor "park" setting (park study) and one environmental exposure unit (EEU) study and within 2 days after the first dose in two randomized, double-blind, placebo-controlled,

parallel-group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1 to 2 weeks after initiation of dosing. Patients should take the medication as directed and should not increase the prescribed dosage in an attempt to increase its effectiveness. Patients should contact their physician if symptoms do not improve, or if the condition worsens. To assure proper use of this nasal spray, and to attain maximum benefit, patients should read and follow the accompanying Patient's Instructions for Use carefully. Administration to young children should be aided by an adult.

Patients should be cautioned not to spray NASONEX Nasal Spray, 50 mcg into the eyes or directly onto the nasal septum.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles, and patients should also be advised that if they are exposed, medical advice should be sought without delay.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 mcg/kg (approximately 1 and 2 times the maximum recommended daily intranasal dose [MRDID] in adults [400 mcg] and children [100 mcg], respectively, on a mcg/m^2 basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg (approximately 2 times the MRDID in adults and children, respectively, on a mcg/m^2 basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary-cell assay, but did not increase chromosomal aberrations in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse-lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay and a rat bone marrow chromosomal aberration assay or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** When administered to pregnant mice, rats, and rabbits, mometasone furoate increased fetal malformations. The doses that produced malformations also decreased fetal growth, as measured by lower fetal weights and/or delayed ossification. Mometasone furoate also caused dystocia and related complications when administered to rats during the end of pregnancy.

In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above (less than the MRDID in adults on a mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately 2 times the MRDID in adults on a mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately 10 times the MRDID in adults on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately 6 times the MRDID in adults on a mcg/m^2 basis) produced delays in ossification, but no malformations.

In rabbits, mometasone furoate caused multiple malformations (eg, flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately 6 times the MRDID in adults on a mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly or domed head) at 700 mcg/kg (approximately 30 times the MRDID in adults on a mcg/m^2 basis). At 2800 mcg/kg (approximately 110 times the MRDID dose in adults on a mcg/m^2 basis), most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (approximately 6 times the MRDID in adults on a mcg/m^2 basis).

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis) caused prolonged and difficult labor and reduced the

number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. NASONEX Nasal Spray, 50 mcg, like other corticosteroids, should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

Nursing Mothers: It is not known if mometasone furoate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be used when NASONEX Nasal Spray, 50 mcg is administered to nursing women.

Pediatric Use: Controlled clinical studies have shown intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including NASONEX Nasal Spray, 50 mcg, should be monitored routinely (eg, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and

effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including NASONEX Nasal Spray, 50 mcg, each patient should be titrated to his/her lowest effective dose.

Seven hundred and twenty (720) patients 3 to 11 years of age with allergic rhinitis were treated with mometasone furoate nasal spray, 50 mcg (100 mcg total daily dose) in controlled clinical trials (see **CLINICAL PHARMACOLOGY, Clinical Studies** section). Twenty-eight (28) patients 2 to 5 years of age with allergic rhinitis were treated with mometasone furoate nasal spray, 50 mcg (100 mcg total daily dose) in a controlled trial to evaluate safety (see **CLINICAL PHARMACOLOGY, Pharmacokinetics** section). Safety and effectiveness in children less than 2 years of age with allergic rhinitis and in children less than 18 years of age with nasal polyps have not been established.

A clinical study has been conducted for 1 year in pediatric patients with allergic rhinitis (ages 3 to 9 years) to assess the effect of NASONEX Nasal Spray, 50 mcg (100 mcg total daily dose) on growth velocity. No statistically significant effect on growth velocity was observed for NASONEX Nasal Spray, 50 mcg compared to placebo. No evidence of clinically relevant HPA axis suppression was observed following a 30-minute cosyntropin infusion.

The potential of NASONEX Nasal Spray, 50 mcg to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

Geriatric Use: A total of 280 patients above 64 years of age with allergic rhinitis or nasal polyps (age range 64 to 86 years) have been treated with NASONEX Nasal Spray, 50 mcg for up to 3 or 4 months, respectively. The adverse reactions reported in this population were similar in type and incidence to those reported by younger patients.

ADVERSE REACTIONS ***Allergic Rhinitis.*** In controlled US and international clinical studies, a total of 3210 adult and adolescent patients ages 12 years and older with allergic rhinitis received treatment with NASONEX Nasal Spray, 50 mcg at

doses of 50 to 800 mcg/day. The majority of patients (n = 2103) were treated with 200 mcg/day. In controlled US and international studies, a total of 990 pediatric patients (ages 3 to 11 years) with allergic rhinitis received treatment with NASONEX Nasal Spray, 50 mcg, at doses of 25 to 200 mcg/day. The majority of pediatric patients (720) were treated with 100 mcg/day. A total of 513 adult, adolescent, and pediatric patients have been treated for 1 year or longer. The overall incidence of adverse events for patients treated with NASONEX Nasal Spray, 50 mcg was comparable to patients treated with the vehicle placebo. Also, adverse events did not differ significantly based on age, sex, or race. Three percent or less of patients in clinical trials discontinued treatment because of adverse events; this rate was similar for the vehicle and active comparators.

All adverse events (regardless of relationship to treatment) reported by 5% or more of adult and adolescent patients ages 12 years and older who received NASONEX Nasal Spray, 50 mcg, 200 mcg/day and by pediatric patients ages 3 to 11 years who received NASONEX Nasal Spray, 50 mcg, 100 mcg/day in clinical trials vs placebo and that were more common with NASONEX Nasal Spray, 50 mcg than placebo, are displayed in the table below.

ADVERSE EVENTS FROM CONTROLLED CLINICAL TRIALS IN SEASONAL ALLERGIC AND PERENNIAL ALLERGIC RHINITIS

(PERCENT OF PATIENTS REPORTING)

	Adult and Adolescent Patients 12 years and older		Pediatric Patients Ages 3 to 11 years	
	NASONEX 200 mcg (n = 2103)	VEHICLE PLACEBO (n = 1671)	NASONEX 100 mcg (n = 374)	VEHICLE PLACEBO (n = 376)
Headache	26	22	17	18
Viral Infection	14	11	8	9
Pharyngitis	12	10	10	10
Epistaxis/Blood-Tinged Mucus	11	6	8	9
Coughing	7	6	13	15
Upper Respiratory Tract Infection	6	2	5	4
Dysmenorrhea	5	3	1	0
Musculoskeletal Pain	5	3	1	1
Sinusitis	5	3	4	4
Vomiting	1	1	5	4

Other adverse events which occurred in less than 5% but greater than or equal to 2% of mometasone furoate adult and adolescent patients (ages 12 years and older) treated with 200-mcg doses (regardless of relationship to treatment), and more frequently than in the placebo group included: arthralgia, asthma, bronchitis, chest pain, conjunctivitis, diarrhea, dyspepsia, earache, flu-like symptoms, myalgia, nausea, and rhinitis.

Other adverse events which occurred in less than 5% but greater than or equal to 2% of mometasone furoate pediatric patients ages 3 to 11 years treated with 100-mcg doses vs placebo (regardless of relationship to treatment) and more

frequently than in the placebo group included: diarrhea, nasal irritation, otitis media, and wheezing.

The adverse event (regardless of relationship to treatment) reported by 5% of pediatric patients ages 2 to 5 years who received NASONEX Nasal Spray, 50 mcg, 100 mcg/day in a clinical trial vs placebo including 56 subjects (28 each NASONEX Nasal Spray, 50 mcg and placebo) and that was more common with NASONEX Nasal Spray, 50 mcg than placebo, included: upper respiratory tract infection (7% vs 0%, respectively). The other adverse event which occurred in less than 5% but greater than or equal to 2% of mometasone furoate pediatric patients ages 2 to 5 years treated with 100-mcg doses vs placebo (regardless of relationship to treatment) and more frequently than in the placebo group included: skin trauma.

Nasal Polyps. In controlled clinical studies, the types of adverse events observed in patients with nasal polyps were similar to those observed for patients with allergic rhinitis. A total of 594 adult patients (ages 18 to 86 years) received NASONEX Nasal Spray, 50 mcg, at doses of 200 mcg once or twice daily for up to 4 months for treatment of nasal polyps. The overall incidence of adverse events for patients treated with NASONEX Nasal Spray, 50 mcg was comparable to patients treated with the placebo except for epistaxis, which was 9% for 200 mcg once daily, 13% for 200 mcg twice daily, and 5% for placebo.

Rare cases of nasal ulcers and nasal and oral candidiasis were also reported in patients treated with NASONEX Nasal Spray, 50 mcg, primarily in patients treated for longer than 4 weeks.

In postmarketing surveillance of this product, cases of nasal burning and irritation, anaphylaxis and angioedema, and rare cases of nasal septal perforation have been reported. Disturbances of taste and smell have been reported very rarely.

OVERDOSAGE There are no data available on the effects of acute or chronic overdosage with NASONEX Nasal Spray, 50 mcg. Because of low systemic bioavailability, and an absence of acute drug-related systemic findings in clinical studies, overdose is unlikely to require any therapy other than observation.

Intranasal administration of 1600 mcg (4 times the recommended dose of NASONEX Nasal Spray, 50 mcg) daily for 29 days, to healthy human volunteers, was well tolerated with no increased incidence of adverse events. Single intranasal doses up to 4000 mcg have been studied in human volunteers with no adverse effects reported. Single oral doses up to 8000 mcg have been studied in human volunteers with no adverse effects reported. Chronic overdosage with any corticosteroid may result in signs or symptoms of hypercorticism (see **PRECAUTIONS**). Acute overdosage with this dosage form is unlikely since one bottle of NASONEX Nasal Spray, 50 mcg contains approximately 8500 mcg of mometasone furoate.

DOSAGE AND ADMINISTRATION **Allergic Rhinitis:** **Adults and Children 12 Years of Age and Older:** The recommended dose for prophylaxis and treatment of the nasal symptoms of seasonal allergic rhinitis and treatment of the nasal symptoms of perennial allergic rhinitis is two sprays (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 mcg).

In patients with a known seasonal allergen that precipitates nasal symptoms of seasonal allergic rhinitis, prophylaxis with NASONEX Nasal Spray, 50 mcg (200 mcg/day) is recommended 2 to 4 weeks prior to the anticipated start of the pollen season.

Children 2 to 11 Years of Age: The recommended dose for treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis is one spray (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 100 mcg).

Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose based on one single-dose, parallel-group study of patients in an outdoor “park” setting (park study) and one environmental exposure unit (EEU) study and within 2 days after the first dose in two randomized, double-blind, placebo-controlled, parallel-group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1 to 2 weeks. Patients should use NASONEX Nasal Spray, 50 mcg only once daily for allergic rhinitis at a regular interval.

Nasal Polyps: Adults 18 years of Age and Older: The recommended dose for nasal polyps is two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg). A dose of two sprays (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 mcg) is also effective in some patients.

Prior to initial use of NASONEX Nasal Spray, 50 mcg, the pump must be primed by actuating ten times or until a fine spray appears. The pump may be stored unused for up to 1 week without repriming. If unused for more than 1 week, reprime by actuating two times, or until a fine spray appears.

Directions for Use: Illustrated **Patient's Instructions for Use** accompany each package of NASONEX Nasal Spray, 50 mcg.

Directions for Cleaning: Illustrated **Applicator Cleaning Instructions** accompany each package of NASONEX Nasal Spray, 50 mcg.

HOW SUPPLIED NASONEX (mometasone furoate monohydrate) Nasal Spray, 50 mcg is supplied in a white, high-density, polyethylene bottle fitted with a white metered-dose, manual spray pump, and blue cap. It contains 17 g of product formulation, 120 sprays, each delivering 50 mcg of mometasone furoate per actuation. Supplied with **Patient's Instructions for Use** (NDC 0085-1197-01).

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light.

When NASONEX Nasal Spray, 50 mcg is removed from its cardboard container, prolonged exposure of the product to direct light should be avoided. Brief exposure to light, as with normal use, is acceptable.

SHAKE WELL BEFORE EACH USE.

Schering®

Schering Corporation

Kenilworth, NJ 07033 USA

XXXXXXXXT

PHARMACIST

Pull to Remove

GIVE TO PATIENT

Patient's Instructions for Use

SHAKE WELL BEFORE EACH USE

NASONEX®

(mometasone furoate monohydrate)

Nasal Spray, 50 mcg*

*calculated on the anhydrous basis

Shake the bottle well before each use. Read complete instructions carefully and use only as directed.

1. Remove the plastic cap (Figure 1).

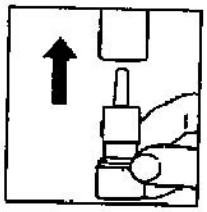


Figure 1

2. The very first time the spray is used, prime the pump by pressing downward on the shoulders of the white applicator using your forefinger and middle finger while supporting the base of the bottle with your thumb (Figure 2). Press down and release the pump ten times or until a fine spray appears. DO NOT spray into eyes. The pump is now ready to use. The pump may be stored unused for up to 1 week without repriming. If unused for more than 1 week, reprime by spraying two times or until a fine spray appears.

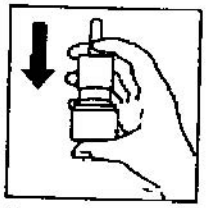


Figure 2

3. Gently blow your nose to clear the nostrils. Close one nostril. Tilt your head forward slightly and, keeping the bottle upright, carefully insert the nasal applicator into the other nostril (Figure 3). DO NOT spray directly onto nasal septum, the wall between the two nostrils.

Figure 3

4. For each spray, press firmly downward once on the shoulders of the white applicator using your forefinger and middle finger while supporting the base of the bottle with your thumb. Breathe gently inward through the nostril (Figure 4).

Figure 4

5. Then breathe out through the mouth.
6. Repeat in the other nostril.
7. Wipe the nasal applicator with a clean tissue and replace the plastic cap.

Pediatric Use: Administration to young children should be aided by an adult. The **Patient's Instructions for Use**, Steps 1 to 7 should be followed.

The correct amount of medication in each spray can only be assured up to 120 sprays from the bottle even though the bottle is not completely empty. You should keep track of the number of sprays used from each bottle of NASONEX Nasal Spray, 50 mcg and discard the bottle after using 120 sprays.

Cleaning: Please see **Applicator Cleaning Instructions** on reverse.

Caution: NASONEX Nasal Spray, 50 mcg is formulated for once- or twice-daily dosing depending on your condition. You should use NASONEX Nasal Spray, 50 mcg, once or twice daily as directed. Since NASONEX Nasal Spray, 50 mcg is not intended to give rapid relief of your nasal symptoms, the prescribed dosage should not be increased by using more often than your physician prescribed in an attempt to increase its effectiveness. NASONEX Nasal Spray, 50 mcg, helps to control ~~the underlying disorders responsible for~~ your condition so it is important that you use it regularly as directed by your physician.

NASONEX NASAL Spray treats seasonal and year-round nasal allergy symptoms in adults and children 2 years and older. Based on single-day studies, done in a park, during pollen season or in a controlled pollen exposure room, improvement in nasal allergy symptoms has been shown to occur within 11 hours after the first dose. In other studies that lasted up to 2 weeks, improvement in nasal symptoms of seasonal allergic rhinitis was shown to occur within 2 days after the first dose. The full benefit of NASONEX Nasal Spray, 50 mcg, in allergic rhinitis is usually achieved within 1 to 2 weeks. NASONEX Nasal Spray can also be used to help prevent seasonal nasal allergy symptoms in adults and children 12 years and older, when treatment starts 2 to 4 weeks before the allergy season.

In patients aged 18 years and older, NASONEX Nasal Spray is also used to treat nasal polyps.

Side effects were generally mild and included headache, viral infection, sore throat, nosebleeds and coughing.

NASONEX Nasal Spray, 50 mcg should not be sprayed into the eyes.

Spraying NASONEX Nasal Spray, 50 mcg directly onto the nasal septum should be avoided.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light.

When NASONEX Nasal Spray, 50 mcg is removed from its cardboard container, prolonged exposure of the product to direct light should be avoided. Brief exposure to light, as with normal use, is acceptable.

SHAKE WELL BEFORE EACH USE.

Schering â

Schering Corporation

Kenilworth, NJ 07033 USA

U.S. Patent No. D355,844

Rev. XX/XX

XXXXXXXX

PHARMACIST

GIVE TO PATIENT

APPLICATOR CLEANING INSTRUCTIONS

Please see reverse for Patient's Instructions for Use

NASONEX®

(mometasone furoate monohydrate)

Nasal Spray, 50 mcg*

*calculated on the anhydrous basis

1. To clean the nasal applicator, remove the plastic cap (Figure 1).

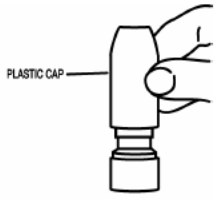


Figure 1

2. Pull gently upward on the white nasal applicator so that it comes free (Figure 2).

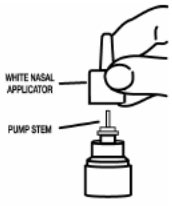


Figure 2

3. Soak the nasal applicator in cold tap water and/or rinse both ends of the nasal applicator under cold tap water and dry. (Figure 3).

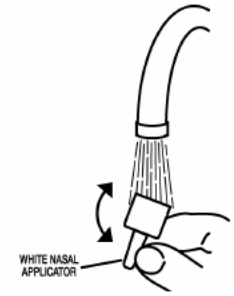


Figure 3

4. Rinse the plastic cap under cold water and dry (Figure 4).

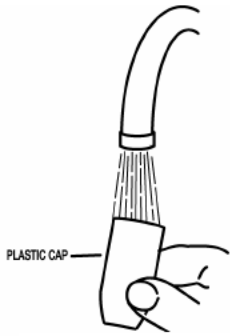


Figure 4

5. Reassemble the nasal applicator being certain the pump stem is reinserted into the applicator's center hole (Figure 5).

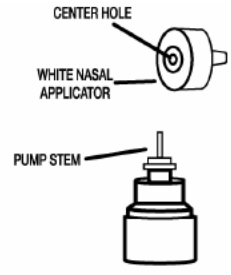


Figure 5

6. Reprime the pump by pressing downward on the shoulders of the white applicator using your forefinger and middle finger while supporting the base of the bottle with your thumb. Press down and release the pump two times or until a fine spray appears. DO NOT spray into eyes. The pump is now ready to use. The pump may

be stored unused for up to 1 week without repriming. If unused for more than 1 week, reprime by spraying two times or until a fine spray appears (Figure 6).

Figure 6

7. Replace the plastic cap (Figure 7).

Figure 7

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Kenilworth, NJ 07033 USA

U.S. Patent No. D355,844

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X-XXXXXXXX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-762/S023

OFFICE DIRECTOR MEMO

DIVISION DIRECTOR'S MEMORANDUM

Date:	December 10, 2004
To:	NDA 20-762 (SE1-023)
From:	Eugene J. Sullivan, MD, FCCP Deputy Director Division of Pulmonary and Allergy Drug Products (HFD-570)
Through:	Badrul A. Chowdhury, MD PhD Director, Division of Pulmonary and Allergy Drug Products
Product:	Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray, 50mcg
Applicant:	Schering Corporation

Administrative and Introduction

On February 26, 2004, the Applicant submitted a supplemental application intended to provide clinical support for the use of Nasonex (mometasone furoate monohydrate) Nasal Spray, 50mcg for the treatment of nasal polyps in patients 18 years of age and older (SE1-023). Nasonex Nasal Spray is an aqueous suspension of the corticosteroid mometasone furoate monohydrate in a metered-dose, manual pump spray unit, intended for intranasal administration. Each actuation delivers a metered spray containing 50 mcg of the active drug substance (calculated on the anhydrous basis). It is currently approved for the treatment of seasonal and perennial allergic rhinitis in patients 2 years of age and older. The recommended dose for these indications is two sprays in each nostril, once daily (total daily dose of 200mcg) in patients 12 years of age and older, and one spray in each nostril once daily (total daily dose of 100mcg) in children aged 2-11. In the current submission, the Applicant proposes two doses of Nasonex Nasal Spray for the treatment of nasal polyps: two sprays in each nostril once daily (total daily dose of 200mcg), and two sprays in each nostril twice daily (total daily dose of 400mcg). The PDUFA goal date for this application is December 26, 2004.

Chemistry, Manufacturing, and Controls

This application is intended to extend the Indications for this currently approved drug product. No CMC information was included or required for this submission.

Pharmacology and Toxicology

Nasonex Nasal Spray is a currently approved product. No new Pharm/Tox data were included or required for this submission. Because the application proposes a dose that is higher than the currently approved dose, the Pharm/Tox team recommended specific changes in the labeling to reflect the new systemic exposure ratio calculations.

Clinical Pharmacology and Biopharmaceutics

The submission did not contain any new Clinical Pharmacology or PK data. The OCPB team had no comments on the application.

Clinical

Clinical Program

The clinical program for this application consisted of two "pivotal" clinical safety and efficacy studies (P01925 and P01926), and two supportive studies (P02573 and Q99-925-01). These studies are reviewed in depth in Dr. Nicklas' Medical Officer Review. The two "pivotal" studies were, with minor exceptions, performed under identical protocols. Both were multi-center, randomized, double-blind, placebo controlled, parallel group studies in which patients aged 18 years and older with nasal polyps received either Nasonex 200mcg QD, Nasonex 200mcg BID, or placebo for a treatment period of 4 months. These studies had two co-primary endpoints: change from baseline in the symptom of nasal congestion/obstruction, averaged over the first month of treatment, and change from baseline to the end of the treatment period in bilateral polyp grade. The nasal congestion/obstruction symptom was an instantaneous self-report of symptoms performed daily, prior to study drug administration, using a categorical scale of 0-3. The polyp grade was a reflection of the size of the polyps, determined by the investigators based on direct visual endoscopic inspection, using a 0-3 scale. The bilateral polyp grade was the sum of the grade from the left and right nostrils. Secondary endpoints in these studies included evaluations of the sense of smell, peak nasal inspiratory flow rate, and rhinorrhea.

Study P02573 was an extension of Study P01925. Patients who demonstrated improvement in Study P01925 were enrolled in Study P02573, in which they received no therapy for a period of 4 months. The intention of this study was to explore the rate of recurrence/worsening of nasal polyps after cessation of treatment.

Study Q99-925-01 was a multi-center, randomized, double-blind, placebo controlled, parallel group clinical study that had been sponsored by an affiliate of the Applicant, for the purpose of local registration. In this study, patients with nasal polyps were randomized to receive Nasonex Nasal Spray 200mcg QD, or placebo, for a period of 16 weeks. In this study, the primary variable was based on the investigator's assessment of the symptom of nasal congestion. The primary endpoint was the proportion of patients demonstrating improvement in this symptom, defined as a reduction in the symptom score of at least 1 point. Secondary endpoints included investigator assessments of polyp size (grade).

Efficacy

As shown in the table below, using the pre-specified statistical analysis plan, Nasonex Nasal Spray was statistically superior to placebo for both co-primary endpoints in Study P01925, but not in Study P01926. Specifically, the change from baseline in polyp grade did not reach statistical significance for either dose group in Study P01926.

Primary Efficacy Endpoints, Studies P01925 and P01926 (Pre-specified Statistical Analysis)					
	Nasonex 200mcg QD	Nasonex 200mcg BID	Placebo	p-value (QD vs Placebo)	p-value (BID vs Placebo)
Study P01925	N= 115	N= 122	N=117		
Polyp Grade, change from baseline	-1.13	-0.95	-0.49	<0.001	0.01
Nasal Congestion, change from baseline	-0.47	-0.61	-0.24	0.001	<0.001
Study P01926	N=102	N=102	N=106		
Polyp Grade, change from baseline	-0.76	-0.98	-0.67	0.62	0.08
Nasal Congestion, change from baseline	-0.42	-0.66	-0.23	0.01	<0.001

The Applicant recognized that the two planned pivotal studies had not achieved the objective of demonstrating statistically significant efficacy of both doses of Nasonex. Therefore, the Applicant submitted the results of Study Q99-925-01 in support of efficacy. However, this study had not been designed to support the requirements for regulatory approval in the US. For instance, the primary endpoint was based on an investigator-assessed symptom, and did not include an anatomical assessment of polyp size in the primary analysis. This issue is discussed in greater detail in Dr. Gebert's Biometrics review. Although the Division determined that the design features of Study Q99-925-01 precluded this study from being considered one of the requisite "pivotal" studies, the Division did determine that the data could be used to support the Applicant's contention that it would be appropriate to deviate from the pre-specified analysis plan for Studies P01925 and P01926, to include baseline polyp grade among the covariates in the statistical analysis (see below). In addition, it also provided supportive evidence of efficacy. In this study, Nasonex Nasal Spray, 200mcg QD was statistically superior to placebo on both nasal congestion/obstruction (investigator assessed), and nasal polyp grade.

The pre-specified analysis of the co-primary endpoints in Studies P01925 and P01926 utilized an ANOVA approach, with treatment, center, and asthma status as factors. The Applicant pointed out that, when baseline polyp grade was added as an additional covariate, the change from baseline bilateral polyp grade was shown to be statistically significant for the BID dose in Study P01926. The Division discussed at length the appropriateness of adding a covariate that was not pre-specified, and ultimately decided that this would be acceptable in this case. This decision was based on a number of factors, including the recognition that it is a commonly accepted practice to include baseline status in such a model, and the observation, based on the data from the pivotal studies and a supportive study (Q99-925-01), that baseline status was an important covariate. The table below shows the results of the primary analyses for Studies P01925 and P01926, using the adjusted statistical model that includes baseline polyp grade in the analyses of polyp grade, change from baseline.

Primary Efficacy Endpoints, Studies P01925 and P01926 (Adjusted Statistical Analysis, to include baseline polyp grade as covariate for analysis of polyp grade, change from baseline)					
	Nasonex 200mcg QD	Nasonex 200mcg BID	Placebo	p-value (QD vs Placebo)	p-value (BID vs Placebo)
Study P01925	N= 115	N= 122	N=117		
Polyp Grade, change from baseline	-1.15	-0.96	-0.50	<0.001	0.01
Nasal Congestion, change from baseline	-0.47	-0.61	-0.24	0.001	<0.001
Study P01926	N=102	N=102	N=106		
Polyp Grade, change from baseline	-0.78	-0.96	-0.62	0.33	0.04
Nasal Congestion, change from baseline	-0.42	-0.66	-0.23	0.01	<0.001

The results of the various secondary endpoints generally supported the efficacy of Nasonex Nasal Spray in the treatment of nasal polyps. Nasonex Nasal Spray was statistically superior to placebo (0<0.05) for the symptoms of rhinorrhea and post nasal drip at both doses in Study P01925, and at the BID dose in Study P01926. These were instantaneous symptom assessments; reflective assessments were not performed. Assessments of peak nasal inspiratory flow were statistically superior to placebo for both doses in both studies. The sense of smell was assessed using a categorical scale ranging from 0-3. In Study P01925, both doses of Nasonex Nasal Spray were superior to placebo at most time points. However, in Study P01926, the QD dose was not superior to placebo, and the BID dose was only superior to placebo during Week 3 and Week 4.

The results of Study P02573 further support the efficacy of Nasonex Nasal Spray in the treatment of nasal polyps. In this study of patients who had previously improved when treated with test drug (active or placebo) in Study P01925 were followed for four months off of treatment. The incidence of recurrence of nasal polyps was greater, and the time to recurrence was shorter in patients who had previously been treated with active drug as compared to those treated with placebo. This likely reflects the fact that patients who improved on placebo in Study P01925 represented a “regression to the mean” phenomenon. Therefore, these patients would be less likely to experience recurrence, as compared to patients who improved on active drug. The observation that nasal polyps frequently recur upon cessation of active treatment is not unexpected with this disease.

In summary, the data submitted with this Application are sufficient to establish the efficacy of Nasonex Nasal Spray in the treatment of nasal polyps. The BID dose was clearly effective, and there was evidence that the QD dose may also be effective in some patients. Given the fact that administration of corticosteroids carries some risk of adverse effect, it would be desirable to use the lowest effective dose. For this reason, it is appropriate to state in the product label that the recommended dose is 200mcg BID, but that some patients may respond to 200mcg QD.

Safety

Safety evaluations included collection of adverse events, vital signs, and laboratory studies, including 24-hour urinary cortisol measurements in a subset of patients. The incidence of specific adverse events was similar in the active and placebo groups, with the exception of epistaxis, which occurred with greater frequency in the active treatment groups. There was no evidence of an adverse effect on vital signs or laboratory values.

Data Quality, Integrity, and Financial Disclosure

All studies were conducted in accordance with accepted ethical standards. During the review of this applications no irregularities were identified that might call into question the quality or integrity of the data. The Division did not request that the Division of Scientific Investigations conduct an audit. Financial disclosure statements did not reveal potentially important conflicts.

Pediatric Considerations

Citing a low occurrence of the disease in children and adolescents, and the assertion that the use of corticosteroids in this population does not represent a meaningful therapeutic benefit over existing treatments, the Applicant requested a waiver of requirements to assess the safety and efficacy of Nasonex Nasal Spray for the treatment of nasal polyps in patients < 18 years of age. The Division considered this request and determined that the incidence of nasal polyps in patients 6-17 years of age is sufficiently high such that a waiver would not be appropriate. The Division also noted that a different corticosteroid product, beclomethasone nasal spray, is indicated for the prevention of recurrence of nasal polyps following surgical resection in patients 6 years of age and older.

Product Name

This application does not propose to change the name of the currently approved product.

Labeling Issues

The Division substantially revised the Applicant's proposed labeling language, and held a telephone conference with the Applicant to come to agreement on the final label. The main point of contention was the advisability of the proposal to include reference to (b) (4) in the product label. The Division determined that the data were not sufficiently persuasive to allow inclusion of (b) (4) even though the statistical analysis plan had specified an approach (b) (4)

Action

The data submitted with this application establish the efficacy and acceptable safety of Nasonex Nasal Spray in the treatment of nasal polyps in patients aged 18 years and older. Therefore the regulatory action will be APPROVAL. No Phase 4 commitments are necessary.

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/s/

Eugene Sullivan
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I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-762/S023

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA efficacy supplement
Submission Number	20-762
Submission Code	SE1-023
Letter Date	26 February 2004
Stamp Date	27 February 2004
PDUFA Goal Date	26 December 2004
Reviewer Name	Richard Nicklas MD
Review Completion Date	8 December 2004
Established Name	mometasone furoate
(Proposed) Trade Name	Nasonex Aqueous Nasal Spray
Therapeutic Class	corticosteroid
Applicant	Schering
Priority Designation	Regular
Formulation	Aqueous Nasal Spray
Dosing Regimen	200 mcg once daily to bid
Indication	nasal polyposis
Intended Population	18 years of age and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The efficacy of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray for the treatment of nasal polyps in adult and adolescent patients 18 years of age and older has been demonstrated by the data provided by the sponsor in this submission. Therefore, approval is granted for this indication.

The two efficacy studies (*studies 1925 and 1926*) submitted under this supplemental NDA were randomized, placebo-controlled, double-blind, parallel group multicenter studies and were designed by the sponsor with input from the Division (see discussion of study design and endpoints below). They were supported by *study Q99-925-01* which was a randomized, placebo-controlled, double-blind, parallel group, multicenter (12) study performed in Denmark, Finland, Norway and Sweden. There were two primary efficacy variables in *studies 1925 and 1926*: 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to endpoint in bilateral polyp grade. A statistically significant difference from placebo for both endpoints was required to demonstrate efficacy. In studies 1925 and 1926, two dosages of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray were evaluated and compared to placebo; 200 mcg once a day and 200 mcg bid (400 mcg per day). The primary efficacy variable in *study Q99-925-01* was the proportion of patients with improvement during the treatment period of 16 weeks in nasal congestion as evaluated by the investigator, with improvement being defined as a reduction in nasal congestion of at least one point. Assessment of polyp size was a secondary outcome variable in this study. Only a Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray dosage of 200 mcg once a day was evaluated in this study.

In *study 1925*, a statistically significant difference favoring Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray compared to placebo was seen for both nasal congestion/obstruction after one month of treatment and for reduction in polyp size at endpoint after both administration of 200 mcg once a day and 200 mcg bid. In addition, there was a statistically significant difference demonstrated between both dosages of Nasonex and placebo favoring Nasonex for all the secondary efficacy variables evaluated. *Therefore, the efficacy of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray for the treatment of nasal polyps was demonstrated in this study at both of the dosages evaluated.* In *study 1926*, both dosages of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray produced a statistically significantly greater improvement in nasal congestion/obstruction than was seen after administration of placebo. However, neither dosage produced a statistically significantly greater effect on polyp size than placebo using the pre-specified analysis, although the 200 mcg bid dosage showed greater improvement (p=0.08 compared to placebo) than did the 200 mcg once a day dosage (p=0.62 compared to placebo). The sponsor did a post-hoc analysis of reduction in polyp size using the baseline as a covariate and based on this analysis, there was a statistically significant difference between Nasonex at a dose of 200 mcg bid and placebo, favoring Nasonex (p =0.05) Efficacy was demonstrated in this study for all secondary efficacy variables after administration of Nasonex 200 mcg bid but not after administration of Nasonex at a dosage of

200 mcg once a day. *Since the sponsor was able to show effectiveness in study 1926 for both primary outcome variables at a dosage of 200 mcg bid (400 mcg per day) using the post-hoc analysis for polyp size, this study can be used to support the effectiveness of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray at a dose of 200 mcg bid in the treatment of nasal polyps. The post-hoc analysis of polyp size in study 1926 is considered appropriate because of the importance of including baseline in this evaluation as demonstrated in study Q99-925-01.*

In study *Q99-925-01*, a statistically significant difference was shown between the group that received Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray and the group that received placebo for both the primary efficacy variable and reduction in polyp size. In addition, a statistically significant difference was shown between the group that received Nasonex and the group that received placebo, favoring the Nasonex group, for all of the other secondary efficacy variables. Reduction in polyp size was not specified as a primary outcome variable. *Although the design of the study in regard to the assessment of polyp size was different from that used in studies 1925 and 1926, it can be used to support the efficacy of a dosage of 200 mcg once a day for the proposed indication.*

In summary, the efficacy of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray at a dosage of 200 mcg twice a day was demonstrated in studies 1925 and 1926 for the treatment of nasal polyps in adult and adolescent patients 18 years and older". The efficacy of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray for the treatment of nasal polyps has been demonstrated in studies 1925 and Q99-925-01 at a dosage of 200 mcg once a day.

Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray has been shown in the data provided by the sponsor and based on previous use in the treatment of allergic rhinitis to be safe for administration at a dose of 200 mcg or 400 mcg per day. A higher incidence of epistaxis was noted after administration of a total daily dose of 400 mcg per day than was noted after administration of a total daily dose of 200 mcg per day or placebo, but was not unacceptably high or inconsistent with this effect seen after administration of other intranasal corticosteroids. There was no conclusive evidence of any significant systemic effect from the intranasal administration of mometasone at a dose of 400 mcg per day.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no post-marketing recommendations on risk management activity.

1.2.2 Required Phase 4 Commitments

The sponsor was informed that a waiver for pediatric studies in patients less than 6 years old is justified for this drug product for the treatment of nasal polyps because of the infrequent occurrence of nasal polyps in this patient population. However, a waiver for pediatric studies is not justified for Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray in the treatment of nasal polyps in patients 6-17 years of age, because nasal polyps, although infrequent, occurs in patients 6-17 years of age. In addition, the labeling for another intranasal

corticosteroid product states that it is indicated for the prevention and recurrence of nasal polyps following surgical removal and is approved for patients 6 years of age and older. The sponsor, by studying Nasonex for the treatment of nasal polyps in patients 6-17 years of age, would have the opportunity to determine the appropriate dose for the treatment of nasal polyps in this patient population.

1.2.3 Other Phase 4 Requests

There are no other phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray is an intranasal corticosteroid which is approved for the treatment of nasal symptoms of seasonal and perennial allergic rhinitis in adults and pediatric patients 2 years of age and older and the prophylaxis of nasal symptoms of seasonal allergic rhinitis in adult and adolescent patients 12 years of age and older. Patients were studied under this efficacy supplement to the NDA in order to gain an indication for the treatment of nasal polyps (b) (4) in adult and adolescent patients 18 years of age and older. The sponsor performed two pivotal efficacy studies (studies 1925 and 1926) and included a supportive study (study Q99-925-01) for efficacy. Study 2573 was a 4 month follow-up study to assess the rate of recurrence of nasal polyps in patients whose condition had improved with up to 4 months of treatment with Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray in study 1925.

There were 664 patients enrolled in studies 1925 and 1926, 441 were randomized to treatment with Nasonex and 223 to placebo. Approximately 90% of the Nasonex and 81% of the placebo patients completed the study. In study Q99-925-01, 298 patients were randomized, 153 to receive Nasonex and 145 to receive placebo. In the 3 studies in which Nasonex was administered, there were 962 patients. There were 370 who received Nasonex 200 mcg qd, 224 who received Nasonex 200 mcg bid and 368 who received placebo for a period of 4 months. Completion of the study occurred in 88% of the Nasonex patients and 70% of he placebo patients. In addition, there were 135 patients included in an observational follow-up study (study 2573) to assess the rate of recurrence of nasal polyps in patients who improved with treatment in study 1925. Patients included in these 3 studies were 18 years of age or older and had bilateral nasal polyps. Patients were required to have a nasal congestion/obstruction score of at least 2 (moderate) for each of the last seven days of the 2 week run-in (studies 1925 and 1926) or four days per week during the last month prior to screening and at the screening and baseline visit (study Q99-925-01).

1.3.2 Efficacy

Studies 1925 and 1926 were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in 664 patients 18 years and older with bilateral nasal polyps, of whom 441 received Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray. Patients received either 200 mcg Nasonex once a day, 200 mcg Nasonex bid or placebo for 4 months. For entry

into the studies, patients had to have a nasal congestion score of 2 or greater for each of the last 7 days of the run-in period. The primary endpoints were: 1) change from baseline in congestion/obstruction averaged over the first month of treatment using a 0-3 categorical scale; and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of the studies. Secondary endpoints included evaluation of loss of smell, peak nasal inspiratory flow (PNIF), rhinorrhea and % responders. Patients with SAR were excluded to ensure that the symptom scoring was consistent throughout the 4 month treatment period. Patients with glaucoma or sub-capsular cataracts were excluded since corticosteroids have been associated with the development of these conditions. Patients were also excluded if they had had sinus or nasal surgery within the previous 6 months, 3 or more nasal surgeries at any time in the past, previous surgery that would make accurate grading of polyps impossible or complete nasal obstruction. The study included 51 sites in the US, Latin America, Europe, Canada, and the Far East. The patient population was a mixed population with mild to severe nasal polyposis, except for nasal congestion and loss of smell, which were moderate to severe.

Study Q99-925-01 (v12, 13) was a randomized, placebo-controlled, double-blind, parallel group, multicenter (12) study performed in Denmark, Finland, Norway and Sweden with the objective of evaluating the efficacy and safety of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray 200 mcg per day in the treatment of nasal polyposis. There were 298 patients between the ages of 20-86 years in the study, of whom 153 received Nasonex Nasal Spray and 145 received placebo. The patient population studied was patients with bilateral nasal polyps with a polyp size of 2 or less and who were symptomatic with a nasal congestion score of 2 or greater for at least 4 days a week during the last month prior to screening, at screening and at baseline. Patients received 2 sprays of Nasonex per nostril (50 mcg per spray) in the morning upon awakening (200 mcg per day). There was a run-in period of 2-4 weeks without treatment followed by a treatment period of 16 weeks. Evaluation was done by investigators at baseline and on days 28, 56, 84, and 112. The primary outcome variable was the proportion of patients with improvement during the treatment period (visits 2-6) in nasal congestion as evaluated by the investigator with improvement being defined as a reduction in nasal congestion of at least one point. Secondary efficacy variables were improvement in rhinorrhea, sense of smell, polyp size measured by endoscopy, PNIF, olfactory threshold, patient-assessed symptoms scores, treatment response score and QOL-related variables. Safety variables included nasal examination and adverse events (v12, p2).

There were 664 patients enrolled in studies 1925 and 1926, 441 were randomized to treatment with Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray and 223 to placebo. Approximately 90% of the Nasonex and 81% of the placebo patients completed the study. In study Q99-925-01, 298 patients were randomized, 153 to receive Nasonex and 145 to receive placebo. Completion of the study occurred in 88% of the Nasonex patients and 70% of he placebo patients. In addition, there were 135 patients included in an observational follow-up study (study 2573) to assess the rate of recurrence of nasal polyps in patients who improved with treatment in study 1925. Patients included in these 3 studies were 18 years of age or older and had bilateral nasal polyps. Patients enrolled in these studies were required to have a nasal congestion/obstruction score of at least 2 (moderate) for each of the last seven days of the 2 week run-in (studies 1925 and 1926) or four days per week during the last month prior to screening and at the screening and baseline visit (study Q99-925-01).

The two randomized, placebo-controlled, double-blind, parallel group multicenter efficacy studies (1925 and 1926) submitted under this supplemental NDA were designed by the applicant with input from the Division (see discussion of study design and endpoints below). The Division informed the applicant that in order to obtain an indication for Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray in the treatment of nasal polyposis, efficacy in studies 1925 and 1926 should be based not just on the effectiveness of Nasonex in relieving nasal congestion/obstruction but on the ability of Nasonex to reduce polyp size as well. As a result, the sponsor chose to have two primary efficacy variables in these studies: 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to endpoint in bilateral polyp grade. A statistically significant difference from placebo for both endpoints was required to demonstrate efficacy. In studies 1925 and 1926, two dosages of Nasonex were evaluated and compared to placebo; 200 mcg once a day and 200 mcg bid (400 mcg per day).

In *study 1925*, a statistically significant difference favoring Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray compared to placebo was seen for both nasal congestion/obstruction after one month of treatment and for reduction in polyp size at endpoint after both administration of 200 mcg once a day and 200 mcg bid. In addition, there was a statistically significant difference demonstrated between both dosages of Nasonex and placebo favoring Nasonex for all the secondary efficacy variables evaluated. *Therefore, the efficacy of Nasonex for the treatment of nasal polyps was demonstrated in this study at both of the dosages evaluated.*

In *study 1926*, both dosages of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray produced a statistically significantly greater improvement in nasal congestion/ obstruction than was seen after administration of placebo. However, neither dosage produced a statistically significantly greater effect on polyp size than placebo, although the 200 mcg bid dosage showed greater improvement ($p=0.08$ compared to placebo) than did the 200 mcg once a day dosage ($p=0.62$ compared to placebo). The sponsor did a post-hoc analysis of reduction in polyp size using the baseline as a covariate and based on this analysis, there was a statistically significant difference between Nasonex at a dose of 200 mcg bid and placebo, favoring Nasonex ($p =0.05$). Efficacy was demonstrated in this study for all secondary efficacy variables after administration of Nasonex 200 mcg bid but not after administration of Nasonex at a dosage of 200 mcg once a day. *Since the sponsor was able to show effectiveness in study 1926 for both primary outcome variables at a dosage of 200 mcg bid (400 mcg per day) using the post-hoc analysis for polyp size, this study can be used to support the effectiveness of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray at a dose of 200 mcg bid in the treatment of nasal polyps. The post-hoc analysis of polyp size in study 1926 was considered appropriate because of the importance of including baseline in this evaluation as demonstrated in study Q99-925-01.*

Parameter	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Dose response
Nasal congestion/obstruction			
1925	p = 0.001	P < 0.001	Yes
1926	p = 0.01	P < 0.001	Yes
Polyp grade			
1925	p <0.001	P = 0.01	No
1926	p = 0.62	P = 0.08	Yes
Sense of smell			
1925	p < 0.001	p = 0.04	No
1926	p = 0.85	p = 0.05	Yes
Rhinorrhea			
1925	p<0.001	p< 0.001	No
1926	p=0.02	p< 0.001	Yes
Post-nasal drainage			
1925	p < 0.001	p = 0.001	No
1926	p = 0.23	p< 0.001	Yes
PNIF			
1925	p < 0.001	p < 0.001	No
1926			
Individual patient improvement			
1925	39%	49%	Yes
1926	18%	28%	Yes

The sponsor submitted a study done in Scandinavia that evaluated both nasal congestion and polyp size (study Q99-925-01) (see discussion of study design and endpoints above). The primary efficacy variable in this study was the proportion of patients with improvement during the treatment period of 16 weeks in nasal congestion as evaluated by the investigator, with improvement being defined as a reduction in nasal congestion of at least one point. Assessment of polyp size was a secondary outcome variable in this study. Only a Nasonex dosage of 200 mcg once a day was evaluated in this study. A statistically significant difference was shown between the group that received Nasonex and the group that received placebo for both the primary efficacy variable and reduction in polyp size. In addition, a statistically significant difference was shown between the group that received Nasonex and the group that received placebo, favoring the Nasonex group, for all of the other secondary efficacy variables. *The possible deficiencies in this study, as described above, have been reviewed and are not considered sufficient to disallow this study as one of the two required pivotal studies for this indication. Therefore, studies 1925 and Q99-925-01 demonstrate the efficacy of Nasonex Nasal Spray at a dosage of 200 mcg once a day for the treatment of nasal polyps.*

1.3.3 Safety

This supplemental NDA has included data from three randomized, placebo-controlled, double-blind clinical studies, 1925, 1926 and Q99-925-01, as well as a follow-up study (2573) designed to assess the recurrence of nasal polyps in patients who had improved significantly in study 1925. In the 3 studies in which Nasonex was administered, there were 962 patients. There were 370 who received Nasonex 200 mcg qd, 224 who received Nasonex 200 mcg bid and 368 who

received placebo for a period of 4 months. In the 594 patients who received Nasonex, no unusual or unexpected adverse events occurred, there were no deaths and there were 18 serious adverse events reported, none of which was considered related to the study drug.

Safety parameters evaluated included adverse events, physical examination, measurement of vital signs and laboratory tests in studies 1925 and 1926, and measurement of 24 hour urinary free cortisol levels in a subset of patients in study 1925. In *study 1925*, there were 115 patients randomized to receive 200 mcg once a day of Nasonex, 122 patients randomized to receive 200 mcg bid of Nasonex and 117 patients randomized to receive placebo. Of these, more than 89% of the patients who received Nasonex and 83% of the patients who received placebo took the study drug for at least 90 days. At least 60% of patients in each treatment group took study drug for at least the pre-specified 120 days. In *study 1926*, 102 patients were randomized to each of the two Nasonex dosage groups and 106 were randomized to the placebo group. Of these, more than 93% of the patients who received Nasonex and 84% of the patients who received placebo took the study drug for at least 90 days. At least 50% of patients in each treatment group took study drug for at least the pre-specified 120 days. In study Q99-925-01, safety parameters were limited to adverse events and vital signs. There were 153 patients who received Nasonex and 145 patients who received placebo. There were 94% of patients who took Nasonex for 56 days or more (78% of placebo patients) and 75% of patients who took Nasonex for 112 days or more (52% of placebo patients).

There were no deaths reported in the studies performed under this supplemental NDA. There were no serious adverse events that were likely to be related to the study drug. There were no unusual adverse events reported that were considered to be related to the study drug. Epistaxis, URIs, headache and pharyngitis were the most frequent adverse events reported by at least 5% of the patients in any treatment group in the combined analysis of studies 1925 and 1926. Epistaxis was the only one of these four adverse events that was reported significantly more frequently by patients receiving Nasonex 200 mcg bid than patients receiving placebo. *With a nasally administered drug product, local nasal adverse events have been documented and are not unexpected.* Local nasal adverse events in studies 1925 and 1926 included epistaxis, nasal burning, nasal dryness, nasal irritation and nasal septal perforation.

Patients who took more than the recommended dose are of interest in regard to possible systemic adverse events since it has been demonstrated that in rare individuals systemic effects may occur from use of inhaled or intranasal corticosteroids. Overdose was reported in studies 1925 and 1926 by 5 patients in the Nasonex 200 mcg once a day group, 3 patients in the Nasonex 200 mcg bid group and 5 patients in the placebo group. Adverse events associated with overuse of the treatment drug were reported by 3 patients. This included 2 patients in the placebo group who reported weight gain and acute sinusitis at the time of the overdose possibly related to the study drug and one patient in the Nasonex 200 mcg bid group who developed a headache at the time of overuse that was considered unrelated to the study drug. In study 2573, patients from study 1925 were followed for 4 months without any evidence of withdrawal effects.

The sponsor submitted a review of safety data *utilizing a dose of 400 mcg per day or more* that contained data (b) (4)

(b) (4) This includes: 1) two clinical pharmacology studies – study C92-022-01 and C93-196-01; 2) one phase 2 placebo-controlled study (C92-011); 3) three phase 3 placebo-controlled studies – C96-195, C97-251 and C/196-252; and three phase 3 open label variable dose studies – C93-014, 193-018 and 193-221 and represents all the data generated through 15 November 2003 on patients who received 400 mcg per day or more of mometasone furoate nasal spray. The adverse events most frequently felt to be due to high dose Nasonex administration were headache, pharyngitis, epistaxis, nasal burning, nasal irritation, rhinitis and sneezing. Only in regard to epistaxis was there a greater incidence in the high dose Nasonex group (9%) than in the placebo group (5%). The overall incidence of treatment-related adverse events was 22 % in both the high dose Nasonex group and the placebo group.

The safety of inhaled and intranasal corticosteroids should focus on local effects that can occur from the administration of the drug product and possible systemic effects from absorption of the corticosteroid. In terms of local effects, Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray, in particular at a dosage of 200 mcg bid, caused more local adverse effects, especially epistaxis, than placebo. *This type of adverse effect is not unexpected with inhalation of corticosteroids and is not a reason for not approving this drug product.* No systemic adverse effects were reported with greater frequency in patients who received Nasonex than in patients who received placebo in the studies performed under this submission. Post-marketing adverse event reporting includes a number of adverse effects that could represent systemic effects of Nasonex, e.g. cataracts, glaucoma, but there is insufficient data provided in these reports to conclude that these adverse events are directly linked to the administration of Nasonex. Elevated SGOT levels were seen with greater frequency in patients who received Nasonex than in patients who received placebo in studies 1925 and 1926. In study 1925, this was a dose-dependent effect while in study 1926 this greater frequency in elevated SGOT was seen only in patients who received 200 mcg bid. *Intranasal corticosteroids are metabolized in the liver. Mometasone undergoes extensive metabolism to metabolites regulated by the cytochrome P-450 3A4 enzyme system. Liver mixed-function oxidases and glucuronyl transferases are important in the metabolism of many glucocorticosteroids. As a result, liver disease, drugs and other chemical that modify liver function can affect the biologic half-life of glucocorticosteroids. However, intranasal corticosteroids have not been reported to produce an increase in liver enzymes and there is nothing unique about this drug product that would support any concern about its hepatic effect. Overall, the sponsor has demonstrated the safety of Nasonex at a dosage of 200 mcg once a day and a dosage of 200 mcg bid.*

1.3.4 Dosing Regimen and Administration

The dosing regimen of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray recommended in the labeling for nasal polyps is two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg) (b) (4) The current recommended dosing regimen in the labeling for the indication of allergic rhinitis is 200 mcg once daily. *The applicant has demonstrated the safety of a dose of 400 mcg per day in the data submitted in this supplement. However, the applicant failed to establish a clear dose response in the studies submitted, since in one of the pivotal studies a dose of 200 mcg once a day was more effective than a dose of 400 mcg per day (study 1925). It has not, therefore, been established that a dose*

of 400 mcg per day is necessary to obtain efficacy in the treatment of nasal polyps in (b) (4) *patients. Moreover,* (b) (4) *The Dosage and Administration section of the labeling should be changed, therefore, to read, "The recommended dose for nasal polyps is two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg). A dose of two sprays (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 mcg) is also effective in some patients."*

1.3.5 Drug-Drug Interactions

There are no important drug-drug interactions that affect the clinical use of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray.

1.3.6 Special Populations

Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray has not been adequately studied in patients less than 18 years of age with nasal polyposis. Evaluation of the efficacy and safety data provided in this supplemental NDA do not indicate any significant differences in the response to Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray based on age, gender, or race.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray is a synthetic 17 heterocyclic glucocorticosteroid. Nasonex Nasal Spray is an aqueous suspension containing mometasone furoate monohydrate as the active ingredient in an aqueous medium containing glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, sodium citrate, 0,25% w/w phyenylethyl alcohol, citric acid, benzalkonium chloride, polysorbate 80 and (b) (4). The active moiety is marketed as a cream, ointment and lotion for the treatment of dermatologic conditions. The anhydrous form is used in a mometasone furoate dry powder inhaler for the treatment of asthma symptoms. Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray is an intranasal corticosteroid preparation. It has been approved for the treatment of nasal symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients 2 years of age and older and for the prophylaxis of the nasal symptoms of seasonal allergic rhinitis in adult and adolescent patients 12 years of age and older. Nasonex Nasal Spray is delivered by a device which is a (b) (4) metered-dose nasal spray and consists of a high-density polyethylene bottle fitted with a metered-dose, manual, (b) (4) Each actuation of the spray delivers 100 mcg of suspension, containing an amount of mometasone furoate monohydrate equivalent to 50 mcg mometasone furoate. It has been approved for use in > 80 countries for the treatment of SAR and PAR in patients 12 year of age and older and in > 60 countries for the treatment of nasal symptoms associated with SAR and PAR in children 2 years of age and older. It has been approved, as well, in approximately 30 countries as adjunctive treatment in combination with antibiotics for the treatment of acute sinusitis in adults and adolescents.

The only other intranasal corticosteroid approved in the United States for the "prevention of recurrence of nasal polyps following surgical removal" is intranasal beclomethasone and the labeling states that "Clinical studies have shown that treatment of the symptoms associated with nasal polyps may have to be continued for several weeks or more before a therapeutic result can be fully assessed. Recurrence of symptoms due to polyps can occur after stopping treatment depending on the severity of the disease."

Nasonex Nasal Spray is now proposed for use in patients with nasal polyps who were studied under this supplemental NDA to obtain an indication for the treatment of nasal polyps (b) (4) (b) (4) in adult and adolescent patients 18 years of age and older. A dosing regimen of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray for nasal polyps that is proposed in the labeling is two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg) (b) (4) 2 sprays in each nostril once daily (total daily dose of 200 mcg) (b) (4)

2.2 Currently Available Treatment for Indications

Nasal polyposis is an inflammatory disease of the nasal and paranasal sinus mucosa with protrusion of the inflamed mucosa into the nasal passageways leading to nasal obstruction, symptoms of rhinitis and loss of smell. These symptoms can significantly decrease quality of life (QOL). Nasal polyps can occur in patients with non-allergic and patients with allergic rhinitis. Elevated histamine and IgE levels have been demonstrated in extracellular polyp fluid. The incidence of nasal polyposis has been estimated to be 2-4% of the general population with a greater frequency in men and in patients > 40 years of age. Nasal polyposis is rare in children (prevalence of about 0.1%). Histologically, nasal polyps are benign growths of the mucosa characterized by proliferation of the epithelial layer, thickening of the basement membrane, edema, focal fibrosis, cellular inflammation (eosinophils, mast cells), increase in cytokines, especially IL-5. The histopathology of nasal polyps in children, most commonly in cystic fibrosis or antrochoanal polyps, is different from that which is seen in adults with bilateral nasal polyps. Surgery may be necessary if nasal polyps are large, interfere with the patient's ability to function and/or are associated with co-morbid conditions e.g. asthma, ASA intolerance and cystic fibrosis. Intranasal corticosteroids are used either as primary treatment or long-term secondary treatment after administration of oral corticosteroids.

The recurrence rate for nasal polyps after surgery is high and in one study 85% of patients who had surgery for nasal polyps were found to have active disease 20 years after surgery. Recurrence of nasal polyps after medical treatment has not been well characterized. The objectives of medical management are to reduce the size of the polyps, reduce signs and symptoms of associated rhinitis, improve nasal air flow, restore a sense of smell and reduce the incidence of recurrence after surgical treatment. There are data in the literature that claim to demonstrate the efficacy of intranasal corticosteroids in reducing the size of polyps and associated symptoms of rhinitis (Tos et al. Am J Rhinol 1998; 12:3; Holmberg et al. Ann Allergy Asthma Immunol 1997; 78:270; Pentilla et al. Clin Exp Allergy 1999; 30:94; Lidholdt et al. Arch Otolaryngol Head Neck Surg 1997; 123:595; Keith et al. Clin Exp Allergy 1998;30:1460; Mygined et al 1975; 5:159; Chalton et al. Br Med J 1985; 291:788), as well as reducing the recurrence of nasal polyps after surgery (Mygind Allergy 1999; 53:12, Johansen et al. Clin Otolaryhngol 1993; 18:524).

The use of a placebo control has been associated with clinical improvement in nasal polyps. Due probably to the removal of allergens or other triggers of nasal symptoms, intranasal saline has been shown to be efficacious in several studies (Garavello W et al. Pediatr Allergy Immunol 2003; 14:140; Rabago D et al. J Fam Pract 2002; 51:1049; Blomqvist EH et al. Acta Otolaryngol 2003; 123:862).

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety is marketed as a cream, ointment and lotion for the treatment of dermatologic conditions. The anhydrous form is used in the mometasone furoate dry powder inhaler for the treatment of asthma symptoms. Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray is an intranasal corticosteroid preparation. It has been approved for the treatment of nasal symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients 2 years of age and older and for the prophylaxis of the nasal symptoms of seasonal

allergic rhinitis in adult and adolescent patients 12 years of age and older. Nasonex Nasal Spray is delivered by a device which is a [redacted] (b) (4) metered-dose nasal spray and consists of a high-density polyethylene bottle fitted with a metered-dose, manual, [redacted] (b) (4) The 50 mcg per spray aqueous nasal solution was approved in the United States on 1 October 1997.

2.4 Important Issues With Pharmacologically Related Products

As reflected in the labeling for Nasonex Nasal Spray and pharmacologically related products, the following issues are considered important: 1) signs of adrenal insufficiency or symptoms of withdrawal after replacement of systemic corticosteroids with an inhaled corticosteroid and the need for careful monitoring of such patients for acute adrenal insufficiency during periods of stress; 2) exacerbation of asthma when replacing systemic corticosteroids with inhaled corticosteroids; 3) rare instances of systemic corticosteroid effects from intranasal corticosteroids; 4) suppression of the immune system in patients on systemic corticosteroids and the unknown risk associated with inhaled corticosteroids; 5) reduction in growth velocity in pediatric patients; 6) rare localized infections of the nose or pharynx; 7) rare development of nasal septal perforation; 8) rare reports of glaucoma or cataracts; 9) inhibitory effects on wound healing after nasal surgery or trauma; and 10) rare patients with adrenal suppression from inhaled corticosteroids.

2.5 Presubmission Regulatory Activity

The clinical program needed to support an indication for the treatment of nasal polyps was initially discussed with the Agency on the conference call of *21 February 2001*. The Division indicated that two studies, and in addition, evaluation of polyp recurrence rate over at least 4 months, would be needed to obtain approval for a nasal polyps indication. The need for co-primary endpoints was also conveyed to the sponsor i.e. change from baseline in polyp grade based on endoscopy and nasal symptom scores. Recommended endpoints were: 1) change from baseline in polyp grade based on rhinoscopy; and 2) nasal symptoms scores. The Division also recommended that improvement in symptoms be shown within 4 weeks and that a follow-up study of at least 4 months was needed to assess rate of recurrence of nasal polyps after treatment was stopped. The Division also recommended that the sponsor consider assessment of adrenal function in a subset of patients, include patients with and without allergic rhinitis and include a pediatric waiver request with the supplemental NDA.

Amended protocols for studies 1925 and 1926 incorporating Agency comments were submitted to IND 35,932 on *20 April 2001*. A follow-up study to assess rate of recurrence of polyps after treatment was stopped was submitted to the IND on 27 July 2001. On *4 August 2001*, the FDA provided the sponsor with statistical comments on studies 1925 and 1926, including clarification of the expected treatment differences, plans for missing values in the analysis and intentions for a stepwise statistical approach in analyzing the co-primary variables. On *7 August 2001*, the Agency provided comments on study 2573. On *24 September 2001*, the sponsor submitted an amended protocol for study 2573. On *5 October 2001*, the sponsor clarified the statistical analysis of the studies. The study design provided 90.2% power to detect a 0.37 change in congestion score and a 99.8% power to detect a 1 point change in polyp grade.

In letters on *28 March 2002* and *24 September 2002*, the sponsor notified the Agency of termination of two sites in study 1925 and one site in study 2573 because of non-compliance with GCP by the investigators at those sites and further information regarding these sites was sent to the Division of Scientific Investigation (DSI) by the sponsor. The sponsor excluded these sites from the primary efficacy and safety analyses of the data.

On *10 January 2003*, the sponsor submitted the data analysis plan for study 1926. Comments on the data analysis plan were made by the Agency on *10 February 2003* that included recommendation that the effect of a history of asthma be included in the analysis and that the sponsor use Dunnett's procedure instead of a step-down procedure. The sponsor responded that they felt that the step-down procedure was a more appropriate model because there is an expected pharmacological relationship between the doses and because the sample size was based on the significance level associated with a step-down procedure. On *14 May 2003*, the revised data analysis plans for studies 1925 and 1926 were submitted to the Agency. On *16 October 2003*, a pre-NDA meeting was held with the Division. At this time, the sponsor presented their proposed clinical program for Nasonex Nasal Spray in the treatment of nasal polyps, which the Division considered adequate for filing this supplemental NDA. The Division pointed out however that there were several significant review issues, including justification of the dose selection, addition of alternative analyses in regard to responder analysis since inferential analysis of responders was not pre-specified, evaluation of a responder analysis based on polyp size alone, use of PNIF results (b) (4) and evaluation of the analyses of the data including and excluding data from sites with GCP violations.

Nasonex was approved for the treatment of SAR and PAR in *October 1997* for patients 12 years of age and older at a dose of 200 mcg once a day and in *July 2002* for patients 2-11 years of age at a dose of 100 mcg once a day. In addition, Nasonex is approved for the prophylaxis of nasal symptoms of SAR in patients 12 years of age and older at a dose of 200 mcg per day.

The Agency concluded that it was not necessary to take this supplement to an Advisory Committee for their review and recommendations.

2.6 Other Relevant Background Information

Beclomethasone, budesonide and fluticasone by intranasal administration are approved for use in the treatment of nasal polyposis or for prophylaxis against recurrence of nasal polyps following surgical removal in the European Union and Canada. In the US, beclomethasone is the only intranasal corticosteroid approved for treatment of nasal polyps, specifically for prophylaxis following surgical removal of nasal polyps.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Nasonex Nasal Spray proposed for the treatment of nasal polyps is not different from the approved marketed product in terms of the active moiety or the formulation. This is an efficacy supplement for a proposed indication (nasal polyps) that is different than the indication proposed

in the approved labeling, i.e. allergic rhinitis. The drug product is the same. This was discussed with Chemistry and there are no CMC issues related to this supplemental NDA.

3.2 Animal Pharmacology/Toxicology

Since this is an efficacy supplement, no new preclinical or toxicology data was submitted. This was discussed with Pharmacology and there are no Pharmacology issues related to this supplemental NDA.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This submission contains efficacy and safety data from three clinical studies and one observational follow-up study. Two of the controlled studies are considered pivotal by the applicant and were designed to include recommendations made by the Agency. These two studies (1925 and 1926) are randomized, double-blind, placebo-controlled parallel multicenter studies with administration of Nasonex at a dose of 200 mcg once a day or bid for a period of 4 months. There were 962 patients 18 years of age and older who participated in these studies, 594 of whom received Nasonex 200 mcg once daily or bid. In addition, the applicant has submitted the results from study 2573, a 4 month follow-up study to assess the rate of recurrence of nasal polyp disease in patients whose condition improved with up to 4 months treatment in study 1925. These three studies reflect the recommendations made by the Division to the sponsor on 21 February 2001 and 14 October 2003. The Division concluded that this database was adequate for filing this supplemental NDA, but noted that safety and efficacy determinations, assessment of the appropriate dose and analysis of the data would be review issues and asked the applicant to perform a responder analysis based on polyp size alone. The applicant has performed this analysis. William LaMear MD was an investigator in study 1925 (site 8). Dr LaMear has been cited for falsifying information in a previous study. The applicant was asked at the pre-NDA meeting to analyze the data with and without inclusion of Dr LaMear's study site. The applicant has done this. The applicant also included a study (Q99-925-01) performed in Scandinavia sponsored by an affiliate for the purpose of local registration.

4.2 Tables of Clinical Studies

study number	# pts	Age Range	Study centers	Study design	Patient population	Treatment dose and duration	Outcome variables	
1925 pivotal for efficacy	354 R 353 T 305 C 122 200 mcg bid 115 200 mcg QD 117 P	18-81 years	US/international	R,PC,PGDB,MC	Bilateral nasal polyposis; moderate signs and symptoms	Nasonex 200 mcg QD and 200 mcg bid; 4 months	Bilateral polyp grade; congestion, rhinorrhea, PND, loss of smell; PNIF, QOL, safety parameters	
1926 pivotal for efficacy	310 R 310 T 274 C 102 200 mcg bid 102 200 mcg QD 106 P:	18-86 years	international	R,PC,PGDB,MC	Bilateral nasal polyposis; moderate signs and symptoms	Nasonex 200 mcg QD and 200 mcg bid; 4 months	Bilateral polyp grade, congestion, rhinorrnea, PND, loss of smell, PNIF, QOL, safety parameters	
Q99-925-01 Support for efficacy	298 R 296 T 235 C 153 200 mcg QD 145 P	20-86 years	Scandinavia	R,PC,DBMC	Bilateral nasal polyposis; moderate signs and symptoms	Nasonex 200 mcg QD; 16 weeks	Improvement in nasal congestion, polyp size, rhinorrhea, loss of smell, PNIF, QOL, safety parameters	
2573	135 E 67 C 58 200 mcg bid 46 200 mcg QD 31 P	18-78 years	US/international	Observational follow-up	Patients who improved in study 1925	No treatment; Observation for 4 months	Bilateral polyp grade, congestion, rhinorrhea, PND, loss of smell, PNIF, safety parameters	

R = randomized
T = treated
C = completed
200 mcg bid = Nasonex 200 mcg bid
200 mcg QD = Nasonex 200 mcg QD
P = placebo

4.3 Review Strategy

The key studies, 1925 and 1926, were reviewed both in terms of the combined data for these two identical studies and then the data from each study individually. The review then focused on study C99-925-01 and study 2573. The study protocol was reviewed first to assure that the study design would allow the conclusions stated by the applicant. Then the appllicant's summary of the data was reviewed, followed by an assessment of individual patient data and data on subsets of patients. The results from identical studies 1925 and 1926 were pooled for assessment of safety parameters. The articles from the literature that were submitted by the applicant were reviewed. The data in the literature did not change the conclusions reached based on the data from studies 1925, 1926 and Q99-925-01.

4.4 Data Quality and Integrity

The applicant selected established investigators and study centers and adequately reviewed the protocol procedures prior to initiating the studies. There was regular monitoring of the all study centers to confirm that the study was being conducted in accordance with the protocol and with adherence to applicable regulatory requirements. Source document verification was accomplished by comparison with case report form (CRF) entries. The accuracy of recording of the protocol-specific key variables was verified in all patients. Discrepancies from CRFs were identified prior to loading the data into the database. The database then underwent a standard checking program and was supplemented by an additional set of study-specific checks. A random sampling of the safety data and study-specific efficacy data from the database was verified against supporting documentation in the CRF. It was concluded that the Division of Scientific Investigations (DSI) did not need to audit any of the studies submitted, based on the fact that the number of patients at the study sites in the key studies, especially study 1925, were similar (i.e. no single large center was driving the study results), no significantly differences at any center were noted and there was no basis for suspecting any irregularities in the pivotal studies.

4.5 Compliance with Good Clinical Practices

The clinical program for nasal polyposis was conducted in accordance with Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines. A placebo control was used in all the studies since nasal polyposis is a relatively benign condition, patients were given the opportunity to discontinue if necessary and rescue medication was provided for patients if there was a worsening of their symptoms. Procedures were in compliance with the US Code of Federal Regulations and the World Medical Association Declaration of Helsinki (v22, s8K, pgs2-4). Informed consent was obtained for the studies submitted and was acceptable.

In letters on 28 March 2002 and 24 September 2002, the sponsor notified the Agency of termination of two sites in study 1925 and one site in study 2573 because of non-compliance with GCP by the investigators at those sites and further information regarding these sites was sent to the Division of Scientific Investigation (DSI) by the applicant. William LaMear MD was an investigator in study 1925 (site 8). Dr LaMear has been cited for falsifying information in a previous study. The applicant was asked at the pre-NDA meeting to analyze the data with and without inclusion of Dr LaMear's study site. The applicant has done this.

Prior to initiation of the studies submitted in this NDA, the study protocol and informed consent form were reviewed and approved by an IEC or IRB. Procedures were in compliance with 21 CFR, Parts 50 and 56 in regard to ethical conduct of the studies. Written informed consent was obtained from patients entered into these studies. The investigators were qualified by training and experience to conduct the studies. A central laboratory, Covance Central Laboratory Services located in Indiana and South Africa, was responsible for performing all clinical laboratory analyses. Contract research organizations monitored some centers in the studies.

Review by the applicant of study Q99-925-01 noted that all CRFs were entered into the database and checked against the original CRF using double proof-reading methods. Computerized checks of variable ranges were performed for all numeric variables in the CRF and diary cards. A

random sample of diary data from 10 patients was checked against the original diary cards. The error rate was 0.001. All errors found on checks were corrected (v22, t8k, p4). The applicant audited the data from studies 1925, 1926 and Q99-925-01.

4.6 Financial Disclosures

Financial disclosure was provided by the applicant consistent with FDA guidance and did not raise any questions about the integrity of the data provided in this Supplemental NDA.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No pharmacokinetic studies were submitted by the applicant in this efficacy supplement. This is appropriate since this is an intranasal formulation and levels of mometasone after administration as a nasal spray to adults and children are virtually undetectable in plasma despite the use of sensitive assays. In-vitro protein binding for mometasone has been shown to be 98-99%. Any portion of the mometasone dose that is swallowed and absorbed undergoes extensive metabolism to multiple metabolites but there are no major metabolites detected in plasma. Any absorbed drug is excreted as metabolites primarily in the bile but to a limited extent in the urine. The effects of renal impairment, hepatic impairment, age or gender on the pharmacokinetics of mometasone has not been adequately studied.

5.2 Pharmacodynamics

Four clinical pharmacology studies have been performed to assess the effect of Nasonex Nasal Spray at various doses on adrenal function. Daily doses of 200 and 400 mcg administered for 36 days was not associated with a statistically significant decrease in mean plasma cortisol levels after Cortrosyn infusion or a statistically significant decrease in the 24 hour urinary free cortisol levels compared to placebo. In a second study, Nasonex Nasal Spray given at a dose of 400 and 1600 mcg per day for 29 days did not produce any statistically significant differences in adrenal function, based on 8 hour Cortosyn infusion and 24 hour urinary free cortisol levels than placebo. In a third study which evaluated single rising doses of Nasonex Nasal Spray from 100-4000 mcg per day, no statistically significant decrease in plasma cortisol AUC, 8 AM cortisol levels, or 24 hour urinary free cortisol levels were seen compared to placebo. A fourth study was submitted with this Supplemental NDA in which a subset of patients with nasal polyposis in study 1925 were evaluated in terms of adrenal function by measuring 24 hour urinary free cortisol levels after 4 months of treatment with Nasonex Nasal Spray. There was no statistically significant decrease in 24 hour urinary free cortisol levels compared to placebo.

5.3 Exposure-Response Relationships

Studies 1925 and 1926 were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in 664 patients 18 years and older with bilateral nasal polyps, of whom 441 received Nasonex. Patients received either 200 mcg Nasonex once a day, 200 mcg Nasonex bid or placebo for 4 months. Study Q99-925-01 was a randomized, placebo-controlled, double-blind,

parallel group, multicenter (12 centers) study performed in Denmark, Finland, Norway and Sweden with the objective of evaluating the efficacy and safety of Nasonex Nasal Spray 200 mcg per day in the treatment of nasal polyposis. There were 298 patients between the ages of 20-86 years in the study, of whom 153 received Nasonex Nasal Spray and 145 received placebo.

The decision to use a dose that was higher than the recommended dose for allergic rhinitis, i.e. 200 mcg bid (400 mcg per day) was based on the dose of other intranasal corticosteroids that have been approved in other countries for the treatment of nasal polyps and data in the literature (Lund et al. Arch Otolaryngol Head Neck Surg 1998; 124:513, Lildholdt et al. Arch Otolaryngol Head Neck Surg 1997; 123:595, Keith et al. Clin Exp Allergy 2000; 30:1460, Jankowski et al. Arch Otolaryngol Head Neck Surg 2001; 127:447) that indicate that a dosage needed to treat nasal polyps is at least equal to that used to treat allergic rhinitis. Due to mechanical obstruction from nasal polyps, it is reasonable to expect that Nasonex Nasal Spray would not be as efficiently distributed over the nasal mucosa as it would in patients with allergic rhinitis.

In study 1925, although there was a statistically significant greater reduction in polyp size after administration of both the 200 mcg once a day and the 200 mcg bid dosages of Nasonex Nasal Spray than after administration of placebo, a greater reduction was seen after the lower dose of Nasonex, i.e. 200 mcg once a day, than was seen after a dosage of 200 mcg bid. On the other hand, Nasonex Nasal Spray at a dosage of 200 mcg bid produced a greater improvement in nasal congestion in study 1925 and a greater improvement in nasal congestion and reduction in polyp size in study 1926 than did a dosage of 200 mcg once a day. Therefore, studies 1925 and 1926 do not provide consistent data for the clinical assessment of dose-response in terms of polyp size, one of the co-primary efficacy variables. In study Q99-925-01, only one dosage was evaluated, 200 mcg once a day which was shown to be effective for the primary efficacy variable and all of the secondary efficacy variables. Therefore, the data submitted by the applicant suggests that 200 mcg once a day is adequate for the treatment of nasal polyps in some patients but in many patients a dosage of 200 mcg bid (400 mcg per day) is necessary.

6 INTEGRATED REVIEW OF EFFICACY

6.1. The proposed indication for Nasonex Nasal Spray is for the treatment of nasal polyps (b) (4) in adult and adolescent patients 18 years of age and older.

6.1.1 Methods

The key data used to support the proposed indication comes from the two pivotal studies, studies 1925 and 1926. The study design and endpoints for these two studies were identical and were based on recommendations made by the Division. Study Q99-925-01 was included in support of the efficacy of Nasonex Nasal Spray, since it was a well designed study looking at similar endpoints. Q99-925-01 assumes greater importance as a second study showing the efficacy of Nasonex Nasal Spray for the proposed indication because of the lack of efficacy of a dose of 200 mcg once a day in study 1926.

The Division informed the sponsor that in order to obtain an indication for Nasonex in the treatment of nasal polyposis, efficacy in studies 1925 and 1926 should be based not just on the effectiveness of Nasonex in relieving nasal congestion/obstruction but in the ability of Nasonex to reduce polyp size as well. As a result, the sponsor chose to have two primary efficacy variables in these studies: 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to endpoint in bilateral polyp grade. A statistically significant difference from placebo for both endpoints was required to demonstrate efficacy. In studies 1925 and 1926, two dosages of Nasonex were evaluated and compared to placebo; 200 mcg once a day and 200 mcg bid (400 mcg per day).

6.1.2 General Discussion of Endpoints

The primary endpoints in studies 1925 and 1926 were: 1) change from baseline in congestion/obstruction averaged over the first month of treatment using a 0-3 categorical scale; and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of the studies. Secondary endpoints included evaluation of loss of smell, peak nasal inspiratory flow (PNIF), rhinorrhea and % responders. Agreement was reached on these co-primary efficacy endpoints between the sponsor and the Division on the conference call of 21 February 2001 and at the pre-NDA meeting with sponsor on 14October 2003. The choice of co-primary efficacy endpoints, with the inclusion of assessment of polyp size, was considered necessary. This was based on the fact that nasal congestion/obstruction, although an important symptom in patients with nasal polyposis, based on the literature and expert opinion, is also an important symptom in patients with allergic rhinitis, for which the drug product had already been shown to be effective. This choice of co-primary efficacy endpoints was considered to provide a reasonable assessment of clinical efficacy of Nasonex Nasal Spray in the treatment of nasal polyposis. *The endpoints chosen by the applicant are appropriate and consistent with the recommendation of the Division*.

A post-hoc analysis was done by the applicant using baseline as a co-variate in the analysis of polyp size in study 1926 (see Biostatistical Review). This analysis showed a statistically significant difference between Nasonex at a dose of 200 mcg bid and placebo (p=0.05) whereas the pre-specified analysis did not (p=0.08). *Given the importance of the baseline balance in the assessment of polyp size, as demonstrated in study Q99-925-01 (see Biostatistical Review), this was an appropriate post-hoc analysis by the applicant.*

The primary efficacy variable in study Q99-925-01 was the proportion of patients with improvement during the treatment period (visits 2-6) in nasal congestion as evaluated by the investigator with improvement being defined as a reduction in nasal congestion of at least one point. Secondary efficacy variables were improvement in rhinorrhea, sense of smell, polyp size measured by endoscopy, PNIF, olfactory threshold, patient-assessed symptoms scores, treatment response score and QOL-related variables. Safety variables included nasal examination, adverse events and vital signs in all three studies and laboratory tests in studies 1925 and 1926. *The endpoints selected for this study are acceptable since polyp size was analyzed, although somewhat differently than in studies 1925 and 1926.*

6.1.3 Study Design

Studies 1925 and 1926 were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in 664 patients 18 years and older with bilateral nasal polyps, of whom 441 received Nasonex. Patients received either 200 mcg Nasonex once a day, 200 mcg Nasonex bid or placebo for 4 months. For entry into the studies, patients had to have a nasal congestion score of 2 or greater for each of the last 7 days of the run-in period. The primary endpoints were: 1) change from baseline in congestion/obstruction averaged over the first month of treatment using a 0-3 categorical scale; and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of the studies. Secondary endpoints included evaluation of loss of smell, peak nasal inspiratory flow (PNIF), rhinorrhea and % responders. Patients with SAR were excluded to ensure that symptom scoring was not disproportionate throughout the 4 month treatment period in any treatment group because they were entered into the study during the time of year when their symptoms would normally be increased. Patients with glaucoma or sub-capsular cataracts were excluded since corticosteroids have been associated with the development of these conditions. Patients were also excluded if they had had sinus or nasal surgery within the previous 6 months, 3 or more nasal surgeries at any time in the past , previous surgery that would make accurate grading of polyps impossible or complete nasal obstruction. The study included 51 sties in the US, Latin America, Europe, Canada, and the Far East. The patient population was a mixed population with mild to severe nasal polyposis, except for nasal congestion and loss of smell, which were moderate to severe.

The study design for studies 1925, 1926 and Q99-925-01 is consistent with the definition of an adequate and well-controlled study as described in the regulations and provide a reasonable vehicle for assessing the efficacy of Nasonex in the treatment of nasal polyposis. Minimization of bias and the choice of a placebo control in these studies are appropriate. The duration of treatment is adequate and consistent with the Division's recommendations to the sponsor. The inclusion/exclusion criteria for these studies was appropriate, with the exception that in study Q99-925-01 it was not specified if patients with allergic rhinitis would be included in/excluded from the study. No dose finding phase 2 studies were done assessing the appropriate dose of Nasonex for the treatment of nasal polyps. The decision to use a dose that was higher than the recommended dose for allergic rhinitis, i.e. 200 mcg bid (400 mcg per day) was based on the dose of other intranasal corticosteroids that has been approved in other countries for the treatment of nasal polyps and data in the literature (Lund et al. Arch Otolaryngol Head Neck Surg 1998; 124:513, Lildholdt et al. Arch Otolaryngol Head Neck Surg 1997; 123:595, Keith et al. Clin Exp Allergy 2000; 30:1460, Jankowski et al. Arch Otolaryngol Head Neck Surg 2001; 127:447) that indicate that a dosage is needed to treat nasal polyps that is at least equal to that used to treat allergic rhinitis. Due to mechanical obstruction from nasal polyps, it is reasonable to expect that Nasonex Nasal Spray would not be as efficiently distributed over the nasal mucosa as it would in patients with allergic rhinitis.

Study Q99-925-01 (v12, 13) was a randomized, placebo-controlled, double-blind, parallel group, multicenter (12) study performed in Denmark, Finland, Norway and Sweden with the objective of evaluating the efficacy and safety of Nasonex Nasal Spray 200 mcg per day in the treatment of nasal polyposis. There were 298 patients between the ages of 20-86 years in the study, of whom 153 received Nasonex Nasal Spray and 145 received placebo. The patient population studied was patients with bilateral nasal polyps with a polyp size of 2 or less and who were

symptomatic with a nasal congestion score of 2 or greater for at least 4 days a week during the last month prior to screening, at screening and at baseline. Patients received 2 sprays of Nasonex per nostril (50 mcg per spray) in the morning upon awakening (200 mcg per day). There was a run-in period of 2-4 weeks without treatment followed by a treatment period of 16 weeks. Evaluation was done by investigators at baseline and on days 28, 56, 84, and 112. The primary outcome variable was the proportion of patients with improvement during the treatment period (visits 2-6) in nasal congestion as evaluated by the investigator with improvement being defined as a reduction in nasal congestion of at least one point. Secondary efficacy variables were improvement in rhinorrhea, sense of smell, polyp size measured by endoscopy, PNIF, olfactory threshold, patient-assessed symptoms scores, treatment response score and QOL-related variables. Safety variables included nasal examination and adverse events (v12, p2).

There were 664 patients enrolled in studies 1925 and 1926, 441 were randomized to treatment with Nasonex and 223 to placebo. Approximately 90% of the Nasonex and 81% of the placebo patients completed the study. In study Q99-925-01, 298 patients were randomized, 153 to receive Nasonex and 145 to receive placebo. Completion of the study occurred in 88% of the Nasonex patients and 70% of he placebo patients. In addition, there were 135 patients included in an observational follow-up study (study 2573) to assess the rate of recurrence of nasalpolyposis in patients who improved with treatment in study 1925. Patients included in these 3 studies were 18 years of age or older and had bilateral nasal polyps. Patients enrolled in these studies were required to have a nasal congestion/obstruction score of at least 2 (moderate) for each of the last seven days of the 2 week run-in (studies 1925 and 1926) or four days per week during the last month prior to screening and at the screening and baseline visit (study Q99-925-01).

6.1.4 Efficacy Findings

6.1.4.1 Study 1925:

The treatment groups were comparable at entry in terms of demographic and disease characteristics. Baseline symptom scores were similar across the three treatment groups. There were similar numbers of patients in each treatment group who were less than 65 years of age and who were 65 years of age and older. Caucasians comprised 43-54% of the patients in the three treatment groups while Hispanics comprised 38-45%. The majority of patients had no history of asthma (79-82%). The number (%) of patients who received treatment for various durations can be seen in the table below (v5, p782).

Duration of treatment	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo
Number randomized	115	122	117
Any treatment	115	121	116
8 days of more	113	121	114
30 days or more	109	120	110
60 days or more	105	112	101
90 days or more	102	111	97
120 days or more	69	81	71
Randomized, not treated	0	0	1

Mean change from baseline in bilateral polyp grade using the ITT population (v3, p75, t11, p170): Mean change from baseline in bilateral polyp grade was a co-primary efficacy variable. A reduction in mean bilateral polyp grade from baseline was seen in all treatment groups (see table below). There was a greater reduction seen after the administration of Nasonex 200 mcg once a day than after the administration of Nasonex 200 mcg bid. There was a statistically significantly greater decrease in bilateral polyp grade seen after administration of either dosage of Nasonex at all time points over the 4 months of treatment than was seen in the placebo group, despite the fact that a considerable placebo effect was seen. There was no significant difference in the results based on analysis of the efficacy-evaluable population (v3, p172) or based on age (v3, p174-175), gender (v3, p176177) or race (v3, p178, 179). The relatively small number of patients > 65 years of age and the small number of patients with asthma prevent make it difficult to draw any meaningful conclusions about efficacy in these subsets of patients (v3, p174) (v3, p181, p182).

Mean change from baseline in bilateral polyp grade using the ITT population in Study 1925

Visit	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value Nasonex 200 mcg qd vs placebo	P value Nasonex 200 mcg bid vs placebo
Baseline	4.21 (n=112)	3.27 (n=121)	4.25 (n=114)		
Month 1	-0.57 (n=111)	- 0.61 (n=119)	-0.33 (n=114)	0.05	0.02
Month 2	-0.87 (n=107)	-0.83 (n=114)	- 0.52 (n=104)	0.04	0.06
Month 3	-1.10 (n=102)	-0.93 (n=111)	- 0.56 (n=99)	0.003	0.04
Month 4	-1.20 (n=102)	-1.14 (n=108)	- 0.63 (n=94)	0.005	0.01
Endpoint	-1.13 (n=112)	-0.95 (n=121)	- 0.49 (n=114)	< 0.001	0.01

COMMENT: A greater mean change from baseline in bilateral polyp grade was seen after a lower dose of Nasonex, i.e. 200 mcg once a day, compared with 200 mcg bid. However, both doses of Nasonex produced a statistically significantly greater mean decrease in polyp grade than did placebo, although there was a mean reduction in polyp grade seen in patients who received placebo as well as patients who received Nasonex. The effectiveness of Nasonex in polyp reduction has been demonstrated in this study. The data from this study would support a dosage of Nasonex 200 mcg once a day in addition to a dosage of 200 mcg bid in the treatment of nasal polyps.

Congestion/obstruction symptom scores (v3, p78, t12, p184): A statistically significant mean decrease in nasal congestion/obstruction was seen with both doses of Nasonex compared to placebo in a dose-dependent fashion at all time points throughout the study. Mean change in congestion/ obstruction was a co-primary efficacy variable. The results were not significantly different when analyzed using the efficacy-evaluable data (v3, p186), or when analyzing the results in terms of presence of asthma (v3, p195, 196), age (v3, p188, 189), gender (v3, p190, 191) or race (v3, p192, 193)

Mean change in congestion/obstruction analyzed using the ITT population in study 1925

Time-point	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value Nasonex 200 mcg qd vs placebo	P value Nasonex 200 mcg bid vs placebo
Baseline	2.29 (n=113)	2.35 (n=122)	2.28 (n=114)		
Week 1	-0.24 (n=113)	-0.37 (n=122)	-0.16 (n=114)	0.20	0.001
Week 2	-0.49 (n=113)	-0.57 (n=121)	-0.20 (n=111)	< 0.001	< 0.001
Week 3	-0.55 (n=111)	-0.72(n=121)	-0.28 (n=110)	0.002	< 0.001
Week 4	-0.58 (n=110)	-0.76 (n=121)	-0.32 (n=109)	0.002	< 0.001
Month 1 **	-0.47 (n=113)	-0.61 (n=122)	-0.24 (n=114)	0.001	< 0.001
Month 2	-0.68 (n=109)	-0.83 (n=119)	-0.32 (n=107)	< 0.001	< 0.001
Month 3	-0.78 (n=104)	-1.01 (n=112)	-0.48 (n=101)	0.004	< 0.001
Month 4	-0.86 (n= 102)	-1.10 (n=109)	-0.50 (n=96)	0.001	< 0.001
Months 1-2	-0.57 (n=113)	-0.72 (n=122)	-0.28 (n=114)	< 0.001	< 0.001
Months 3-4	-0.83 (n=104)	-1.07 (n=112)	-0.48 (n=101)	< 0.001	< 0.001

** Specified as time point for analysis in comparison with placebo.

COMMENT: There was a statistically significantly greater mean reduction in nasal congestion/obstruction after administration of Nasonex in a dose-dependent manner than was seen after the administration of placebo. This is consistent with the demonstrated effectiveness of Nasonex on nasal symptoms in the data submitted for approval of this drug product for allergic rhinitis. Over the last two months of treatment, the improvement of 0.83 after 200 mcg once a day and 1.07 after 200 mcg bid represents a clinically significant effect as well. After one month of treatment, the effect size of 0.47 in the 200 mcg once a day group and 0.62 in the 200 mcg bid group is consistent with what has been demonstrated in other studies of intranasal cortico-steroids and is considered to represent a change that is consistent with clinical efficacy. Based on the data in this study, Nasonex is effective for reduction in nasal congestion/ obstruction in patients who have bilateral nasal polyps. The number of patients in this study who had documented evidence of perennial allergic rhinitis is not stated. It is, therefore, unclear if exclusion of such patients from the data analysis would change the differences seen between Nasonex and placebo.

Loss of smell: Loss of smell was considered a "key" secondary efficacy variable and a pre-specified approach to statistical analysis was developed. At baseline, moderate-severe loss of smell was reported by > 70% of patients in this study. For change from baseline, see table below (v3, p81, t13, p198). Loss of smell was assessed using a categorical scale of 0-3, with 0 = normal sense of smell, 1 = sense of smell mildly lost with no perception of subtle odors, e.g. strawberry, orange, lemon, 2 = sense of smell moderately lost with no perception of more characteristic odors, e.g. garlic, onion, coffee, and 3 = sense of smell totally lost, patient could not smell anything.

Improvement in sense of smell over the period of treatment in study 1925

Time-point	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value N 200 qd vs placebo	P value N 200 bid vs placebo
Baseline	2.27 (n=113)	2.24 (n=122)	2.32 (n=114)		
Week 1	-0.20 (n=113)	-0.14 (n=122)	-0.05 (n=114)	0.02	0.17
Week 2	-0.33 (n=113)	-0.21 (n=121)	-0.04 (n=111)	< 0.001	0.04
Week 3	-0.47 (n=111)	-0.31 (n=121)	-0.12 (n=110)	< 0.001	0.03
Week 4	-0.48 (n=110)	-0.31 (n=121)	-0.16 (n=109)	< 0.001	0.09
Month 1 *	-0.37 (n=113)	-0.24 n=122)	-0.09 (n=114)	< 0.001	0.04
Month 2	-0.42 (n=109)	-0.39 (n=119)	-0.18 (n=107)	0.01	0.03
Month 3	-0.49 (n=104)	-0.52 (n=112)	-0.23 (n=101)	0.02	0.006
Month 4	-0.60 (n=102)	-0.54 (n=109)	-0.27 (n=96)	0.004	0.02
Months 1-2	-0.41 (n=113)	-0.32 (n=122)	-0.14 (n=114)	< 0.001	0.03
Months 3-4	-0.56 (n=104)	-0.55 (n=112)	-0.25 (n=101)	0.003	0.004

* pre-specified time point for analysis in comparison with placebo

COMMENT: *Although both doses of Nasonex were statistically significantly greater at most time points compared to placebo in regard to improvement in smell, a greater effect was seen with 200 mcg once a day than was seen with 200 mcg bid.* [redacted] (b) (4)

Other symptoms and PNIF (v3, pgs82-87, t14-16, p200,202,204): Consistently across all secondary parameters, there was a statistically significantly greater improvement from baseline after treatment with either dose of Nasonex compared to treatment with placebo at all time points except week 1 with the lower dose of Nasonex in regard to PNIF. Rhinorrhea was evaluated using a 0-3 categorical scale where 0 = none, 1 = mild requiring blowing of nose with little or no discomfort, 2 = moderate requiring frequent blowing of the nose, annoying and caused discomfort, and 3 = severe, consistent blowing of the nose, interfered with daily activities and/or sleep. PND was evaluated using a 0-3 categorical scale where 0 = none, 1 = mild, causing little or no discomfort, 2 = moderate, annoying, causing discomfort, and 3 = severe, interfered with daily activities and/or sleep. PNIF was obtained using a nasal peak flow meter. Patients measured PNIF each morning right after assessment of symptoms and before drug administration testing 3 times and recording the highest result.

Secondary outcome variables assessed in study 1925

Time-point	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value N 200 mcg qd vs placebo	P value N 200 mcg bid vs placebo
Rhinorrhea					
Baseline	1.66 (n=113)	1.62 (n=122)	1.58 (n=114)		
Month 1	-0.29 (n=113)	-0.42 (n=122)	-0.03 (n=114)	< 0.001	< 0.001
Months 3-4	-0.50 (n=104)	-0.70 (n=112)	-0.24 (n=101)	0.01	< 0.001
Post-nasal drip					
Baseline	1.55 (n=113)	1.43 (n=122)	1.48 (n=114)		
Month 1	-0.36 (n=113)	-0.24 (n=122)	-0.01 (n=114)	< 0.001	0.001
Months 3-4	-0.54 (n=104)	-0.48 (n=112)	-0.11 (n=101)	< 0.001	< 0.001
PNIF					
Baseline	87.6 L/min (n=113)	92.7 L/min (n=121)	83.9 L/min (n=114)		
Month 1	21.1 (n=113)	25.1 (n=121)	10.3 (n=114)	0.003	< 0.001
Months 3-4	39.1 (n=104)	43.5 (n=112)	14.6 (n=101)	< 0.001	< 0.001

COMMENT: The secondary parameters evaluated during this study support the efficacy of Nasonex at a dose of 200 mcg once a day and a dose of 200 mcg bid in the treatment of [redacted](b) (4) *nasal polyps.*

Percentage of patients with improvement (v3, p88, t17, p206): Improvement was defined as a decrease in bilateral polyp grade of 1.0 or more from baseline to the last visit and a decrease in congestion /obstruction score of 0.5 or more from baseline to the average of the last 8 days of the study. Using this definition, 43% (48/111 patients) who received Nasonex 200 mcg once a day and 57% (68/119 of patients) who received Nasonex 200 mcg bid improved compared to 34% (38/112 of patients) who received placebo. There was a statistically significant difference between the 200 mcg bid dose of Nasonex and placebo ($p < 0.001$) but not between the 200 mcg once a day dose of Nasonex and placebo ($p=0.16$).

Individual patient improvement in polyp grade and congestion/obstruction *based on a one point or greater reduction from baseline to endpoint* can be seen in the table below (v3, p146-166)

Number of patients (%) who had improvement from baseline in polyp grade, congestion/obstruction and/or both

Treatment	↓ polyp grade ≥ 1	↓ congestion ≥ 1	↓ both polyp grade and congestion ≥ 1
Nasonex 200 mcg qd	73/112 (65%)	59/113 (52%)	44/112 (39%)
Nasonex 200 mcg bid	80/121 (66%)	77/122 (63%)	59/121 (49%)
Placebo	53/114 (47%)	38/114 (33%)	26/114 (23%)

Investigator's assessment of therapeutic response (v3, p89, t18, p 211): This assessment used a categorical scale of 0 = complete relief, virtually no symptoms present, 1 = marked relief, symptoms greatly improved, 2 = moderate relief, symptoms present, but noticeably improved, 3 = slight relief, symptoms present and only minimal improvement and 4 = no relief, symptoms unchanged or worse than baseline. There was a statistically significantly greater improvement based on this global assessment at endpoint in the patients who received either dose of Nasonex compared to placebo ($p < 0.001$).

6.1.4.2. Study 1926:

The treatment groups were comparable at entry in terms of demographic and disease characteristics. Baseline symptom scores were similar across the three treatment groups. There were similar numbers of patients in each treatment group who were less than 65 years of age and who were 65 years of age and older. Caucasians comprised 64-67% of the patients in the three treatment groups while Hispanics comprised 28%. The majority of patients had no history of asthma (81-85%).

Mean change from baseline in bilateral polyp grade using the ITT population (v8, p69, t11, p141): A reduction in mean bilateral polyp grade from baseline was seen in all treatment groups (see table below). Mean change from baseline in bilateral polyp grade was a co-primary efficacy variable. There was a greater reduction seen after the administration of Nasonex 200 mcg bid than after the administration of Nasonex 200 mcg once a day, although the improvement after 200 mcg bid was not statistically significantly different than placebo (p=0.08). A considerable placebo effect was seen. There was no significant mean difference in the results based on analysis of the efficacy-evaluable population (v8, p143). On the other hand, mean improvement in patients who received 200 mcg once a day was less than or essentially the same in patients who received placebo if patients were younger than 65 years of age (n=92)(v8, p145-146), males (n=70) (v8, p147-148) or non-Caucasians (n=38) (v8, p149-150). Patients 65 years of age and older (n=9), females (n=31) and Caucasians (n=63) had a greater decrease after 200 mcg once a day than after placebo. The relatively small number of patients > 65 years of age and the small number of patients with asthma prevent any meaningful conclusions with respect to the impact of either elderly age (v8, p145) or asthma on reduction in polyp grade (v8, p152,153). There was a slight imbalance in baseline polyp grade. When baseline polyp grade was added as a covariate in the analysis, there was a statistically significant difference between the change seen in the Nasonex 200 mcg bid group and the placebo group at endpoint (p = 0.05).

Mean change from baseline in bilateral polyp grade using the ITT population in Study 1926

Visit	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value Nasonex 200 mcg qd vs placebo	P value Nasonex 200 mcg bid vs placebo
Baseline	4.00 (n=101)	4.10 (n=101)	4.17 (n=100)		
Month 1	-0.36 (n=100)	- 0.51 (n=100)	-0.34 (n=97)	0.91	0.23
Month 2	-0.52 (n=96)	-0.88 (n=97)	- 0.56 (n=93)	0.81	0.06
Month 3	-0.61 (n=97)	-0.89 (n=96)	- 0.56 (n=89)	0.77	0.07
Month 4	-0.81 (n=93)	-0.98 (n=93)	- 0.78 (n=88)	0.88	0.27
Endpoint	-0.76 (n=101)	-0.98 (n=101)	- 0.67 (n=100)	0.62	0.08

COMMENT: A greater mean change from baseline in bilateral polyp grade was seen after administration of Nasonex 200 mcg bid compared with 200 mcg once a day. However, neither dosage of Nasonex produced a statistically significantly greater mean decrease in polyp grade than did placebo, although there was a mean reduction in polyp grade seen in patients who received placebo as well as patients who received Nasonex. Although there is a strong trend favoring the Nasonex 200 mcg bid dosage over placebo, there was not a statistically significant difference between either dosage of Nasonex and placebo in terms of mean polyp grade unless

the analysis included baseline as a co-variate. When this re-analysis was done, there was a statistically significant difference between Nasonex 200 mcg bid and placebo (p = 0.05). Given the importance of baseline balance in terms of polyp size as demonstrated in study Q99-925-01 (see discussion below), this re-analysis can be accepted as demonstrating the effectiveness of Nasonex at at dosage of 200 mcg bid in reducing polyp size and supports the findings in study 1925.

Congestion/obstruction symptom scores (v8, p71, t12, p): A statistically significant mean decrease in nasal congestion/obstruction was seen with both doses of Nasonex compared to placebo in a dose-dependent fashion at most time points throughout the study. Mean change in congestion/ obstruction was a co-primary efficacy variable. Average change from baseline was taken over each of the four months and over each of the first four weeks. The results were not significantly different when analyzed using the efficacy-evaluable data (v8, p157), or when analyzing the results in terms of presence of asthma (v8, p166, 167), age (v8, p159, 160), gender (v8, p161, 162) or race (v8, p163, 164).

Mean change from baseline in nasal congestion/obstruction using the ITT population in Study 1926

Time-point	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value Nasonex 200 mcg qd vs placebo	P value Nasonex 200 mcg bid vs placebo
Baseline	2.23 (n=101)	2.20 (n=100)	2.18 (n=104)		
Week 1	-0.25 (n=101)	-0.38 (n=100)	-0.12 (n=104)	0.07	< 0.001
Week 2	-0.43 (n=100)	-0.65 (n=99)	-0.22 (n=99)	0.01	< 0.001
Week 3	-0.48 (n=99)	-0.81(n=98)	-0.30 (n=96)	0.04	< 0.001
Week 4	-0.54 (n=99)	-0.83 (n=98)	-0.36 (n=95)	0.05	< 0.001
Month 1 **	-0.42 (n=101)	-0.66 (n=100)	-0.23 (n=104)	0.01	< 0.001
Month 2	-0.66 (n=98)	-0.90 (n=96)	-0.43 (n=95)	0.02	< 0.001
Month 3	-0.74 (n=97)	-1.04 (n=94)	-0.58 (n=88)	0.14	< 0.001
Month 4	-0.86 (n= 95)	-1.09 (n=92)	-0.61 (n=87)	0.02	< 0.001
Months 1-2	-0.53 (n=101)	-0.76 (n=100)	-0.31(n=104)	0.005	< 0.001
Months 3-4	-0.78 (n=97)	-1.05 (n=94)	-0.59 (n=88)	0.06	< 0.001

** Specified as time point for analysis in comparison with placebo.

COMMENT: There was a statistically significantly greater mean reduction in nasal congestion/obstruction in a dose-dependent manner after administration of Nasonex than after administration of placebo. This finding is consistent with the demonstrated effectiveness of Nasonex on nasal symptoms in patients with allergic rhinitis. Over the last two months of treatment, the improvement of 0.78 after 200 mcg once a day and 1.05 after 200 mcg bid represents a clinically significant effect as well. The improvement of 0.42 and 0.66 after the administration of Nasonex 200 mcg once a day and Nasonex 200 mcg bid, respectively, is also consistent with the effect size shown with other intranasal corticosteroids and is considered to be a clinically significant change. Based on this data, Nasonex is effective in the reduction in nasal congestion/obstruction in patients who have bilateral nasal polyposis.

Individual symptom scores:

Loss of smell was a "key" secondary efficacy variable and a pre-specified statistical analysis was developed for analysis of this parameter. At baseline, moderate-severe loss of smell was reported by > 60% of patients in this study. For change from baseline, see table below (v8, p73, t13, p169). Loss of smell was assessed using a categorical scale of 0-3, with 0 = normal sense of smell, 1 = sense of smell mildly lost with no perception of subtle odors, e.g. strawberry, orange, lemon, 2 = sense of smell moderately lost with no perception of more characteristic odors, e.g. garlic, onion, coffee, and 3 = sense of smell totally lost, patient could not smell anything.

Mean improvement in sense of smell (decrease in loss of smell) in the ITT population in study 1926

Time-point	Nasonex 200 mcg qd AM	Nasonex 200 mcg bid	Placebo	P value N 200 qd vs placebo	P value N 200 bid vs placebo
Baseline	2.03 (n=101)	1.94 (n=100)	1.96 (n=104)		
Week 1	-0.03 (n=101)	-0.03 (n=100)	-0.03 (n=104)	0.94	0.96
Week 2	-0.09 (n=100)	-0.18 (n=99)	-0.06 (n=99)	0.66	0.12
Week 3	-0.06 (n=99)	-0.22 (n=98)	-0.03 (n=96)	0.74	0.03 •
Week 4	-0.05 (n=99)	-0.26 (n=98)	-0.03 (n=95)	0.77	0.009 •
Month 1 **	-0.06 (n=101)	-0.18 n=100)	-0.05 (n=104)	0.85	0.05 •
Month 2	-0.16 (n=98)	-0.30 (n=96)	-0.12 (n=95)	0.70	0.08
Month 3	-0.26 (n=97)	-0.36 (n=94)	-0.26 (n=88)	0.98	0.37
Month 4	-0.33 (n=95)	-0.40 (n=92)	-0.23 (n=87)	0.37	0.11
Months 1-2	-0.11 (n=101)	-0.24 (n=100)	-0.10 (n=104)	0.83	0.06
Months 3-4	-0.29 (n=97)	-0.38 (n=94)	-0.24 (n=88)	0.67	0.21

** Specified as time point for analysis in comparison with placebo.

COMMENT: In this study, a dose of 200 mcg once a day of Nasonex was not effective in improving sense of smell in patients with bilateral nasal polyposis. A dose of 200 mcg bid was not effective in improving a sense of smell beyond a period of one month. Based on a comparison of Nasonex at a dosage of 200 mcg bid and placebo at the pre-specified time point for analysis, this data supports the effectiveness of Nasonex, when given at a dose of 200 mcg bid in improving a sense of smell in patients with bilateral nasal polyposis. However, the data is not convincing since a statistically significantly different effect from placebo for the group that received Nasonex 200 mcg bid was only seen at week 3, week 4 and over the first month of treatment and not at any other time point. (b) (4)

Other symptoms and PNIF (v8, pgs74-78, t14-16, pgs171-175): Rhinorrhea was evaluated using a 0-3 categorical scale where 0 = none, 1 = mild requiring blowing of nose with little or no discomfort, 2 = moderate requiring frequent blowing of the nose, annoying and caused discomfort, and 3 = severe, consistent blowing of the nose, interfered with daily activities and/or sleep. PND was evaluated using a 0-3 categorical scale where 0 = none, 1 = mild, causing little or no discomfort, 2 = moderate, annoying, causing discomfort, and 3 = severe, interfered with daily activities and/or sleep. PNIF was obtained using a nasal peak flow meter. Patients measured PNIF each morning right after assessment of symptoms and before drug administration testing 3 times and recording the highest result. Average change from baseline was taken over

each of the four months and over each of the first four weeks, except for peak nasal inspiratory flow where averages were taken as well over each two month interval.

Mean change in secondary endpoints in study 1926

Time-point	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value N 200 mcg qd Vs placebo	P value N 200 mcg bid vs placebo
Rhinorrhea					
Baseline	1.53 (n=101)	1.58 (n=100)	1.57 (n=104)		
Month 1	-0.28 (n=101)	-0.47 (n=100)	-0.11 (n=104)	0.02	< 0.001
Months 3-4	-0.58 (n=97)	-0.73 (n=94)	-0.38 (n=88)	0.07	0.001
Post-nasal drip					
Baseline	1.47 (n=101)	1.46 (n=100)	1.41 (n=104)		
Month 1	-0.19 (n=101)	-0.38 (n=100)	-0.10 (n=104)	0.23	< 0.001
Months 3-4	-0.47 (n=97)	-0.60 (n=94)	-0.36 (n=88)	0.32	0.04
PNIF					
Baseline	102 L/min (n=101)	95.4 L/min (n=100)	97.7 L/min (n=104)		
Month 1	16.7(n=101)	25.6 (n=100)	5.4 (n=104)	< 0.001	< 0.001
Months 3-4	31.7 (n=96)	44.9 (n=94)	13.3 (n=88)	< 0.001	< 0.001

COMMENT: The secondary parameters evaluated during this study support the efficacy of Nasonex at a dose of 200 mcg once a day and a dose of 200 mcg bid in the treatment of rhinorrhea and PNIF. Nasonex at a dosage of 200 mcg once a day did not improve post-nasal drainage (b) (4)

Percentage of patients with improvement (v8, p79, t17, p177): Improvement was defined as a decrease in bilateral polyp grade of 1.0 or more from baseline to the last visit and a decrease in congestion /obstruction score of 0.5 or more from baseline to the average of the last 8 days of the study. Using this definition, 34% (34/101 patients) who received Nasonex 200 mcg once a day and 49% (49/100 of patients) who received Nasonex 200 mcg bid improved compared to 25% (24/98 of patients) who received placebo. There was a statistically significant difference between the 200 mcg bid dose of Nasonex and placebo (p <0.001) but not between the 200 mcg once a day dose of Nasonex and placebo (p=0.16).

Individual patient improvement in polyp grade and congestion/obstruction *based on a one point or greater reduction from baseline to endpoint* can be seen in the table below (v8, p120-137)

Number of patients (%) who had improvement from baseline in polyp grade, congestion/obstruction and/or both

Treatment	↓ polyp grade ≥ 1	↓ congestion ≥ 1	↓ both polyp grade and congestion ≥ 1
Nasonex 200 mcg qd	52/101 (52%)	30/101 (30%)	18/101 (18 %)
Nasonex 200 mcg bid	60/101 (60%)	48/100 (48%)	28/100 (28%)
Placebo	49/100 (49%)	18/104 (18%)	6/100 (6%)

Investigator's assessment of therapeutic response (v8, p80, t18, p182): This assessment used a categorical scale of 0 = complete relief, virtually no symptoms present, 1 = marked relief,

symptoms greatly improved, 2 = moderate relief, symptoms present, but noticeably improved, 3 = slight relief, symptoms present and only minimal improvement and 4 = no relief, symptoms unchanged or worse than baseline. There was a statistically significantly greater improvement based on this global assessment at endpoint in the patients who received either dose of Nasonex compared to placebo ($p < 0.001$).

Health-Related Quality of Life (QOL) (v8, p86, t19): The QOL was evaluated using the SF-36 scales, Work Productivity and Activity Inventory (WPAI-SHP) and the generic treatment satisfaction questionnaire. The SF-36 and WPAI-SHP were collected at baseline, month 1, month 4, and at discontinuation. The generic treatment satisfaction questionnaire was collected at month 4 or at the time of discontinuation. There were 295/310 patients (95%) who completed the SF-36 at both baseline and endpoint and 283/310 patients (91%) who completed the SPAI-SHP. The SF-36 assessed 8 domains of health over the previous week. Domains included: 1) physical functioning; 2) role physical; 3) bodily pain; 4) general health; 5) vitality; 6) social functioning; 7) role emotional; and 8) mental health. Two additional summary measures of physical (PCS) and mental (MCS) were constructed based on all the eight domains of the SF-36. The SF-36 is scored from 0-100 with the lower score indicating greater disease burden. Since the mean baseline scores for all domains of the SF-36 showed that the QOL in the study population was similar to that in the general population in the US, no specific QOL burden was evident in the study population. The mean baseline scores for the SF-36 domains were similar across treatment group. At endpoint, there was no statistically significant difference between either the Nasonex 200 mcg once a day or the Nasonex 200 mcg bid treatment group and placebo were noted for the vitality domain, which was the pre-specified primary domain. Since there was no significant difference between active treatment and placebo for the primary domain, no further analysis of the data was done. Neither active treatment group showed any increase in work productivity over that seen in the placebo group. In addition, the generic treatment satisfaction data did not show any clear benefit of treatment.

6.1.4.3 Study Q99-925-01:

Improvement in the primary efficacy variable, investigator-assessed nasal congestion, was defined as a reduction of at least one point from baseline to the last visit (see table below) (v12, p52, t9, p81). There was a statistically significant difference between the Nasonex and placebo groups based on analysis of both the ITT and the per protocol population favoring Nasonex.

Improvement nasal congestion, baseline to the last visit in study Q99-925-01 based on ITT population (v12, p52, t9)

Category	Nasonex 200 mcg QD (n=152)	Placebo (n=139)	P value
Nasal congestion			
Improvement	113 (74.3%)	65 (46.8%)	< 0.001
No improvement	39 (25.7%)	74 (53.2%)	

Improvement in secondary efficacy variables; number (%) of patients with improvement at endpoint in study Q99-925-01 based on ITT population (v12, p54, t10)

Category	Nasonex 200 mcg QD (n=152)	Placebo (n=139)	P value
Polyp size			
Improvement	63 (41.4%)	37 (26.6%)	0.003
No improvement	89 (58.6%)	102 (73.4%)	
Sense of smell			
Improvement	56 (36.8%)	31 (22.3%)	0.007
No improvement	96 (63.2%)	108 (77.7%)	
Rhinorrhea			
Improvement	79 (52%)	49 (35.3%)	0.004
No improvement	73 (48%)	90 (64.7%)	
Therapeutic response			
Complete relief	15 (9.9%)	3 (2.2%)	< 0.001
Marked relief	50 (32.9%)	26 (18.7%)	
Moderate relief	48 (31.6%)	35 (25.2%)	
Treatment failure	39 (25.7%)	75 (54%)	

Change in polyp size was based on investigator selection of the largest polyp and following change in the size of that polyp throughout the study. Investigators were instructed to grade the size of the polyps in both nostrils at the screening visit, choose the grade from the most severe side and follow the largest polyp and how it changed in size at all subsequent visits.

Mean change in polyp grade at time-points during study Q99-925-01 (v12, p223)

Time-point	N	Nasonex 200 mcg qd	N	Placebo	P value
Baseline	152	1.85	139	1.94	
Month 1	149	-0.22	132	-0.05	0.007
Month 2	146	-0.18	115	-0.12	0.39
Month 3	140	-0.32	105	-0.18	0.07
Month 4	138	-0.36	104	-0.22	0.08
Endpoint	152	-0.35	139	-0.12	0.001

Other secondary efficacy outcome variables: The mean increase in *PNIF* from baseline was 22 L/min in the Nasonex group and 10 L/min in the placebo group ($p = 0.025$) at endpoint. The mean increase in *olfactory threshold* was 0.90 in the Nasonex group and 0.83 in the placebo group ($p = 0.66$). In regard to daily symptoms of nasal congestion, rhinitis and sense of smell from baseline to endpoint, see table below (v12, p117). *Quality of life assessment* in the ITT population showed that the % of patients with improvement from baseline to endpoint for nose breathing was 47.4% in the Nasonex group and 26.6% in the placebo group ($p < 0.001$) (v12, p131), or smell and taste was 42% in the Nasonex group and 39% in the placebo group ($p = 0.58$) (v121, p134), for interference with daily activities was 61.8% in the Nasonex group and 45.3% in the placebo group (p 0.003) (v12, p138), for sleeping disturbances was 57.2% in the Nasonex group and 37.4% in the placebo group ($p = 0.001$) (v12, p141) and for improvement in smell and taste was 42.1% in the Nasonex group and 38,8% in the placebo group ($p = 0.58$). Usage of

rescue medication at least once during the study was 34.2% in the Nasonex group and 50.7% in the placebo group (p = 0.006). There were 34.2% of the Nasonex group who required *rescue medication* compared to 50.7% of the placebo group (v121, p216).

Mean change from baseline in study Q99-925-01 in daily symptoms

Parameter	Nasonex 200 mcg qd	Placebo	P value
Nasal congestion AM	- 0.59	- 0.23	< 0.001
Nasal congestion PM	- 0.59	- 0.24	< 0.001
Rhinorrhea AM	- 0.43	- 0.08	< 0.001
Rhinorrhea PM	- 0.38	- 0.12	< 0.001
Sense of smell AM	- 0.24	- 0.07	0.004
Sense of smell PM	- 0.24	- 0.08	0.005

6.1.4.4. Study 2573:

Study 2573 was a 4 month follow-up study to assess the rate of recurrence of nasal polyps in patients whose condition improved with up to 4 months of treatment with Nasonex Nasal Spray in study 1925. This was a double-blind, multicenter (27 centers in 10 countries), followup study to study 1925 in which patients received Nasonex either once a day or bid at a dose of 200 mcg or placebo. Patients were entered into study 2573 if they had improved with treatment in study 1925 and met the inclusion/exclusion criteria and were then followed for up to 4 months without additional treatment to assess the rate of recurrence of nasal polyps after cessation of treatment.

Improvement with treatment in study 1925 was defined as: 1) the bilateral polyp grade, i.e. the sum of the grade of the polyps from the left and from the right nasal fossa with a maximum possible bilateral polyp grade of 6 points, as assessed by the investigator by endoscopy, decreased from baseline to the end of treatment by at least one point; and 2) the average of the last eight non-missing congestion/obstruction scores (maximum score was 3) recorded by the patient during treatment in study 1925 decreased from the baseline score by at least 0.5 points. Nasal polyps were graded on a 0-3 categorical scale where 0 = no polyps, 1 = polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate; and 3= large polyps reaching to or below the lower border of the inferior turbinate or polyps medial to the middle turbinate (v14, p32).

In study 2573, patients were evaluated for polyp size which was graded via nasal endoscopy at the beginning of treatment and monthly throughout the study and patients assessed weekly nasal congestion/obstruction, rhinorrhea, postnasal drainage, loss of smell, and PNIF throughout the study. Symptoms and signs were graded by patients on a categorical scale from 0-3 i.e. none, mild, moderate or severe (v14, pgs33, 34). PNIF was measured by patients weekly (v14, p34). Recurrence was considered to have occurred if the bilateral polyp grade as assessed by endoscopy had increased from the study 2573 baseline by at least one point at the termination of the study AND the last two congestion/obstruction scores increased from the baseline score by at least 0.5 points on each of the last two scores. Other endpoints included change from baseline in other nasal symptoms/signs and change from baseline in PNIF averaged over each month as well as for the entire 4 month observation period.

There were 135 patients in the study (82 males and 53 females) between the ages of 18-78 years. Of these, 46 received 200 mcg once a day of Nasonex in study 1925, 58 received 200 mcg bid of Nasonex in study 1925 and 31 received placebo. These patients were not randomly selected and therefore no inferential analyses among the treatment groups were done. Placebo patients were entered into study 2573 to maintain the blind for study 1925 which was ongoing.

There were 135 patients from 27 centers in 10 countries enrolled in this study. Site 21 was terminated because of significant departure from GCP including fabrication of source document information for non-existent visits and data from this site was excluded from all efficacy and pooled safety analyses (v15, p593). More than 90% of the patients entered into the study remained in the study for at least 1 month. More than 57% remained for at least 3 months. There were 68 patients (50%) who discontinued treatment before 4 months of treatment (see below; v14, p49, t7). A patient was considered to have completed the study is his/her last visit occurred after day 100. As a result, the numbers below taken from table 7 in volume 14 below as patients who completed the study in each treatment group will be different than the number of patients taken from table 16 in volume 14 below who completed 120 days or more.

Patient disposition in studies 1925 and 2573 (v14, p49, t7)

Study 1925	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo
Patients randomized	115	122	117
Patients completing study	101 (88%)	109 (89%)	95 (81%)
Patients improved	48 (43%)	68 (57%)	38 (34%)
Study 2573			
Patients enrolled	46	58	31
Patients completing study	22 (48%)	27 (47%)	18 (58%)
Patients discontinued	24 (52%)	31 (47%)	13 (42%)
Adverse event	2 (4%)	0	0
Relapse/recurrence	14 (30%)	26 (45%)	9 (29%)
Lost to follow-up	1 (2%)	2 (3%)	0
Did not wish to continue	4 (9%)	2 (3%)	2 (6%)
Non-compliance	1 (2%)	1 (2%)	1 (3%)
Did not meet entry criteria	2 (4%)	0	1 (3%)

There were 15 patients (11%) who had one or more protocol violations that included not meeting study entry criteria, non-compliance and unacceptable concomitant medications, that excluded

them from the evaluation of efficacy. Of these, 6 (13% of patients) were in the Nasonex 200 mcg qd group, 6 (10% of patients) were in the Nasonex 200 mcg bid group and 3 (10% of patients) were in the placebo group (v14, p51, t8). The two data sets analyzed were all patients enrolled in the study (ITT principle) and efficacy-evaluable patients who met the eligibility and evaluability criteria established prior to the study.

Number (%) of patients in study 2573 who remained in the study over time (v14, p69, t16)

Duration	Nasonex 200 mcg qd (n=46)	Nasonex 200 mcg bid (N=58)	Placebo (n=31)
8 or more days	46 (100%)	56 (97%)	31 (100%)
30 or more days	42 (91%	52 (90%)	29 (94%)
60 or more days	32 (70%)	38 (66%)	24 (77%)
90 or more days	25 (54%)	30 (52%)	22 (71%)
120 or more days	8 (17%)	15 (26%)	9 (29%)
Mean	85.6	83.2	94.9
Median	102	91	114
Range	26-127	1-140	20-140

The subset of patients that enrolled in study 2573 did not appear to represent a different subset of patients than the original group in study 1925 indicating that there was no prognostic demographic characteristic that might have suggested that a given patient in study 1925 would improve in study 2573 (see table below; v14, p53, t9).

Category	Nasonex 200 mcg qd (n=46)	Nasonex 200 mcg bid (n=58)	Placebo (n=31)
Mean age	47.7 years	46.6 years	47.7 years
Age range	18-78 years	19-74 years	22-78 years
18-64 years	40 (87%)	54 (93%)	28 (90%)
65 years and older	6 (13%	4 (7%)	3 (10%)
Female/male percentage	37%/63%	41%/59%	39%/61%
Caucasian/Black/Asian/Hispanic	52%/2%/2%/43%	47%/2%/3%/48%	48%/6%/0/45%
Asthma history	5 (11%)	12 (21%)	7 (23%)
PAR history	3 (7%)	8 (14%)	8 (26%)

The percentage of patients who had recurrence of polyps was lower and the time to recurrence was longer in patients who had not received Nasonex in study 1925 than in patients who had received either dosage of Nasonex in study 1925 (see table below; v14, p55-56, t10-11). Among patients who had received Nasonex in study 1925, there was less recurrence and a longer time to recurrence in patients who had received the lower dosage of Nasonex.

Number (%) of patients with recurrence of polyps (v14, p55, t10) and time to recurrence (v14, p56, t11) study 2573

Category	Nasonex 200 mcg qd (n=46)	Nasonex 200 mcg bid (n=55) *	Placebo (n=31)
Recurrence **	15 (32.6%)	23 (41.8%)	7 (22.6%)
Non-recurrence, completed	19 (41.3%)	26 (47.3%)	17 (54.8%)
No-recurrence, dropped out	12 (26.1%)	6 (10.9%)	7 (22.6%)
Time to recurrence ***	81 days	61 days	123 days

* 3 of the 58 patients in this group had missing recurrence status and were not included in the analysis

** recurrence was defined as an increase in bilateral polyp grade of 1 point or more relative to baseline AND an increase of 0.5 points or more in the last two consecutive congestion/obstruction scores relative to baseline

*** based on quartile estimates from Kaplan-Meier survival analysis; 25th percentile

The mean change in polyp grade at endpoint in study 2573 was greater in the groups that received Nasonex during study 1925, especially the group that received 200 mcg bid, than the group that received placebo in that study (see table below). In addition, the bilateral polyp grade at baseline of study 2573 can be seen in the following table (v14, p106). There was no significant difference in comparison of the change from baseline between treatment groups based on age (v14, pgs 131-132). There was less of a change in polyp grade in females (n=17, 23, and 12 in the 200 mcg qd, 200 mcg bid and placebo groups, respectively) than in males (n=29, 33, and 19 in the 200 mcg qd, 200 mcg bid and placebo groups, respectively) in all treatment groups (v14, pgs133-134). There was also a greater change in polyp grade in Caucasians (n=24. 26, 15 in the 200 mcg qd, 200 mcg bid and placebo groups, respectively) than in non-Caucasians (n=22, 30, 16 in the 200 mcg qd, 200 mcg bid and placebo groups, respectively) in all treatment groups (v14, pgs 135-136)

Comparison of frequency of polyp grade at endpoint in treatment groups in study 1925

Number of patients	Nasonex 200 mcg qd (n=46)	Nasonex 200 mcg bid (n=56)	Placebo (n=31)
Bilateral polyp grade 0-1	14 (30%)	7 (12%)	9 (29%)
Bilateral polyp grade 2	8 (17%)	17 (29%)	7 (23%)
Bilateral polyp grade 3	9 (20%)	13 (22%)	9 (29%)
Bilateral polyp grade 4	7 (15%)	9 (16%)	3 (10%)
Bilateral polyp grade 5	1 (2%)	4 (7%)	1 (3%)
Bilateral polyp grade 6	1 (2%)	0	1 (3%)

Mean change in polyp grade over 4 months from rollover to endpoint in study 2573 (v14, p59, t12)

Visit	n	Nasonex 200 mcg qd	N	Nasonex 200 mcg bid	N	Placebo
Baseline *	46	4.20	56	4.36	31	4.16
Roll-over **	46	-2.28	56	-2.00	31	-2.06
Month 1	344	-2.20	55	-1.51	29	-1.72
Month 2	37	-2.11	42	-1.60	25	-2.00
Month 3	27	-2.11	34	-1.62	23	-1.61
Month 4	23	-1.83	27	-1.56	18	-1.89
Endpoint	46	-1.59 (-0.69 from rollover)	56	-1.02 (-0.98 from rollover)	31	-1.48 (-0.58 from rollover)

* baseline of study 1925
** roll-over= last visit from study 1925

In the Nasonex 200 mcg qd group (n=46), there were 13 patients who had an increased polyp grade of 1 (28%), 7 patients who had an increased polyp grade of 2 (15%), 2 patients who had an increased polyp grade of 3 (4%) and one patient who had an increased polyp grade of 4 (2%). By comparison, in the Nasonex 200 mcg bid group (n=56), there was an increased polyp grade of 1 in 26 patients (46%), 2 in 9 patients (16%), 3 in 1 patient (2%) and 4 in 2 patients (4%). In the placebo group (n=31), there was an increased polyp grade of 1 in 6 patients (19%), 2 in 5 patients (16%), 3 in no patients and 4 in one patient (3%). More severe worsening of polyps (2-4 point change) was not seen with greater frequency in the two Nasonex groups than in the placebo group, but a one point change was seen in 28% and 46% of the Nasonex 200 mcg qd and Nasonex 200 mcg bid groups, respectively, compared to 19% of the placebo group (v14, pgs 85-93).

COMMENT: There was a greater incidence of recurrence of polyps in patients who had received Nasonex in study 1925. Iin fact, the greatest incidence of recurrence was in the group that had received the higher dose of Nasonex. The placebo group in this study is atypical of patients with nasal polyps in general since they had to have improved significantly in study 1925 while receiving only placebo in order to qualify for study 2573. Moreover, there were at least 41% of patients who did not have a recurrence of nasal polyps after using Nasonex.

The mean change in nasal congestion/obstruction at endpoint in study 2573 was greater in the groups that received Nasonex in study 1925 than in the group that received placebo in that study (see table below). There was no significant difference in the mean change seen in any of the treatment groups based on age or gender (v14, pgs 147-150). In Caucasians, there was a greater increase in nasal congestion from roll-over to endpoint in the Nasonex 200 mcg bid group than in the Nasonex 200 mcg qd group while in non-Caucasians, there was a greater increase in nasal congestion from roll-over to endpoint in the Nasonex 200 mcg qd group than in the Nasonex 200 mcg bid group. In the placebo group, there was improvement in nasal congestion in Caucasians and worsening in non-Caucasians (v14, pgs 151-152).

Mean change in nasal congestion/obstruction over 4 months from rollover to endpoint in study 2573 (v14, p61, t13)

Category	n	Nasonex 200 mcg qd	n	Nasonex 200 mcg bid	N	Placebo
Baseline *	46	2.29	56	2.34	31	2.31
Roll-over *	46	-1.43	55	-1.53	31	-1.00
Week 1	45	-1.42	56	-1.44	31	-1.20
Week 2	46	-1.31	56	-1.39	31	-1.05
Week 3	45	-1.18	54	-1.30	31	-1.04
Week 4	42	-1.28	48	-1.29	27	-0.99
Month 1	46	-1.29	56	-1.36	31	-1.08
Month 2	38	-1.21	45	-1.24	26	-1.18
Month 3	29	-1.34	34	-1.44	22	-1.12
Month 4	21	-1.28	528	-1.55	18	-1.25
Endpoint	46	-1.00 (-0.43 from rollover)	56	-1.14 (-0.39 from rollover)	31	-0.97 (-0.03 from rollover)

* baseline of study 1925
* rollover = average of month 4 from study 1925

The mean change in loss of sense of smell at endpoint in study 2573 did not change significantly in any of the three treatment groups compared to the average value at month 4 in study 1925 (see table below)

Mean change in loss of smell over 4 months from rollover to endpoint in study 2573 (v14, p62, t14)

Category	n	Nasonex 200 mcg qd	n	Nasonex 200 mcg bid	n	placebo
Baseline *	46	1.99	56	1.99	31	1.97
Rollover **	46	-0.96	55	-0.73	31	-0.61
Week 1	45	-1.03	56	-0.81	31	-0.89
Week 2	46	-0.92	56	-0.83	31	-0.74
Week 3	45	-0.88	54	-0.77	31	-0.84
Week 4	42	-0.94	48	-0.76	27	-0.68
Month 1	46	-0.95	56	-0.78	31	-0.80
Month 2	38	-0.91	45	-0.74	26	-0.97
Month 3	29	-0.92	34	-0.74	22	-0.73
Month 4	21	-0.99	28	-0.85	18	-0.70
endpoint	46	-0.84	56	-0.66	31	-0.77

There was a decrease in PNIF from the end of treatment in study 1925 until the endpoint in study 2573 in both groups that had received Nasonex in study 1925 while the PNIF increased slightly in the group that had received placebo in study 1925. The decrease in PNIF would be expected in the Nasonex groups because of withdrawal from the active treatment (see table below).

Change in peak nasal flow rate (liters/minute) from rollover to endpoint in study 2573 (v14, p64. t15)

Category	n	Nasonex 200 mcg qd	N	Nasonex 200 mcg bid	N	placebo
Baseline *	46	87.9	56	83.3	31	81.5
Rollover **	46	43.5	55	50.8	31	29.7
Week 1	45	40.9	56	46.6	31	33.4
Week 2	46	39.5	56	41.0	31	31.6
Week 3	45	36.4	54	37.4	30	31.5
Week 4	42	36.6	48	39.6	27	35.8
Month 1	46	38.0	56	41.1	31	32.1
Month 2	38	35.2	45	35.5	25	29.3
Month 3	29	33.7	34	31.9	22	28.9
Month 4	20	41.8	28	32.1	18	26.0
endpoint	46	28.9	56	29.9	31	33.1

6.1.5 Clinical Microbiology

There was no clinical microbiology review for this drug product.

6.1.6 Efficacy Conclusions

The efficacy of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray at a dosage of 200 mcg once a day and 200 mcg bid for the treatment of nasal polyps in adult and adolescent patients 18 years and older has been demonstrated. The efficacy of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray has been sufficiently demonstrated, (i.e. in two well designed studies), at a dosage of 200 mcg once a day and at a dose of 200 mcg bid, to approve this drug product for the treatment of nasal polyps. The efficacy of a dosage of Nasonex Nasal Spray 200 mcg once a day was demonstrated in studies 1925 and Q99-925-01 while the efficacy of a dosage of Nasonex Nasal Spray 200 mcg twice a day was demonstrated in studies 1925 and 1926.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

There were 594 patients who received Nasonex in studies 1925, 1926 and Q99-925-01. No unusual or unexpected adverse events occurred, there were no deaths and there were 18 serious adverse events reported, none of which was considered related to the study drug. The safety of inhaled corticosteroids should focus on local effects that can occur from the inhalation of the drug product and possible systemic effects from absorption of a corticosteroid. In terms of local effects, Nasonex, in particular at a dosage of 200 mcg bid, caused more local adverse effects, especially epistaxis, than placebo. *This type of adverse effect is not unexpected with inhalation of corticosteroids and is not a reason for not approving this drug product.* No systemic adverse effects were reported with greater frequency in patients who received Nasonex than in patients who received placebo in the studies performed under this submission. Post-marketing adverse event reporting included a number of adverse effects that could represent systemic effects of

Nasonex, e.g. cataracts, glaucoma, but there is insufficient data in these reports to conclude that these adverse events represent an adverse effect from Nasonex. Elevated SGOT levels were seen in with greater frequency in patients who received Nasonex than in patients who received placebo in studies 1925 and 1926. In study 1925, this was a dose-dependent effect while in study 1926 this greater frequency in elevated SGOT was seen only in patients who received 200 mcg bid. *Intranasal corticosteroids are metabolized in the liver. Mometasone undergoes extensive metabolism to metabolites regulated by the cytochrome P-450 3A4 enzyme system. Liver mixed-function oxidases and glucuronyl transferases are important in the metabolism of many glucocorticosteroids. As a result, liver disease, drugs and other chemical that modify liver function can affect the biologic half-life of glucocorticosteroids. However, intranasal corticosteroids have not been reported to produce an increase in liver enzymes and there is nothing unique about this drug product that would support any concern about its hepatic effect. Overall, the sponsor has demonstrated the safety of Nasonex at a dosage of 200 mcg once a day and a dosage of 200 mcg bid.*

7.1.1 Deaths

There were no deaths in studies 1925, 1926, Q99-925-01 or 2573. The only death reported from the post-marketing data was an intra-uterine death considered unlikely to be related to Nasonex Nasal Spray.

7.1.2 Other Serious Adverse Events

Studies 1925 and 1926 were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in 664 patients 18 years and older with bilateral nasal polyps, of whom 441 received Nasonex. Patients received either 200 mcg Nasonex once a day, 200 mcg Nasonex bid or placebo for 4 months. There were 8 patients who had serious adverse events in studies 1925 and 1926, the two controlled studies performed by Schering. In 5 of these patients, treatment was interrupted but there were no patients who were discontinued from treatment. All the serious adverse events in these studies were considered unlikely related to the study drug.

In *study 1926*, there were 6 serious adverse events recorded, one in the Nasonex 200 mcg once a day group, 2 in the Nasonex 200 mcg bid group and three in the placebo group. A 55 year old Caucasian male who had received Nasonex 200 mcg once a day for 29 days developed atrial flutter and fibrillation for which the patient was hospitalized and treated (v8, p261). The patient had a history of atrial fibrillation and screening ECG showed sinus bradycardia and prolonged QT interval (v8, p276). Three serious adverse events were reported for 2 patients in the Nasonex 200 mcg bid group: 1) coronary artery stenosis in a 58 year old Caucasian male which was noted on the screening ECG, 7 days prior to initiation of treatment. The patient was randomized into the study but the ECG findings were confirmed after one month of treatment with the study drug for which the patient was hospitalized and had cardiac catherization (procedure) (v8, p262, 272); and 2) choroidal neovascularization in a 27 year old Asian male which began after 32 days of treatment and for which treatment was interrupted (v8, p262, v21, p51). This event was considered by an ophthalmologist to be a consequence of the patient's pre-existing myopia (v8, p271) Four serious adverse events were reported for 3 patients in the placebo group: 1) an arrhythmia in a 42 year old Hispanic male that began on the 72nd day of treatment for which the patient was hospitalized and treatment with the study drug interrupted (v8, p275); 2) pneumonia

and pleurisy in a 57 year old Caucasian male that occurred after 47 days of treatment for which the patient was hospitalized and treated (v8, p274); and 3) edema of the tongue in a 43 year old Caucasian female that began after 106 days of treatment, was moderate in severity and required interruption of study treatment (v8, p273).

Eight patients in *study Q99-925-01* had serious adverse events, all of which were considered unrelated to the study drug (see Appendix, 10.1.a and 10.1.b). In study Q99-925-01, serious adverse events were reported in 5 patients in the Nasonex group and 4 patients in the placebo treatment group. None were considered related to the study drug. The serious adverse events (v21, pgs54-56) in the Nasonex group were: 1) severe, unrelated cholelithiasis requiring hospitalization in a 67 year old male; 2) moderate unrelated anemia due to vitamin B12 deficiency requiring hospitalization in a 64 year old female; 3) moderate unrelated pneumonia requiring hospitalization in a 35 year old male; 4) mild unrelated toothache and possibly related sinusitis requiring additional therapy; and 5) myocardial infarction with severe unrelated cardiac failure requiring hospitalization. The patient with cardiac failure was an 83 year old male who had a previous history of heart disease. Two and one half weeks after starting therapy the patient developed a myocardial infarction. The patient recovered and study medication was continued. The serious adverse events in the placebo group were: 1) moderate unrelated hemorrhagic stroke requiring additional therapy and hospitalization; 2) moderate unrelated asthma requiring hospitalization; 3) mild unrelated rotator cuff syndrome requiring additional therapy and hospitalization; and 4) moderate unrelated asthma requiring hospitalization (v12, p70, t15).

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1. Overall profile of dropouts

Number (%) of randomized patients who completed randomized treatment, number (%) who discontinued and reasons for discontinuation in study 1925 (v3, p68, t8)

Category	Nasonex 200 mcg qd	Nasonex 200 mcg bid	placebo
Patients randomized	115	100	100
Patients completed study	101 (88%)	109 (89%)	95 (81%)
Patients discontinued	14 (12%)	13 (11%)	22 (19%)
d/c due to adverse event	2 (2%)	4 (3%)	4 (3%)
d/c due to treatment failure	3 (3%)	1 (1%)	6 (5%)
d/c lost to follow-up	2 (2%)	1 (1%)	3 (3%)
d/c did not wish continue	4 (3%)	4 (3%)	3 (3%)
d/c non-compliance	2 (2%)	2 (2%)	2 (2%)
d/c did not meet entry criteria	1 (1%)	1 (1%)	4 (3%)

Number (%) of randomized patients who completed randomized treatment, number (%) who discontinued and reasons for discontinuation in study 1926 (v8, p61, t8)

Category	Nasonex 200 mcg qd	Nasonex 200 mcg bid	placebo
Patients randomized	102	102	108
Patients completed study	94 (92%)	93 (91%)	87 (82%)
Patients discontinued	8 (8%)	9 (9%)	19 (18%)
d/c due to adverse event	0	0	1 (1%)
d/c due to treatment failure	1 (1%)	3 (3%)	5 (5%)
d/c lost to follow-up	0	0	2 (2%)
d/c did not wish continue	3 (3%)	1 (1%)	4 (4%)
d/c non-compliance	2 (2%)	3 (3%)	1 (1%)
d/c did not meet entry criteria	2 (2%)	2 (2%)	6 (6%)

Number (%) of randomized patients who completed double-blind treatment and number (%) who discontinued and reason for discontinuation study Q99-925-01(v12, p46. t4)

Category	Nasonex 200 mcg QD (n=153)	Placebo (n=145)
Number (%) completed DB period	134 (87.6%)	101 (69.7%)
Total discontinued	19 (12.4%)	44 (30.3%)
Reason for discontinuation		
Adverse event	1 (0.7%)	4 (2.8%)
Treatment failure	8 (5.2%)	27 (18.6%)
Treatment failure/noncompliance	0	1 (0.7%)
Significant inter-current illness	0	2 (1.4%)
Did not wish to continue	2 (1.3%)	0
Noncompliance with protocol	4 (2.6%)	6 (4.1%)
Other	4 (2.6%)	4 (2.8%)

7.1.3.2 Adverse events associated with dropouts

Overall profile of dropouts due to adverse events (v21, p43, t20)

Study/center/ pt #	Age/gender/ race	Day of onset	Adverse event	Severity	Relationship to drug
Nasonex 200 mcg bid					
1925/6/37	59/m/C	86	Sinusitis	Mild	Unlikely
1925/6/41	42/f/B	-7	Headache	Moderate	Probable
1925/22/73	49/f/C	33	Sinusitis	Moderate	Unlikely
1925/33/602	39/f/C	17	Panic attack	Moderate	Unlikely
Nasonex 200 mcg QD					
1925/6/38	45/m/C	3	Urticaria	Moderate	Possibly
1925/49/576	43/m/C	1	↑free cortisol urine	Ode	Unlikely
Placebo					
1926/9/319	68/m/C	15	Loss of taste	Severe	Unlikely
1925/13/91	50/f/B	43	Sinusitis	Moderate	Unlikely
1925/18/174	81/m/B	52	Epistaxis ↑	Severe	Possibly

1925/41/1007	49/f/H	-6	Nasal burning	Severe	Possibly
1925/46/743	40/m/H	26	Paroniria	Mild	Unlikely

In *study 1925*, there were 10 *discontinuations* due to adverse events, 2 of which were in the Nasonex once a day group, 4 of which were in the Nasonex bid group and 4 of which were in the placebo group. The two patients in the Nasonex 200 mcg bid group were discontinued because of an unlikely-related increase in free cortisol in the urine and moderate possibly related urticaria. The four patients in the Nasonex 200 mcg bid group were discontinued because of moderately severe probably related headache, unlikely related mild-moderate sinusitis (2) and unlikely related moderate panic attack. The patients in the placebo group who were discontinued were discontinued because of unlikely related moderate sinusitis, possibly related severe nasal burning, mild unlikely related nightmares and possibly related "aggravated" epistaxis (v3, pgs 327-329).

There were 7 patients who *interrupted treatment* because of an adverse event, 2 in the Nasonex 200 mcg once a day group, 3 patients in the Nasonex 200 mcg bid group and 2 patients in the placebo group. Treatment interruption occurred because of severe unlikely related tooth abscess and URI in one patient and moderate possible alopecia in another patient in the Nasonex 200 mcg qd group, severe unlikely related appendicitis, mild unlikely related constipation as well as mild probably related epistaxis and nasal irritation in one patient in the Nasonex 200 mcg bid group and moderate somnolence and severe unlikely related loss of consciousness in one patient and moderate unlikely URI in another patient in the placebo group (v3, pgs 338-340).

In *study 1926*, there was 1 *discontinuation* due to an adverse event, a 68 year old Caucasian male in the placebo group who developed severe loss of taste after 15 days of treatment considered unrelated to the study drug (v8, p97, 265).

There were 7 patients who *interrupted treatment* because of an adverse event: an 80 year old Caucasian female in the Nasonex 200 mcg once a day group who developed a URI after 115 days of treatment (v8, p267); 3 patients in the Nasonex 200 mcg bid group (a 27 year old Asian male who developed retinal neovascularization, a 31 year old Caucasian male who developed influenza-like symptoms after 105 days of treatment and a 54 year old Caucasian male who developed a URI after 71 days of treatment)(v8, p268);and 3 patients in the placebo group (a 60 year old Caucasian male who had an inguinal hernia repair after 55 days of treatment, a 43 year old Caucasian female who developed edema of the tongue after 106 days of treatment and a 42 year old Hispanic male who developed an arrhythmia after 72 days of treatment (v8, p269). Treatment interruption occurred because of an URI in the one patient in the Nasonex 200 mcg qd group, influenza-like symptoms, retinal neovascularization and URI in the three patients in the Nasonex 200 mcg bid group and arrhythmia, tongue edema and a procedure (without adverse event) in the three patients in the placebo group (v8, p98, t25).

In *study Q99-925-01*, discontinuation of study drug because of an adverse event occurred in 3 patients who received Nasonex and 7 patients who received placebo. The Nasonex patients were discontinued because of: 1) treatment failure after 46 days of treatment; 2) moderate unrelated nasal congestion after 111 days of treatment; and 3) mild related thyroiditis after 28 days of treatment. The placebo patients were: 1) moderate possibly related vertigo; 2) moderate possibly related sore throat; 3) moderate unrelated rheumatoid arthritis; 4) severe probably related nasal

irritation; 5) moderate related nasal irritation; 6) moderate unrelated hemorrhagic stroke; and 7) severe unrelated dyspnea (v12, p71, t16). Randomized treatment was interrupted in 2 patients who received Nasonex and 3 patients who received placebo. In the Nasonex group, interruption was due to mild epistaxis probably related to study treatment in both patients. In the placebo group, interruption was due to moderate possibly related sore throat + nasal congestion, moderate probably related nasal irritation and moderate unrelated rheumatoid arthritis (v12, p71).

7.1.3.3 Other significant adverse events

See discussion above. The sponsor defined "other significant adverse events" as those leading to interruption of treatment, discontinuation from the study or unintended pregnancies (v21, p42). There were no patients in studies 1925 and 1926 who received Nasonex 200 mcg once a day who had a severe adverse event that was considered related to the study drug. There were two such patients in the Nasonex 200 mcg bid group: one who developed a headache and one who developed a migraine. There were no patients who had a severe life-threatening adverse event in either study 1925 or study 1926.

7.1.4 Other Search Strategies

The literature was reviewed for data on the safety of Nasonex Nasal Spray in particular and mometasone in general. No reports of significant adverse events associated with the use of intranasal mometasone were found. A study evaluating specific histopathological changes in the nose did not demonstrate any adverse tissue changes in the nasal mucosa in patients who received a dose of 200 mcg per day for 12 months based on nasal biopsy (Minshall et al. otolaryngol Head Neck Surg 1998; 118:648). It has been concluded from data in the literature (Leone et al. Chest; 2003; 124:2329) in regard to inhaled corticosteroids in general that: 1) the use of inhaled corticosteroids is not associated with a reduction in bone density in children with asthma; 2) adult patients with asthma generally do not sustain a significant reduction in bone mineral density in response to inhaled corticosteroid treatment, although the effect may become clinically important in patients receiving high dose inhaled corticosteroids for many years; 3) the risk of subcapsular and nuclear cataracts associated with inhaled corticosteroid use is negligible in young patients with asthma but may be elevated in older patients; 4) there is insufficient data regarding difference in the risk of cataract formation between different inhaled corticosteroid formulations; 5) the risk of glaucoma associated with inhaled corticosteroid use is likely to be small but further study is warranted; 6) there is insufficient information regarding difference in the risk of glaucoma between various formulations; 7) the risk of skin thinning and easy bruising is elevated in patients receiving inhaled corticosteroids with dose, duration of treatment and patient gender being important variables affecting overall risk; and 8) there is insufficient information regarding differences in the risk of skin thinning between various inhaled corticosteroid formulations.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Patients were questioned and/or examined by the investigator for evidence of adverse events at all visits in studies 1925, 1926 and Q99-925-01. The questioning of patients in regard to the possible occurrence of adverse events was to be generalized such as "how have you been feeling since your last visit?" The presence or absence of specific adverse events was not to be elicited.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were reported using preferred terms. A treatment emergent adverse event was any adverse event that began in the treatment period or began prior to the treatment start date and worsened in severity while on treatment. Any adverse event that began prior to the treatment start date and did not increase in severity during treatment or began after the treatment stop date were not considered to be treatment emergent. The applicant's approach to categorizing adverse events and the groupings used for specific adverse events was appropriate.

7.1.5.3 Incidence of common adverse events

Adverse events (considered related and unrelated to administration of the study drug) occurring in at least 3% of patients in any treatment group in study 1925 (v3, p101-102, t21)

Adverse events	Nasonex 200 mcg QD N=115	Nasonex 200 mcg bid N=122	Placebo N=117
Dizziness	0	1(1%)	3 (3%)
Headache	9 (8%)	10 (8%)	14 (12%)
Hypertension	1 (1%)	0	4 (3%)
Viral infection	3 (3%)	3 (2%)	1 (1%)
Pharyngitis	6 (5%)	3 (2%)	3 (3%)
Sinusitis	4 (3%)	4 (3%)	6 (5%)
URI	12 (10%)	13 (11%)	12 (10%)
Overdose *	3 (3%)	1 (1%)	5 (4%)
Back pain	4 (3%)	2 (2%)	2 (2%)
Bronchitis	6 (5%)	3 (2%)	2 (2%)
Epistaxis	8 (7%)	15 (12%)	6 (5%)
Nasal dryness	2 (2%)	2 (2%)	3 (3%)

* None of the 4 patients who took more than the recommended dose of Nasonex had any adverse events considered to be related to overdose of this medication.

Adverse events (considered related and unrelated to administration of the study drug) occurring in at least 3% of patients in any treatment group or 2% in either or both active treatment groups and none in the placebo group in study 1926 (v8, p90-91, t21)

Adverse events	Nasonex 200 mcg QD N=102	Nasonex 200 mcg bid N=102	Placebo N=106
Dizziness	2 (2%)	1(1%)	0
Headache	11 (11%)	13 (13%)	10 (9%)
Abdominal pain	0	1 (1%)	3 (3%)
Arthrosis	1 (1%)	2 (2%)	0
Pharyngitis	4 (4%)	3 (3%)	5 (5%)
Sinusitis	1 (1%)	3 (3%)	1 (1%)
URI	16 (16%)	13 (13%)	13 (12%)
Overdose *	2 (2%)	2 (2%)	0
Back pain	3 (3%)	2 (2%)	2 (2%)
Bronchitis	3 (3%)	3 (3%)	0
Coughing	3 (3%)	4 (4%)	3 (3%)
Epistaxis	6 (6%)	15 (15%)	5 (5%)
Nasal burning	1 (1%)	2 (2%)	0
Nasal irritation	0	1 (1%)	3 (3%)
Pruritis	2 (2%)	1 (1%)	0

* None of the 4 patients who took more than the recommended dose of Nasonex had any adverse events considered to be related to overdose of this medication (v8, pgs278-281).

Adverse events (considered related and unrelated to administration of the study drug) occurring in at least 3% of patients in any treatment group or 2% in the active treatment group and none in the placebo group in study Q99-925-01 (v12, p64, t12)

Adverse events	Nasonex 200 mcg QD N=153	Placebo N=143
Influenza-like symptoms	5 (3.3%)	1 (0.7%)
Headache	16 (11%)	5 (3.5%)
Sinusitis	5 (3.3%)	3 (2.1%)
Back pain	3 (2%)	0
Pharyngitis	4 (2.6%)	8 (5.6%)
URI	45 (29.4%)	31 (21.7%)
Coughing	7 (4.6%)	6 (4.2%)
Epistaxis *	21 (13.7%)	6 (4.2%)
Accidental injury	3 (2%)	0

Epistaxis, URIs, headache and pharyngitis were the most frequent adverse events reported by at least 5% of the patients in any treatment group in the combined analysis of studies 1925 and 1926. Epistaxis was the only one of these four adverse events that was reported significantly

more frequently by patients receiving Nasonex 200 mcg bid than patients receiving placebo. With a nasally inhaled drug product, local nasal adverse events are expected. Local nasal adverse events in studies 1925 and 1926 included epistaxis, nasal burning, nasal dryness, nasal irritation and nasal septal perforation (see table below). These adverse events are not unlike those seen in studies where Nasonex was evaluated in the treatment of allergic rhinitis.

Local Adverse Events in studies 1925 and 1926

Adverse event	Nasonex 200 mcg qd (n=217)	Nasonex 200 mcg bid (n=224)	Placebo (n=223)
Epistaxis	14 (6%)	30 (13%)	11 (5%)
Nasal irritation	2 (1%)	3 (1%)	5 (2%)
Nasal burning	2 (1%)	2 (1%)	2 (1%)
Nasal dryness	2 (1%)	2 (1%)	3 (1%)
Nasal disorder	1 (<1%)	1 (1%)	0
Epistaxis aggravated	0	0	1 (<1%)
Nasal septum perforation	1 (<1%)	0	0

Local Adverse Events in Study Q99-925-01

Adverse event	Nasonex 200 mcg qd (n=153)	Placebo
Epistaxis	21 (13.7%)	6 (4.1%)
Nasal disorder	1 (0.7%)	0
Nasal ulcer	1 (0.7%)	0
Nasal irritation	0	4 (2.8%)

7.1.5.4 Common adverse event tables

See section 7.1.5.3.

7.1.5.5 Identifying common and drug-related adverse events

There were 4 adverse events reported by at least 2% of patients in any treatment group in the pooled results for studies 1925 and 1926 that were considered by investigators to be related to the study drug as shown in the table below.

Adverse event	Nasonex 200 mcg qd (n=217)	Nasonex 200 mcg bid (n=224)	Placebo (n=223)
Headache	4 (2%)	10 (4%)	9 (4%)
URI	3 (1%)	2 (1%)	4 (2%)
Epistaxis	11 (5%)	28 (13%)	10 (4%)
Nasal irritation	2 (1%)	2 (1%)	4 (2%)

7.1.5.6 Additional analyses and explorations

An analysis of adverse events based on subgroup analysis of age, gender, race and asthma history (v21, p71. t30) in studies 1925 and 1926 can be seen in the table below.

Number of patients	Nasonex 200 mcg qd	N	Nasonex 200 mcg bid	n	Placebo	N
18-64 years	96 (50%)	191	101 (52%)	196	101 (53%)	192
≥ 65 years	14 (54%)	26	16 (57%)	28	17 (55%)	31
Females	34 (49%)	70	45 (52%)	87	48 (58%)	83
Males	76 (52%)	147	72 (53%	137	70 (50%)	140
Caucasian	73 (58%)	126	75 (57%)	131	57 (49%)	117
Hispanic	31 (43%)	72	33 (44%)	75	48 (58%)	83
Other Race	6 (32%)	19	9 (50%)	18	13 (57%)	23
Asthma	23 (64%)	36	33 (73%)	45	27 (64%)	42
No asthma	87 (48%)	181	84 (47%)	179	91 (50%)	181

There was a higher incidence of URIs and epistaxis in patients who received Nasonex and had asthma than in patients who received Nasonex and did not have asthma (see table below)(v21, p72, t31)

Adverse event	Nasonex 200 mcg qd	N	Nasonex 200 mcg bid	N	Placebo	n
URI						
Patients with asthma	5 (14%)	36	12 (27%)	45	3 (7%)	42
Pts without asthma	23 (13%)	181	14 (8%)	179	22 (12%)	181
Epistaxis						
Patients with asthma	3 (8%)	36	8 (18%)	45	3 (7%)	42
Pts without asthma	11 (6%)	181	14 (8%)	179	22 (12%)	181

7.1.6 Less Common Adverse Events

Patients who took more than the recommended dose are of interest in regard to possible systemic adverse events since it has been demonstrated that in rare individuals systemic effects may occur from use of inhaled corticosteroids. Overdose was reported in studies 1925 and 1926 by 5 patients in the Nasonex 200 mcg once a day group, 3 patients in the Nasonex 200 mcg bid group and 5 patients in the placebo group. Adverse events associated with overuse of the treatment drug were reported by 3 patients. This included 2 patients in the placebo group who reported weight gain and acute sinusitis at the time of the overdose possibly related to the study drug and one patient in the Nasonex 200 mcg bid group who developed a headache at the time of overuse that was considered unrelated to the study drug. In study 2573, patients from study 1925 were followed for 4 months without any evidence of withdrawal effects.

7.1.7 Laboratory Findings

7.1.7.1. Overview of laboratory testing in the development program

Blood chemistries and hematology were done at baseline and at the conclusion of studies 1925 and 1926. No laboratory evaluations were done in studies 2573 or Q99-925-01.

7.1.7.2. Selection of studies and analyses for drug-control comparisons of laboratory values

Studies 1925 and 1926 provided data to assess change in laboratory values after 4 months of treatment. Reviewer assessment focused primarily on laboratory values which could be increased or decreased by a systemic corticosteroid effect, e.g. serum calcium, blood glucose, and on tests of liver and renal function.

7.1.7.3 Standard analyses and explorations of laboratory data

Laboratory tests were obtained at baseline and at visit 7 in studies 1925 and 1926. Median, minimum and maximum values at baseline and endpoint in regard to changes from baseline by treatment for routine laboratory tests were evaluated. Changes noted after administration of Nasonex at the two dosage levels was evaluated first and then compared with the change seen after administration of placebo if there was a significant change seen in the Nasonex groups. No significant median changes were seen in hematology or blood chemistry values when all patients were included in the analysis. Laboratory results were evaluated in terms of gender, age and race.

See table below for number (%) of patients with a shift from a normal baseline value to a value outside the normal reference range that could be clinically significant and was greater in one or both of the Nasonex groups than in the placebo group in studies 1925 and 1926.

Laboratory test *Study 1925*	N	Baseline normal Outside normal reference range after treatment
Hematocrit		Low
Nasonex 200 mcg qd	96	2 (2%)
Nasonex 200 mcg bid	98	0
Placebo	90	0
Glucose		High
Nasonex 200 mcg qd	100	4 (4%)
Nasonex 200 mcg bid	105	5 (5%)
Placebo	97	1 (1%)
SGOT		High
Nasonex 200 mcg qd		6 (6%)
Nasonex 200 mcg bid		8 (8%)
Placebo		2 (2%)
SGPT		High

Nasonex 200 mcg qd	102	2 (2%)
Nasonex 200 mcg bid	107	9 (8%)
Placebo	97	1 (1%)
Laboratory test *Study 1926*	N	Baseline normal Outside normal reference range after treatment
WBC		Low
Nasonex 200 mcg qd	78	None
Nasonex 200 mcg bid	81	2 (2%)
Placebo	80	None
Neutrophils		Low
Nasonex 200 mcg qd	77	None
Nasonex 200 mcg bid	75	4 (5%)
Placebo	80	2 (2%)
Glucose		High
Nasonex 200 mcg qd	68	7 (8%)
Nasonex 200 mcg bid	72	4 (5%)

Placebo	65	4 (5%)
SGOT		High
Nasonex 200 mcg qd	83	2 (2%)
Nasonex 200 mcg bid	73	7 (7%)
Placebo	73	3 (4%)
BUN		High
Nasonex 200 mcg qd	85	4 (4%)
Nasonex 200 mcg bid	88	2 (2%)
Placebo	84	1 (1%)

There was one patient (pt 700) in study 1925, a 33 year old male who received Nasonex 200 mcg once a day who had an elevated SGPT at baseline (134 U/L) (normal range 6-43 u/L) but was included in the study because the patient appeared to be in good health and did not have symptoms or signs of liver disease. The patient had a further increase in SGPT after treatment with Nasonex to 235 U/L on day 8 (visit 3) that was repeated and was 240 U/L. The patient had an associated increase in SGOT to 90 U/L. The patient was referred to a hepatologist and found to have inflammatory hepatopathy on hepatic ultrasound. Subsequently, these tests were repeated and the SGPT was 26 U/L and the SGOT was 23 U/L. During the period when the liver enzymes were elevated the patient was asymptomatic. There was another patient (pt 548) who received Nasonex 200 mcg once a day who had an SGOT at baseline of 97 U/L that was 35 U/L at the end of the study and had no adverse event during the study (v3, p115, t27).

The greater incidence of elevated glucose levels in patients who received Nasonex was not seen in study 1926 described below, but could represent a systemic effect from intranasal mometasone in some patients. Overall, the sponsor has demonstrated the safety of Nasonex at a dosage of 200 mcg once a day and a dosage of 200 mcg bid.

7.1.7.3.1 Analyses focused on measures of central tendency

There was no significant change from baseline to endpoint in the median value for any laboratory test in either of the two Nasonex treatment groups, with the exception of *eosinophils* which decreased 16.7% in the Nasonex 200 mcg once a day group, 12.5% in the Nasonex 200 mcg bid group and 4.1% in the placebo group (v21, pgs 59-63). This included hematology parameters, e.g. hemoglobin, WBC, platelet count, and neutrophils as well as blood chemistry parameters, e.g. serum potassium, serum glucose, and liver function tests. *A decrease in eosinophils is a recognized corticosteroid effect. Although there was a greater decrease in patients who received Nasonex than was seen in patients who received placebo, there was no dose-response, i.e. there was a greater reduction in patients who received the lower dose of Nasonex.* Mean urinary free cortisol levels decreased 1.1 nmol/mmol in the Nasonex 200 mcg once a day group and 0.9 nmol/mmol in the placebo group and increased 1.2 nmol/mmol in the Nasonex 200 mcg bid group. *These are not clinically significant differences* (v21, p68).

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

A clinically significant laboratory value was defined as any blood chemistry value 2.6 times or more above the upper limit of the normal reference range, a hemoglobin level of 9.4 g/dL or less, a platelet count of 74,000 cells/microL or less or a WBC of 2,900 cells/microL or less. Based on this definition, in the pooled data from studies 1925 and 1926, there were 5 clinically significant abnormal laboratory values – 2 in the Nasonex 200 mcg once a day group, one in the Nasonex 200 mcg bid group and 2 in the placebo group. In the Nasonex 200 mcg once a day group, one patient had an SGPT value of 235 U/L at endpoint (the patient had a baseline value of 134 U/L)(NRR = 6-43) and one patient had an SGOT at baseline of 97 (NRR = 11-36) which was 35 U/L at endpoint. In the Nasonex 200 mcg bid group one patient (Paget's Disease) had an alkaline phosphatase level of 767 U/L at endpoint (baseline was 677 U/L)(NRR = 35-131 U/L). One placebo patient (leukemia) had a leukocyte count of 37.54 (baseline 28.11) (NRR= 3.8-10.7) and one (diabetes mellitus) had a screening glucose of 22.7 mmol/L (NRR=3.9-6.4).

There were 164 patients from 28 centers in study 1925 who were included in the analysis of 24 hour urinary free cortisol levels. There was no clinically significant suppression of urinary free cortisol in any patient who received Nasonex. One patient who received 200 mcg bid of Nasonex had a significant increase in urinary free cortisol from 18.1 nmol/mmol at baseline to 74.3 nmol/mmol at endpoint. Of patients who had a urine cortisol level above the level of quantitation at baseline, 18%, 5% and 11 % of patients in the Nasoenex 200 mcg once a day, Nasonex 200 mcg bid and placebo groups, respectively had values below the level of quantitation at endpoint.

Based on shift tables for hematologic laboratory values (v22, p632), there was no clinically significant difference between the three treatment groups in studies 1925 and 1926 in the number or percent of patients who had a normal baseline value and a low value after treatment for hgb, hct, RBC count, WBC count, platelet count, neutrophils or any other parameter and there was no clinically significant difference in the number or percent of patients who had a normal baseline value and a high value after treatment for eosinophils. For possibly significant shifts in blood chemistry values see the table below (v22, p634).

Selected individuals who had a normal baseline value and a value after treatment that was high in studies 1925 and 1926.

Parameter	Nasonex 200 mcg QD	Nasonex 200 mcg bid	placebo
BUN	6 (3%)	4 (2%)	3 (2%)
Creatinine	2 (1%)	0	5 (3%)
Glucose	11 (6%)	9 (5%)	5 (3%)
SGOT	8 (4%)	14 (7%)	5 (3%)
SGPT	9 (5%)	13 (7%)	8 (4%)
Bilirubin	3 (2%)	2 (1%)	2 (1%)

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no marked outliers or dropouts because of laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations were done.

7.1.7.5 Special assessments

7.1.7.5.1. Age (v21, pgs282-358)

Assessment of laboratory values in patients 65 years of age and older in studies 1925 and 1926 showed no clinically significant changes in median values for any laboratory value in any of the treatment groups with the exception of eosinophils which decreased 12.5% in patients who received Nasonex 200 mcg once a day and 25% in patients who received Nasonex 200 mcg bid compared to an increase of 17% in patients who received placebo.

7.1.7.5.2. Gender (v22, pgs360-436)

Assessment of laboratory values in males and females in studies 1925 and 1926 showed no clinically significant changes in median values for any laboratory value in either gender in any of the treatment groups.

7.1.7.5.3. Race (v22, pgs438-552)

Assessment of laboratory values for Caucasian, Hispanic and non-Caucasian, non-Hispanic patients in studies 1925 and 1926 showed no clinically significant changes in median values for any laboratory value in any race in any of the treatment groups.

7.1.7.5.4. Asthma Status (v22, pgs554-630)

Assessment of laboratory values for patients with a history of asthma and patients without a history of asthma in studies 1925 and 1926 showed no clinically significant changes in median

values for any laboratory value in either patients with or without asthma in any of the treatment groups.

7.1.7.5.5 24 hour urinary free cortisol levels:

Samples were collected starting from the morning prior to visit 1 and visit 7 or upon early termination in a subset of patients in study 1925. There were 164 patients from 28 sites who had baseline 24 hour urinary free cortisol levels and at least one post-baseline value, and who were included in the analysis. Although the protocol only required 90 patients to be tested, by the time that the sites were notified that the accrual target had been reached, 213 patients had been tested. For mean changes from baseline in the three treatment groups and pair-wise p values comparing the treatment groups, see the table below (v3, p118, t28). One patient (#43-643) who received 200 mcg bid of Nasonex had a baseline value of 18.1 nmol/mmol and an endpoint value of 74.3 nmol/mmol. There were 18% of the Nasonex 200 mcg qd group, 5% of the Nasonex bid group and 11% of the placebo group who had values above the level of quantitation at baseline and below the level of quantitation at endpoint.

Urine cortisol corrected for creatinine – nmol/mmol (patients without missing values at both visits)

Time-point	Nasonex 200 mcg QD (n=49)	Nasonex 200 mcg bid (n=59)	Placebo (n=56)	P value comparison of Nasonex 200 mcg qd and placebo	P value comparison of Nasonex 200 mcg bid and placebo
Baseline (nmol/mmol)	5.1	5.9	5.3	0.86	0.34
End-point (nmol/mmol)	4.0	7.2	4.4	0.82	0.03
Change from baseline (nmol/mmol)	-1.1	1.2	-0.9	0.89	0.09

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured in studies 1925, 1926, Q99-925-01 and 2573. No clinically significant changes were noted in any of the treatment groups. Vital signs were obtained at each visit and included blood pressure, pulse rate and respiratory rate.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs were assessed for all the studies submitted by the sponsor.

7.1.8.3 Standard analyses and explorations of vital signs data

No clinically significant changes in median, minimum or maximum values were seen in any of the treatment groups for systolic blood pressure, diastolic blood pressure, pulse rate or

respiratory rate in studies 1925 and 1926. There were no clinically significant median changes in vital signs based on gender, age (patients 18-64 vs patients 65 years of age and older) or race. There were 3 patients (2%) in the 200 mcg once a day group who had an increase in systolic blood pressure of greater than 30%, whereas there were no patients in the other two treatment groups who had such an increase. There was no clinically significant difference in terms of change in diastolic blood pressure or pulse rate between the three treatment groups.

7.1.8.3.1 Analyses focused on measures of central tendencies

There were no clinically significant median changes from baseline in systolic blood pressure, diastolic blood pressure or pulse rate in any of the treatment groups (v22, pgs639-640). Maximum changes seen in the groups that received Nasonex were generally seen in the placebo group, as well.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Number (percent) of patients with degree of change from baseline in vital signs in studies 1925 and 1926 (v22, p669)

Parameter	↓ > 30%	↓ 10-30%	↑ 10-30%	↑ > 30%
Systolic blood pressure (mm Hg)				
Nasonex 200 QD	0	32 (15%)	20 (9%)	0
Nasonex 200 bid	0	20 (9%)	22 (10%)	6 (3%)
Placebo	0	22 (10%)	23 (10%)	0
Diastolic blood pressure (mm Hg)				
Nasonex 200 QD	1 (<1%)	49 (23%)	29 (14%)	2 (1%)
Nasonex 200 bid	1 (<1%)	42 (19%)	36 (16%)	5 (2%)
Placebo	2 (1%)	41 (19%)	40 (18%)	9 (4%)
Pulse rate (bpm)				
Nasonex 200 QD	0	33 (16%)	37 (18%)	3 (1%)
Nasonex 200 bid	0	46 (21%)	40 (18%)	5 (2%)
Placebo	1 (<1%)	34 (15%)	36 (16%)	10 (5%)

COMMENT: *Overall, there is no suggestion based on shift tables for vital signs that Nasonex at a dose of either 200 mcg once a day or a dose of 200 mcg bid has a significant effect on vital signs with one possible exception. There were 6 patients (all between the age of 18-64 years) receiving the higher dose of Nasonex who had an increase in systolic blood pressure of 30 mm Hg or greater, compared to no such increases in the groups receiving the lower dose of Nasonex or placebo. It is possible that this represents increased systemic bioavailability of Nasonex in these patients after administration of 200 mcg bid (400 mcg per day). However, systemic corticosteroid effect is usually associated with an increase in diastolic blood pressure as well, and there were more placebo patients who had an increase in diastolic blood pressure of 30 mm Hg or greater than there were patients who had such an increase after receiving Nasonex at either dose.Check with endocrinology on this point. While an occasional patient may get a*

significant systemic effect from any inhaled corticosteroid, this data does not indicate any particular risk of such an effect from the intranasal administration of Nasonex at a dosage of 200 mcg bid (400mcg per day) that would justify not approving this drug product at this dosage because of safety concerns.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no patients who were dropped out of the study because of vital sign abnormalities. Changes in vital signs that could be considered clinically significant outliers were seen in the group that received placebo as well as the groups that received Nasonex.

7.1.8.4 Additional analyses and explorations

7.1.8.4.1. Age (v22, p645):

There was no clinically significant median change from baseline in systolic blood pressure, diastolic blood pressure or pulse rate in patients 65 years of age and older in any treatment group in studies 1925 and 1926. There was no significant median difference between changes from baseline seen in patients 65 years of age and older who received Nasonex and patients in the same age group who received placebo. The 6 patients who had an increase in systolic blood pressure of 30 mm Hg or greater were all 18-64 years of age and there were no clinically significant differences in the number (%) of patients who had a shift in vital signs in any treatment group based on whether they were < 65 years of age or 65 years of age or older in studies 1925 and 1926 (v22, p671). *There are no safety concerns about the administration of Nasonex Nasal Spray to elderly patients.*

7.1.8.4.2. Gender (v22, pgs648-652)

There was no clinically significant median change from baseline in systolic blood pressure, diastolic blood pressure or pulse rate based on gender in any treatment group in studies 1925 and 1926. There was no significant median difference between changes from baseline seen in males and females who received Nasonex and those who received placebo in terms of vital signs. In female patients (v22, p675), there was a greater incidence of increased systolic blood pressure of 10% or greater and diastolic blood pressure of 10-29% in patients who received Nasonex than patients who received placebo although there was not a consistent dose response seen in studies 1925 and 1926. *These changes do not represent any significant safety concern*.

7.1.8.4.3. Race (v22, pgs654-661)

There was no clinically significant median change from baseline in systolic blood pressure, diastolic blood pressure or pulse rate based on race in any treatment group in studies 1925 and 1926. There was no significant median difference between changes from baseline seen in Caucasians, Hispanics and non-Caucasian non-Hispanic patients who received Nasonex and those who received placebo in terms of vital signs. Shift tables did not indicate any propensity for a clinically significant change in vital signs in Caucasians, Hispanics or non-Caucasians non-

Hispanics in studies 1925 and 1926 (v22, pgs679-683). *There are no safety concerns raised by the data based on patient race.*

7.1.8.4.4. Asthma Status (v22, pgs663-667)

There was no clinically significant median change from baseline in systolic blood pressure, diastolic blood pressure or pulse rate based on history of asthma in any treatment group in studies 1925 and 1926. There was no significant median difference between changes from baseline seen in asthmatic and non-asthmatic patients who received Nasonex and those who received placebo in terms of vital signs. Shift tables did not indicate any propensity for a clinically significant change in vital signs in patients with a history of asthma compared with patients who did not have a history of asthma in studies 1925 and 1926(v22, p685). *There is no safety concern raised by the data in regard to asthma status of patients.*

7.1.9 Electrocardiograms (ECGs): ECGs were not performed in the studies submitted under this supplemental NDA. *This is acceptable since cardiac effects from intranasal corticosteroids are not anticipated and ECGs performed in studies to evaluate Nasonex in the treatment of allergic rhinitis did not show any significant adverse effect of Nasonex on the heart.*

7.1.10 Immunogenicity: This drug product does not have any recognized immunogenicity potential. It is recognized that corticosteroids when given systemically can modify immune responses, but there is no data, to this reviewer's knowledge, that implicates inhaled corticosteroids, such as Nasonex, in any negative effect on the immune system.

7.1.11 Human Carcinogenicity: No formal studies were done in humans evaluating the carcinogenic effect of Nasonex Nasal Spray. Carcinogenicity studies in rodents showed no statistically significant increase in the incidence of tumors at inhalation doses approximately 1.5-2 times the maximum recommended daily intranasal dose in adults and children and mometasone furoate was not mutagenic. There were no patients who developed malignancy while receiving Nasonex for the treatment of nasal polyps.

7.1.12 Special Safety Studies: No studies were performed to demonstrate a safety advantage over therapeutic alternatives or to assess cumulative irritancy or contact sensitization. A subset of patients was evaluated to determine if there was any systemic effect of Nasonex Nasal Spray on the HPA axis (see review of study 1925 under Review of Individual Study Reports below) and no such effect was demonstrated.

7.1.13 Withdrawal Phenomena and/or Abuse Potential: In the pivotal studies 1925 and 1926, there were 5 patients who received 200 mcg of Nasonex once a day and 3 patients who received Nasonex 200 mcg bid who were reported as overdoses. None of these patients developed any other adverse event considered related to the study drug as a result of taking more than the recommended dose of Nasonex. There is no pharmacologic basis or clinical data to suggest that abuse or dependency is associated with the use of Nasonex. The labeling for Nasonex warns that the replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by

signs of adrenal insufficiency and symptoms of withdrawal, such as joint and/or muscular pain, lassitude, and depression. This is a well recognized but infrequently seen event, the potential for which is not changed when Nasonex is administered for nasal polyposis instead of for allergic rhinitis. The studies performed under this supplemental NDA did not include patients who were withdrawn from systemic corticosteroids. Study 2573 was a study in which patients previously treated in study 1925 were followed for up to 4 months without treatment to assess recurrence of polyps. There was no evidence of withdrawal effects in this study other than the recurrence of polyps in many patients.

7.1.14 Human Reproduction and Pregnancy Data: There was one pregnancy reported during the studies submitted by the sponsor under this supplemental NDA. The patient was discontinued from study 1925 during the placebo run-in period. There are no adequate and well controlled studies in pregnant women receiving Nasonex Nasal Spray. Mometasone plasma levels are not measurable after intranasal administration of the maximal recommended dose and therefore it is unlikely that there is significant fetal exposure making the potential for reproductive toxicity low. Nasonex carries a Pregnancy Category C rating, since, as with other corticosteroid preparations its administration to rodents and rabbits has been associated with increased fetal malformations. Therefore, the labeling indicates that Nasonex should be used in pregnant women only if the potential benefits justify the potential risk to the fetus. There is no new data in this submission to change that recommendation. In the post-marketing database there was one report of fetal growth retardation and one report of intra-uterine death. No specific data on these reports was provided.

7.1.15 Assessment of Effect on Growth: No studies specifically evaluating the effect of Nasonex on growth were done as part of this supplemental NDA. The potential for inhaled corticosteroids to produce an effect on growth has been the subject of Advisory Committee Meetings and Agency interaction with sponsors of this type of drug product. The current labeling states that "Controlled clinical studies have shown intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients….The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown."

7.1.16 Overdose Experience

Patients who took more than the recommended dose of Nasonex Nasal Spray are of interest in regard to possible systemic adverse events since it has been demonstrated that in rare individuals systemic effects may occur from use of inhaled and/or intranasal corticosteroids. Overdose was reported in studies 1925 and 1926 by 5 patients in the Nasonex 200 mcg once a day group, 3 patients in the Nasonex 200 mcg bid group and 5 patients in the placebo group. Adverse events associated with overuse of the treatment drug were reported by 3 patients. This included 2 patients in the placebo group who reported weight gain and acute sinusitis at the time of the overdose considered by the investigator to be possibly related to the study drug and one patient in the Nasonex 200 mcg bid group who developed a headache at the time of overuse that was considered by the investigator to be unrelated to the study drug. In study 2573, patients who

received Nasonex in study 1925 were followed for 4 months after Nasonex had been discontinued, without any evidence of withdrawal effects.

7.1.17. Post-marketing Experience

Since Nasonex was first marketed in 1997, as of 15 November 2003, there were 2890 individual spontaneous adverse events reported. Of these, 448 were serious and consistent with the pharmacologic properties of nasally inhaled corticosteroids or were considered idiosyncratic reactions. The ten most frequently reported adverse events overall were: epistaxis (228 reports), headache (179 reports), irritation of the nasal passages (182), decreased therapeutic response (136), ineffective drug (78), pharyngitis (56), cough (53), dizziness (46), dyspnea (47) and anosmia (37) (v21, p77. t32). The twelve most frequently reported serious adverse events were: anosmia (19), nasal septum perforation (15), epistaxis (15), headache (12), dyspnea (11), cataract (9), angioneurotic edema (9), glaucoma (8), nasal irritation (8), asthma (7), intraocular pressure increased (7) and hypertension (7) (v22, pgs697-719).

COMMENT: Hypertension, cataracts and glaucoma are recognized corticosteroid side effects and could represent a systemic effect related to intranasal administration of a corticosteroid drug product. In addition, there were a small number of reports of cushinoid features, hyperadrenocorticism, and other adverse events that reflect a systemic glucocorticoid effect. Adverse event reporting of post-marketing events is sketchy at best and even with a summary of these adverse events to review, establishing a direct relationship of specific adverse events to the administration of Nasonex is difficult, at best. Adverse events such as anosmia, nasal perforation and nasal irritation are well recognized local adverse effects of intranasal corticosteroids and do not represent an unacceptable safety issue for this type of drug product. The data from post-marketing surveillance does not suggest any new safety issues related to the use of Nasonex.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

This supplemental NDA has included data from three randomized, placebo-controlled, double-blind clinical studies, 1925, 1926 and Q99-925-01, as well as a follow-up study (2573) designed to assess the recurrence of nasal polyps in patients who had improved significantly in study 1925. In the 3 studies in which Nasonex was administered, there were 962 patients. There were 370 who received Nasonex 200 mcg qd, 224 who received Nasonex 200 mcg bid and 368 who received placebo for a period of 4 months. *This database, in conjunction with the extensive database provided from studies performed in patients with allergic rhinitis is adequate to support a determination of safety for Nasonex Nasal Spray.*

7.2.1.1 Study type and design/patient enumeration

study number	# pts	Age Range	Study centers	Study design	Patient population	Treatment dose and duration	Outcome variables	
1925 pivotal for efficacy	354 R 353 T 305 C 122 200 mcg bid 115 200 mcg QD 117 P	18-81 years	US/international	R,PC,PG DB,MC	Bilateral nasal polyposis; moderate signs and symptoms	Nasonex 200 mcg QD and 200 mcg bid; 4 months	Bilateral polyp grade; congestion, rhinorrhea, PND, loss of smell; PNIF, QOL, safety parameters	
1926 pivotal for efficacy	310 R 310 T 274 C 102 200 mcg bid 102 200 mcg QD 106 P:	18-86 years	international	R,PC,PG DB,MC	Bilateral nasal polyposis; moderate signs and symptoms	Nasonex 200 mcg QD and 200 mcg bid; 4 months	Bilateral polyp grade, congestion, rhinorrnea, PND, loss of smell, PNIF, QOL, safety parameters	
Q99-925-01 Support for efficacy	298 R 296 T 235 C 153 200 mcg QD 145 P	20-86 years	Scandinavia	R,PC,DB MC	Bilateral nasal polyposis; moderate signs and symptoms	Nasonex 200 mcg QD; 16 weeks	Improvement in nasal congestion, polyp size, rhinorrhea, loss of smell, PNIF, QOL, safety parameters	
2573	135 E 67 C 58 200 mcg bid 46 200 mcg QD 31 P	18-78 years	US/international	Observational follow-up	Patients who improved in study 1925	No treatment; Observation for 4 months	Bilateral polyp grade, congestion, rhinorrhea, PND, loss of smell, PNIF, safety parameters	

R = randomized
T = treated
C = completed
200 mcg bid = Nasonex 200 mcg bid
200 mcg QD = Nasonex 200 mcg QD
P = placebo

7.2.1.2 Demographics

Demographics on all randomized patients in studies 1925 and 1926 (v21, p79)

Study	Rx	Age (yrs) (mean)	Age 18-64	Age ≥65	Female/ Male %	Caucasian/ Black/ Asian/ Hispanic	Hx asthma %	Hx PAR %
1925 (v3, p72, t10)								
N=115	200 mcg qd	46.7	86%	14%	34/66	62/4/5/44	18	20
N=122	200 mcg bid	48.3	85%	15%	39/61	66/6/2/47	21	25
N=117	Placebo	47.5	87%	13%	39/61	50/11/0/53	21	17
1926								
N=102	200 mcg qd	47.2	90%	10%	30/70	64/0/7/28	15	14
N=102	200 mcg bid	47.6	90%	10%	38/62	65/1/8/28	19	18
N=106	Placebo	50.9	85%	15%	35/65	67/0/8/28	16	21
1925/1926								
N=217	200 mcg qd	46.9	88%	12%	32/68	126/4/12/72	17	17
N=224	200 mcg bid	48	88%	12%	39/61	131/7/10/75	20	21
N=223	Placebo	49.1	86%	14%	37/63	117/11/8/83	19	19

Distribution of baseline symptom scores in studies 1925 and 1926 (v21, p82)

Category	Nasonex 200 mcg QD	Nasonex 200 mcg bid	placebo
Number of patients	217	224	223
Bilateral polyp grade 0,1	1 (<1)	0	0
Bilateral polyp grade 2	39 (18%)	25 (11%)	32 (14%)
Bilateral polyp grade 3	30 (14%)	32 (14%)	30 (13%)
Bilateral polyp grade 4	60 (28%)	84 (38%)	76 (34%)
Bilateral polyp grade 5	40 (18%)	37 (17%)	33 (15%)
Bilateral polyp grade 6	47 (22%)	46 (21%)	52 (23%)
Nasal congestion 0-<1	1 (<1%)	2 (1%)	4 (2%)
Nasal congestion 1-<2	17 (8%)	21 (9%)	16 (7%)
Nasal congestion 2-<3	198 (91%)	199 (89%)	200 (90%)
Nasal congestion missing	1 (<1%)	2 (1%)	3 (1%)

7.2.1.3 Extent of exposure (dose/duration)

Length of exposure (days)(studies 1925 and 1926)	Nasonex 200 mcg QD (N=217)	Nasonex 200 mcg bid (n=224)	Placebo (n=223)
8 days or more	214 (99%)	223 (100%)	220 (99%)
30 days or more	208 (96%)	218 (97%)	207 (93%)
60 days or more	203 (94%)	208 (93%)	191 (86%)
90 days or more	198 (91%)	206 (92%)	186 (83%)
120 days or more	123 (57%)	134 (60%)	127 (57%)
150 days or more	0	0	1 (<1%)
Randomized, not treated	0	0	1 (<1%)
Mean	113.3	114.4	107.4

Median	120	120	120
Range	1-146	7-144	4-162

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The sponsor submitted a review of safety data utilizing a dose of 400 mcg per day or more that contained data (b) (4) This includes: 1) two clinical pharmacology studies – study C92-022-01 and C93-196-01; 2) one phase 2 placebo-controlled study (C92-011); 3) three phase 3 placebo-controlled studies – C96-195, C97-251 and C/196-252; and three phase 3 open label variable dose studies – C93-014, 193-018 and 193-221 and represents all the data generated through 15 November 2003 on patients who received 400 mcg per day or more of mometasone furoate nasal spray.

Studies in which patients received 400 mcg per day or more of mometasone furoate (17, pgs 11-16, t2)

Study number	Study design	Patient population	dosage and duration of Rx	Outcome variables	Number/gender
C92-022-01	R, third party B, PC, ATC, MD, PG, SC (US) study	Healthy adult male volunteers 21-40 years	Nasonex 400 mcg QD (12 pts) 1600 mcg QD (12 pts) 29 days	Plasma cortisol concentrations AEs	48 R, 48 Rx, 48 completed 48 males\0 females
C93-196-01	R, third party B, PC, ATC, MD, PG, SC (US) study	Healthy adult male volunteers 22-44 yrs with allergic rhintis	Nasonex 200 mcg QD (16 pts) 400 mcg QD (16 pts) 36 days	Plasma cortisol concentrations after cosyntropin infusion AEs	64, R, 64 Rx, 64 completed 64 males 0 females
C93-014	R, open, ATC, PG, MC (19 in US), long term safety study	Perennial rhinitis for at least 2 yrs 12-74 years	Nasonex 100-400 mcg QD (98 pts), BDP 168 mcg bid 52 weeks	Assessment of overall condition AEs, labs, VS, ECGs, PE	296 R, 293 Rs, 229 completed 140 males, 153 females
I93-018	R, open, ATC, MC (21 in Canada and Europe), long-term safety	Perennial rhinitis for at least 2 yrs 12-67 years	Nasonex 100-400 mcg QD (80 pts), BDP 200 mcg bid 52 weeks	Assessment of overall condition, AEs, labs, VS, ECGs, PE	229 R, 228 Rx, 167 completed 125 males, 103 females
I93-221	MC, open, non-comparative study	Perennial rhinitis for at least 2 yrs, moderate or more severe 12-68 years	Nasonex 100-400 mcg QD 26 weeks	Assessment of overall condition AEs, labs, VS, ECGs, PE	333 enrolled, 331 Rx, 292 completed 156 males, 175 females
C92-011	R, DB, PC, PG, MC (15 centers US), DR study	Moderate symptomatic SAR 18-66 years	Nasonex 50-800 mcg QD, 95 patients 800 mcg QD 28 days	Symptom scores, assessment to Rx AEs, labs, VS, ECGs, PE	480 R, 478 Rx, 427 completed 320 males, 154 females
C96-195	R, DB, PC, PG, MC (29 centers US) study	Recurrent sinusitis with acute moderate	Nasonex 400 mcg bid plus Augmentin 875	Average AM/PM TSS over days 1-15;	548 R, 514 Rx, 200 completed both acute and

		exacerbations 12-73 years 185 males, 329 females	mg bid acutely 21 days 200 mcg bid 11 months	time to the first confirmed recurrence AEs, labs, VS, ECGs, plasma cortisol conc, PE	chronic phase 254 received 400 mcg bid for 21 days, 181 received 200 mcg bid for 11 months
C97-251	R, DB, PC, PG, MC (61 centers US) study	Acute moderate sinusitis 8-78 years	Nasonex 200 and 400 mcg bid with Augmentin 875 mg bid 21 days	Average AM/PM TSS, global assessment of symptoms and response AEs, labs, VS, ECGs, plasma cortisol conc, PE	967 R, 967 Rx, 844 completed 318 Nasonex 200 mcg bid 324 Nasonex 400 mcg bid 403 males 564 females
C/196/252	R, DB, PG, PC, MC (19 centers in 5 countries) study	Recurrent sinusitis 13-75 years	Nasonex 200 mcg bid (168 pts) 12 months	Time to recurrence, AEs, labs, VS, ECGs, plasma cortisol conc, PE	340 R, 340 Rx, 195 completed 109 males 231 females

Extent of exposure: (v17, p22, t3) There were 884 (76%) patients in the placebo controlled high dose (800/400 mcg/day) pooled data who received Nasonex for < 6 months and 180 patients (16%) who received Nasonex for at least one year. There were 82 patients (7%) who received Nasonex between 6 months and one year duration. The median time of Nasonex treatment was 22 days with a range of 1-405 days.

Demographics: (v17, p23, t4);

Demographic data for the pooled placebo controlled high dose studies

Demographic	Nasonex 800/400 mcg/day (n=1159)	Placebo (n=853)
Females	686 (59%)	499 (58%)
Males	473 (41%)	354 (42%)
Caucasian	1053 (91%)	758 (89%)
Asian	10 (1%)	10 (1%)
Black	46 (4%)	42 (5%)
Hispanic	42 (4%)	26 (3%)
Other race	8 (1%)	17 (2%)
Median age	39	38
Age range	8-78	12-76
6-11 years	1 (< 1%)	0
12-17 years	63 (5%)	44 (5%)
18-64 years	1059 (91%)	782 (92%)
65 years and older	36 (3%)	27 (3%)

Adverse events: Treatment emergent adverse events were those events that began on or after the treatment start date and up to 30 days after treatment was stopped or which began prior to treatment and worsened during the treatment period. Ophthalmologic examination (in one study after 52 weeks of treatment) was performed in some patients looking for posterior sub-capsular

cataracts or increased intraocular pressure. Patients were also in some studies (C92-022-01, C93-196-01, C96-195, C97-251 and C/196-252) evaluated in terms of HPA axis suppression. The data was pooled by the sponsor in regard to whether patients received high doses of Nasonex in placebo controlled studies (2012 patients in studies C92-011, C96-195, C97-251 and C/196-252), variable doses in open studies (506 patients in studies C93-014, I93-018 and I93-221) or 200 mcg per day (3774 patients in studies C92-011, C92-280, C93-013, C93-014, C93-184, C93-215, C94-052, C94-092, C94-145, I92-200, I92-293, I93-018, I93-133, I93,-180, I94-001, I94-079 and I94-139). Adverse events from studies C92-022-01 (48 patients) and C93-196-01 (64 patients) are summarized individually by the sponsor. A dose of 400 mcg per day has been approved in other countries. Epistaxis was the only adverse event that occurred significantly more frequently in the group that received Nasonex than in the group that received placebo in the pooled placebo controlled high dose studies (see table below).

Adverse events from the pooled placebo controlled high dose studies (v17, p25, t5) that occurred with an incidence of greater than 5% in one or both treatment groups

Adverse event	Nasonex 800/400 mcg/day (n=1159)	Placebo (n=853)
Overall	711 (61%)	518 (61%)
Heachache	205 (18%)	176 (21%)
Vaginitis	67 (10%)	43 (9%)
Diarrhea	96 (8%)	58 (7%)
Viral infection	81 (7%)	65 (8%)
Pharyngitis	123 (11%)	85 (10%)
Epistaxis	121 (10%)	48 (6%)
Rhinitis	93 (8%)	72 (8%)

NOTE: Most of the reports of vaginitis and diarrhea were reported in the acute bacterial sinusitis studies where Augmentin was concomitantly administered with Nasonex and were generally attributed to the antibiotic.

The ten most frequently reported adverse events in patients receiving high doses of Nasonex compared to the incidence of these adverse events in patients who received a dose of 200 mcg per day in studies of less than 6 months duration (v17, p31, t8)

Adverse event	Nasonex 800/400 mcg /day (n=884)	Placebo (n=600) for high dose studies	Nasonex 200 mcg/day (n=1721)	Placebo (n=1665) for low dose studies
Headache	117 (13%)	95 (16%)	400 (23%)	366 (22%)
Vaginitis	49 (10%)	26 (8%)	Not in top ten	Not in top ten
Diarrhea	76 (9%)	39 (7%)	Not in top ten	Not in top ten
Epistaxis	64 (7%)	30 (5%)	169 (10%)	104 (6%)
Pharyngitis	57 (6%)	38 (6%)	180 (10%)	162 (10%)
Nausea	41 (5%)	22 (4%)	Not in top ten	Not in top ten
Rhinitis	31 (4%)	23 (4%)	55 (3%)	55 (3%)
Dyspepsia	26 (3%)	17 (3%)	Not in top ten	Not in top ten
MS pain	23 (3%)	16 (3%)	65 (4%)	49 (3%)
Vomiting	20 (2%)	9 (2%)	Not in top ten	Not in top ten

The adverse events most frequently felt to be due to high dose Nasonex administration in individual patients were headache, pharyngitis, epistaxis, nasal burning, nasal irritation, rhinitis and sneezing. Only in regard to epistaxis was there a greater incidence in the high dose Nasonex

group (9%) than in the placebo group (5%). The overall incidence of treatment-related adverse events was 22 % in both the high dose Nasonex group and the placebo group.

The ten most frequently reported adverse events in patients receiving high doses of Nasonex compared to the incidence of these adverse events in patients who received a dose of 200 mcg per day in studies of 6-12 months duration (v17, p32, t9)

Adverse event	Nasonex 800/400 mcg/day (n=82)	Placebo (n=76) for high dose studies	Nasonex 200 mcg/day (n=82)
Headache	29 (35%)	18 (24%)	24 (29%)
Vaginitis	6 (10%)	3 (6%)	Not in top ten
Diarrhea	8 (10%)	5 (7%)	Not in top ten
Epistaxis	18 (22%)	5 (7%)	10 (12%)
Pharyngitis	22 (27%)	12 (16%)	12 (15%)
Nausea	8 (10%)	5 (7%)	Not in top ten
Rhinitis	16 (20%)	14 (18%)	Not in top ten
Earache	9 (11%)	6 (8%)	Not in top ten
Viral infection	15 (18%)	12 (16%)	21 (26%)
MS pain	11 (13%)	8 (11%)	Not in top ten

COMMENT: In studies of longer duration more adverse events will be reported simply because there was more time to report them. Although the top ten adverse events reported in the high dose Nasonex group in studies up to 6 months duration are, for the most part, the same adverse events reported most frequently in studies of 6-12 months duration in this treatment group, the incidence is similar in the Nasonex and placebo groups in the studies of 6 months duration whereas in the studies of 6-12 months duration, there is a much greater difference between the frequency of these adverse events in the Nasonex and the placebo groups consistently. Furthermore, in the studies of 6 months duration, where the same adverse events were reported in the high dose and low dose Nasonex groups, the incidence generally was greatest in the low dose studies. In the studies of 6-12 months duration, the frequency of adverse events, where the same adverse event was reported frequently in the high and low dose Nasonex groups, was generally higher in the high dose Nasonex group as compared to the low dose Nasonex group. These findings suggest, not surprisingly, that with continued administration over time, adverse events possibly related to local effects of intranasal administration of corticosteroids, e.g. epistaxis, headache, pharyngitis, occur more frequently.

The ten most frequently reported adverse events in patients receiving high doses of Nasonex compared to the incidence of these adverse events in patients who received a dose of 200 mcg per day in studies of 12 months or longer duration (v17, p34, t10)

Adverse event	Nasonex 800/400 mcg/day (n=180)	Placebo (n=158) for high dose studies	Nasonex 200 mcg/day (n=280)
Headache	59 (33%)	63 (40%)	120 (43%)
Vaginitis	12 (11%)	14 (13%)	Not in top ten
Viral infection	52 (29%)	43 (27%)	76 (27%)
Epistaxis	39 (22%)	13 (8%)	43 (15%)
Pharyngitis	44 (24%)	35 (22%)	52 (19%)
Back pain	23 (13%)	17 (11%)	Not in top ten
Rhinitis	46 (26%)	35 (22%)	Not in top ten
Myalgia	18 (10%)	16 (10%)	28 (10%)

Allergy	17 (9%)	10 (6%)	Not in top ten
MS pain	26 (14%)	15 (9%)	42 (15%)

Severe/life-threatening adverse events reported by at least 1% of patients in any treatment group based on pooled results for high dose studies (v17, p37, t12)

Adverse event	Nasonex 800/400 mcg/day (n=1159)	Placebo (n=853)
Overall	155 (13%)	126 (15%)
Headache	46 (4%)	27 (3%)
Migraine	13 (1%)	8 (1%)
Diarrhea	21 (2%)	11 (1%)
Nausea	11 (1%)	2 (<1%)
Vomiting	7 (1%)	3 (<1%)
Viral infection	11 (1%)	8 (1%)
Pharyngitis	10 (1%)	12 (1%)
Back pain	2 (<1%)	6 (1%)
MS pain	6 (1%)	4 (<1%)
Bronchitis	2 (<1%)	5 (1%)

Serious Adverse Events: A 31 year old man had normal liver enzymes at screening in study C92-011 (SGOT 14 U/L, SGPT 17 U/L) developed elevated liver enzymes after 15 days of treatment with Nasonex 800 mcg per day (SGOT 169 U/L, SGPT 175 U/L) which returned to normal 5 weeks after discontinuing treatment. *As previously noted, in studies 1925 and 1926 there was a higher incidence of elevation of liver enzymes in patients whose liver enzymes were normal at baseline after administration of Nasonex Nasal Spray than after administration of placebo. In study 1925, this was seen for both SGOT and SGPT at both dosages while in study 1926, it was seen only for SGOT at 200 mcg twice a day. There is no basis for expecting an effect of an inhaled corticosteroid on liver enzymes. Patients will not be receiving a dose of 800 mcg per day for the treatment of nasal polyps. Such increases are seen not infrequently in drug studies in patients who receive placebo. Therefore, while a relationship between administration of the study drug and this finding can not be ruled out, this particular case does not increase concern about the safety of Nasonex Nasal Spray.*

7.2.2.1 Other studies

The database for the safety evaluation of this supplemental NDA consisted of the pooled and individualized data from studies 1925 and 1926, study Q99-925-01, data from the 4 month safety update and data from all studies for any indication in which patients received a dose of 400 mcg per day or more. Study reports and case report forms were not submitted for the studies included in the 4 month safety update and in the data from studies using a dose of 400 mcg per day or more and therefore the data from these studies was not integrated into the data from the 3 studies that contained safety data from the use of Nasonex Nasal Spray for the treatment of nasal polyps.

7.2.2.2 Postmarketing experience

Since Nasonex was first marketed in 1997, as of 15 November 2003, there were 2890 individual spontaneous adverse events reported. Of these, 448 were serious and consistent with the pharmacologic properties of nasally inhaled corticosteroids or were considered idiosyncratic

reactions. The ten most frequently reported adverse events overall were: epistaxis (228 reports), headache (179 reports), irritation of the nasal passages (182), decreased therapeutic response (136), ineffective drug (78), pharyngitis (56), cough (53), dizziness (46), dyspnea (47) and anosmia (37) (v21, p77. t32). The twelve most frequently reported serious adverse events were: anosmia (19), nasal septum perforation (15), epistaxis (15), headache (12), dyspnea (11), cataract (9), angioneurotic edema (9), glaucoma (8), nasal irritation (8), asthma (7), intraocular pressure increased (7) and hypertension (7) (v22, pgs697-719).

7.2.2.3 Literature

The references supplied by the applicant were reviewed. In addition, the literature through PubMed was searched by the reviewer for data on the safety of Nasonex Nasal Spray in particular and mometasone in general. Search terms such as adverse events + mometasone, adverse events + Nasonex, and adverse events + corticosteroids were used. No reports of significant adverse events associated with the use of intranasal mometasone were found. A study evaluating specific histopathological changes in the nose did not demonstrate any adverse tissue changes in the nasal mucosa in patients who received a dose of 200 mcg per day for 12 months based on nasal biopsy (Minshall et al. otolaryngol Head Neck Surg 1998; 118:648). It has been concluded from data in the literature (Leone et al. Chest; 2003; 124:2329) in regard to inhaled corticosteroids in general that: 1) the use of inhaled corticosteroids is not associated with a reduction in bone density in children with asthma; 2) adult patients with asthma generally do not sustain a significant reduction in bone mineral density in response to inhaled corticosteroid treatment, although the effect may become clinically important in patients receiving high dose inhaled corticosteroids for many years; 3) the risk of subcapsular and nuclear cataracts associated with inhaled corticosteroid use is negligible in young patients with asthma but may be elevated in older patients; 4) there is insufficient data regarding difference in the risk of cataract formation between different inhaled corticosteroid formulations; 5) the risk of glaucoma associated with inhaled corticosteroid use is likely to be small but further study is warranted; 6) there is insufficient information regarding difference in the risk of glaucoma between various formulations; 7) the risk of skin thinning and easy bruising is elevated in patients receiving inhaled corticosteroids with dose, duration of treatment and patient gender being important variables affecting overall risk; and 8) there is insufficient information regarding differences in the risk of skin thinning between various inhaled corticosteroid formulations.

7.2.3 Adequacy of Overall Clinical Experience

There is extensive safety data on Nasonex Nasal Spray in studies of allergic rhinitis, primarily at a dose of 200 mcg once a day. In addition to the data submitted in studies 1925, 1926 and Q99-925-01, the applicant has submitted data from studies where 400 mcg per day or more were received by 1492 patients. As a result, the extent and duration of exposure of patients to the study drug was adequate for the safety assessment of Nasonex Nasal Spray. There were also adequate numbers of important demographic subsets who received the study drug. In this regard, in studies 1925 and 1926, there were 126, 72 and 19 Caucasian, Hispanic and non-Caucasian non-Hispanic patients in the safety database, respectively who received Nasonex 200 mcg once a day. There were 131, 75 and 18 Caucasian, Hispanic and non-Caucasian, non-Hispanic patients, respectively who received Nasonex 200 mcg bid. There were 117, 83 and 23 Caucasian, Hispanic, and non-Caucasian non-Hispanic patients, respectively who received placebo in these

studies. The doses used and the duration of exposure were adequate to assess safety. The design of the studies submitted was adequate to address specific questions relating to safety. Effect on HPA axis was assessed and local and systemic corticosteroid effects were monitored to look for class effects of glucocorticosteroids. The relevance of the safety assessments were not limited because of exclusion of any subset of patients from the study.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No preclinical studies were performed relative to this supplemental NDA. None were necessary because of the preclinical data available from previous submissions for the use of Nasonex Nasal Spray in the treatment of allergic rhinitis.

7.2.5 Adequacy of Routine Clinical Testing

The methods used and the frequency of evaluation for the safety parameters assessed in the studies submitted under this supplemental NDA were adequate to support the safety of Nasonex Nasal Spray in the treatment of nasal polyposis.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Assessment of the metabolism of Nasonex Nasal Spray and drug-drug interaction has been previously performed by the applicant prior to the approval of this drug product for the treatment of allergic rhinitis and no further studies were required for this supplemental NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant assessed the potential for Nasonex Nasal Spray to have an effect on the HPA axis in a subset of patients in study 1925 and no such effect was demonstrated. The applicant also provided data on patients who had received a dose of Nasonex Nasal Spray that was higher than the recommended dose, i.e. 400 mcg per day or more. No evidence of any systemic effect or exaggerated local effect from doses of Nasonex higher than the recommended dose was seen.

7.2.8. Assessment of Quality and Completeness of Data

The data submitted by the applicant to support the safety of Nasonex Nasal Spray is based on studies well designed to obtain meaningful data on safety parameters. The applicant has submitted a comprehensive analysis of this data.

7.2.9. Additional Submissions, Including Safety Update

7.2.9.1. Overview of studies submitted with the 4 month safety update
On 25 June 2004, the applicant submitted a four month safety update. The applicant considered relevant clinical data to be data from studies in which higher doses of Nasonex were administered (> 400 mcg per day) or studies being performed for the indication of nasal polyposis. The cut-off date for safety data included in this supplemental NDA was 15 November 2003. As of 28 May 2004, one study has been finalized (study 3033) and there have been two

"clinically completed" studies (2683 and 3251) (studies with a final un-blinded database but no completed clinical study report). In addition, data from two ongoing studies (2692 and 3218) were submitted. Study design, demographics, extent of exposure, adverse events, and clinically meaningful laboratory abnormalities are reported for studies 3033 and 2683. For study 3251, only study design and demographics and blinded serious adverse events are provided since this was an investigator-initiated study conducted in the UK and no other information is available at this time. Study design and demographics as well as blinded serious adverse events are submitted for the two ongoing studies, 2692 and 3218. This safety update provided safety information on 1041 patients from the finalized study 3033 and the "clinically completed" study 2683. In these studies, 243 patients received Nasonex 200 mcg qd, 265 patients received Nasonex 200 mcg bid and 251 patients received amoxicillin 500 mg tid and 282 patients received placebo. Safety information was also provided on an additional 1047 patients from the "clinically completed" study 3251 and the two ongoing studies, 2692 and 3218.

Overview of clinical studies included in the 4 month safety update

Study #	# centers	Study design	Patient population	Dosage	Duration	# pts R/T	Age range	Gender M/F
3033	9 Germany	R, DB, PC, PG	Chronic sinusitis	200 mcg bid	16 weeks	60/59 30/Rx	19-64	28/32
2683	71 international US	R, DR, DB, DD, PC, ATC, PG	Acute rhinosinusitis	200mcg qd 200 mcg bid amoxicillin 500 mg tid for 10 days	15 days followed by 14 day observation	981/981 243 qd 235 bid 251 Am 252 P	12-76	341/640
3251	1 UK *	R, DB, PC, investigator-initiated	Cytokine profile in biopsied nasal polyp tissue	200 mcg qd	3 weeks	5	NP ***	NP
2692	79 international	R, DR, DB, DD, PC, ATC, PG	Acute rhinosinusitis	200 mcg qd, 200 mcg bid, amoxicillin 500 mg tid for 10 days	15 days followed by 14 day observation	973/958	12-87	313/660
3218	10 Sweden **	R, DB, PC	Post-surgical treatment of nasal polyps	200 mcg qd	24 weeks	69 enrolled	adults	NP

* Enrollment was terminated due to difficulties in patient recruitment
** Enrollment remains open until 31 December 2004 unless target of 146 patients is reached
*** NP = not provided

7.2.9.2. Extent of exposure

Study 3033: There were 4 patients who received Nasonex who were discontinued from the study due to lack of efficacy (1) and loss of contact (3) and 2 patients in the placebo group who were discontinued from the study because of lack of efficacy (1) and loss of contact (1). One patient randomized to the Nasonex group did not receive any study medication. The remaining 53

patients (25 in the Nasonex group and 28 in the placebo group) received treatment during the entire 4 month study period.

Study 2683: Treatment for 15 days occurred in 82%, 82%, 85% and 78% of the patients in the Nasonex 200 mcg qd, Nasonex 200 mcg bid, Amoxicillin 500 mg tid and placebo groups, respectively (submission of 25 June 2004, p14, t2).

7.2.9.3. Adverse events: assessed at all study visits

Study 3033: (submission 25 June 2004, p18, t3); There were no serious adverse events reported in this study. In the Nasonex treatment group, there were 5 patients who reported 6 adverse events (16.7%) including nasal bleeding and dryness (severity not indicated), moderate pruritis, moderate cough, mild epistaxis, and mild laryngitis. In the Placebo treatment group, there were 9 patients who reported 10 adverse events (30%) including moderate infection (2), mild epistaxis (2), mild acute prostatitis, mild headache, mild headache and tongue pain, moderate acute sinusitis, mild hypotonia.

There were no deaths reported and all serious adverse events were considered to be unlikely related to the study drug. In Study 2683 (submission of 35 June 2004, p19, t4), there were 3 patients (1 patient in the Nasonex 200 mcg qd group and 2 patients in the placebo group) who had serious adverse events. The patient in the Nasonex group was a 14 year old male who had a significant increase in liver enzymes noted on blood drawn before treatment was initiated (p21 t5). In Study 2692, there were 7 patients who had serious adverse events. The blind remains for this ongoing study so whether these patients were receiving one of the two dosages of Nasonex, amoxicillin or placebo is not known at this time (p22-23, t5). Serious adverse events in this study included a 48 year old female who had elevation in liver enzymes considered unlikely by the investigator to be related to the study drug, a 21 year old male who had elevated liver enzymes at screening, a 62 year old male with an MI considered by the investigator to be unlikely to be related to the study drug, a 48 year old female with diabetes considered by the investigator to be unlikely to be related to the study drug, a 46 year old female with intestinal obstruction considered by the investigator to be unlikely to be related to the study drug and two patients with hyperglycemia, 42 and 62 year old males considered by the investigator to be unlikely to be related to the study drug (p31-32). In Study 3218, there was one patient who was considered to have had a serious adverse event. The patient developed epistaxis requiring hospitalization. The study blind remains in place and the treatment received by the patient is not known.

Adverse events leading to discontinuation (p24-25, t6): In Study 3033, one patient who received Nasonex developed moderate possibly related pruritus and one patient in the placebo group developed mild possibly related epistaxis. In Study 2683, adverse events leading to discontinuation included: one patient who received Nasonex 200 mcg qd (insomnia); 7 patients who received Nasonex 200 mcg bid (headache, ECG abnormal, pharyngitis, bronchitis, nasal irritation, dry throat, cellulits and pruritis); 5 patients who received amoxicillin (allergic reaction, bronchitis, sputum increased, rash (2); and 6 patients who received placebo (fever, diarrhea, nausea and vomiting, urinary tract infection, asthma aggravated and bronchitis).

Number of patients (%) with adverse events that occurred in 2% or greater in one of the treatment groups AND occurred with a greater frequency in one of the two Nasonex treatment groups than in the other treatment groups

Adverse event	Nasonex 200 mcg qd (N=243)	Nasonex 200 mcg bid (n=235)	Amoxicillin 500 mg tid (n=251)	Placebo (n=252)
Dizziness	5 (2.1%)	6 (2.6%)	3 (1.2%)	5 (2%)
Fever	6 (2.5%)	2 (0.9%)	2 (0.8%)	3 (1.2%)
Earache	3 (1.2%)	5 (2.1%)	4 (1.6%)	2 (0.8%)
Abdominal pain	5 (2.1%)	7 (3%)	3 (1.2%)	3 (1.2%)
Pharyngitis	10 (4.1%)	11 (4.7%)	6 (2.4%)	11 (4.4%)
Epistaxis	9 (3.7%)	14 (6%)	13 (5.2%)	13 (5.2%)
Nasal burning	5 (2.1%)	2 (0.9%)	3 (1.25)	1 (0.4%)

Spontaneously reported adverse events post-marketing: Nasonex is approved in 88 countries and marketing began in October 1997 with estimated patient exposure through December 2003 of 2,774,709,240 patient days. Between 15 November 2003 and 30 April 2004, there were 286 spontaneous adverse event reports for Nasonex. Spontaneous adverse events for which there were at least 5 reports include: epistaxis (22), nasal irritation (15), headache (11), nasal congestion (9), cough (6), ineffectiveness (6), drug exposure during pregnancy (5), intentional misuse (5) and pain (5). The post-marketing safety data are consistent in pattern with the adverse events reported in studies submitted under this supplemental NDA and do not raise any safety concerns. Spontaneously reported adverse events are sketchy at best and are difficult to attribute to a specific medication. Nevertheless, it should be noted that the following reported adverse events are consistent with a systemic effect of inhaled corticosteroids: increased weight, blood corticotrophin increased, edema (2), lenticular opacities (2), blood glucose increased (2), candidiasis, visual disturbance, cataract (2), osteoporosis, corneal erosion, myalgia (2), agitation, hypertension, increased intracranial pressure, and increased intraocular pressure.

Laboratory tests (except studies 3251 and 3218): baseline and last treatment visit: No clinically meaningful abnormalities were reported in study 3033. There were 18 patients in study 2683 who met the sponsor's definition of a clinically meaningful laboratory abnormatlity, i.e. blood chemistry result 2.6 times or greater above the upper limit of the NRR, a hemoglobin concentration of 9.4 g/dL or less, a platelet count of 74,000 cells/uL or less or WBC of 2900 cellls/uL or less. Of these, 8 patients received Nasonex 200 mcg qd, 2 patients received Nasonex 200 mcg bid, one patient received amoxicillin and 7 patients received placebo. Of the Nasonex 200 mcg qd group, three patients had laboratory values that were clinically meaningful before starting treatment. In this group, on day 1 (visit 1) one patient had a creatinine level of 335 umol/L (NRR 53-115) which by day 6 was within the NRR, one patient had a leukocyte count of 2.8 (NRR 3.5-10.5) which was 6.9 on day 17, one patient had an SGOT of 133 U/L (NRR 0-41) which was 52 on day 17, and one patient had a SGPT value of 121 U/L (NRR 0-45) that increased to 163 U/L on day 10 associated with a SGOT value of 170. The latter patient's SGOT at baseline was 94 U/L. Finally, there was one patient in this group who had a screening SGPT of 24 U/L which rose on day 15 to a value of 132 U/L and was 75 U/L 9 days after the conclusion of treatment. In the Nasonex 200 mcg bid group, there was one patient who on day 1 had an LDH of 1761 U/L (NRR 100-242) which was 537 U/L on day 15. Another patient in this group who had an SGOT of 20 U/L at screening developed an SGOT of 158 on day 16 which decreased to 40 U/L 5 days after the end of treatment. Similar increases in SGOT and SGPT

were also seen in the group that received placebo (p26, t7). *Intranasal corticosteroids are metabolized in the liver. Mometasone undergoes extensive metabolism to metabolites regulated by the cytochrome P-450 3A4 enzyme system. Liver mixed-function oxidases and glucuronyl transferases are important in the metabolism of many glucocorticosteroids. As a result, liver disease, drugs and other chemical that modify liver function can affect the biologic half-life of glucocorticosteroids. However, intranasal corticosteroids have not been reported to produce an increase in liver enzymes and there is nothing unique about this drug product that would support any concern about its hepatic effect. Overall, the sponsor has demonstrated the safety of Nasonex at a dosage of 200 mcg once a day and a dosage of 200 mcg bid.*

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Epistaxis, considered in most cases to be related to the treatment drug, was reported significantly more frequently by patients receiving Nasonex 200 mcg bid than patients receiving placebo. With a nasally inhaled drug product, local nasal adverse events are expected. Local nasal adverse events in studies 1925 and 1926 included epistaxis, nasal burning, nasal dryness, nasal irritation and nasal septal perforation. These adverse events are not unlike those seen in studies where Nasonex was evaluated in the treatment of allergic rhinitis.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The sponsor pooled the safety review from studies 1925 and 1926. This is acceptable given the fact that these studies were identically designed with similar patient populations, quantitatively and qualitatively, who received the same dosages of the study drug. The data from study Q99-925-01 was not pooled with the other studies. This is acceptable since the study design and the collection of data was significantly different in study Q99-925-01 than in studies 1925 and 1926.

7.4.1.1 Pooled data vs. individual study data

The interpretation of the data based on assessment of safety parameters when evaluating the pooled data for studies 1925 and 1926 was the same as when evaluating the individual study data for these two studies.

7.4.1.2 Combining data

Because of the similarity of studies 1925 and 1926, pooling of the data was not based on weighting of the studies but was simply a combining of the number of patients with a particular adverse event over the number of patients in the two studies.

7.4.2 Explorations for Predictive Factors

No predictive factors that could affect the safety profile of Nasonex Nasal Spray were identified in the data submitted by the applicant.

7.4.2.1 Explorations for dose dependency for adverse findings

No explorations for dose dependency for adverse findings were done.

7.4.2.2 Explorations for time dependency for adverse findings

No explorations for time dependency for adverse finding were done.

7.4.2.3 Explorations for drug-demographic interactions

See sections 7.1.8.4., 7.1.7.5 and 7.1.5.6 above.

7.4.2.4 Explorations for drug-disease interactions

See sections 7.1.8.4.4., 7.1.7.5.4 and 7.1.5.6 above.

7.4.2.5 Explorations for drug-drug interactions

No explorations for drug-drug interactions were done.

7.4.3 Causality Determination

Epistaxis, considered in most cases to be related to the treatment drug, was reported significantly more frequently by patients receiving Nasonex 200 mcg bid than patients receiving placebo. With a nasally inhaled drug product, local nasal adverse events are expected. Local nasal adverse events in studies 1925 and 1926 included epistaxis, nasal burning, nasal dryness, nasal irritation and nasal septal perforation. These adverse events are not unlike those seen in studies where Nasonex was evaluated in the treatment of allergic rhinitis.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

A dose of 200 mcg once a day in the AM was selected because it is the approved dose for allergic rhinitis. Other intranasal corticosteroids, e.g. beclomethasone, budesonide, fluticasone, that have been approved for nasal polyposis at a dosage that is at least equal that approved for allergic rhinitis in other countries. A dose of 200 mcg bid was included because of the possible decrease in study drug distribution due to mechanical obstruction caused by nasal polyps.

In terms of efficacy, the applicant was able to show a dose response in one of the two pivotal studies (study 1926) but not in the other (study 1925). In regard to safety, a dose response was seen only in regard to epistaxis and the incidence of SGPT values that went from normal at baseline to above the upper limit of the normal reference range after treatment. Dose modification is not needed based on gender, race, age, or any underlying condition.

The two dosages that were evaluated for Nasonex Nasal Spray are 200 mcg once a day and 200 mcg bid. The applicant has not demonstrated conclusively that a dosage of 200 mcg bid will be more effective than a dosage of 200 mcg once a day on a consistent basis. Nevertheless, both dosages have been shown to be effective.

The proposed dose in the product labeling for nasal polyps is "two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg). (b) (4) *The applicant has demonstrated the safety of a dose of 400 mcg per day in the data submitted in this supplement. However, the applicant failed to establish a clear dose response in the studies submitted, since in one of the pivotal studies a dose of 200 mcg once a day was more effective than a dose of 400 mcg per day (study 1925). It has not, therefore, been established that a dose of 400 mcg per day is necessary to obtain efficacy in the treatment of nasal polyps in* (b) (4) *patients. Moreover,* (b) (4) *The Dosage and Administration section of the labeling should be changed, therefore, to read, "The recommended dose for nasal polyps is two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg). A dose of two sprays (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 mcg) is also effective in some patients."*

8.2 Drug-Drug Interactions

There is no discussion in the current labeling for Nasonex Nasal Spray about drug-drug interactions. No such interaction would be anticipated based on the class of drug, the route of administration and the dose being delivered locally. There is no basis for suspecting any increased potential for drug-drug interaction when Nasonex Nasal Spray is administered for the treatment of nasal polyposis than would be anticipated when this drug product is administered for the treatment of allergic rhinitis.

8.3 Special Populations

There are no special dosage considerations when Nasonex Nasal Spray is prescribed for the treatment of nasal polyps based on race, gender, age or underlying medical conditions, including pregnancy and lactation. The applicant has adequately assessed and analyzed the data in regard to race, gender, age and the presence or absence of asthma. The evaluation was adequate for assessment of these subsets of patients. An evaluation of the safety data provided by the applicant in regard to age, gender and race is discussed below.

8.3.1. Age:

Adverse events in patients 65 years of age and older in studies 1925 and 1926 (v21, p108) occurring in two or more patients in either of the active treatment groups

Adverse event	Nasonex 200 mcg qd ≥ 65 yrs	Nasonex 200 mcg qd all pts studied pooled 1925/1926	Nasonex 200mcg bid ≥ 65 yrs	Nasonex 200mcg bid all pts pooled studies 1925/1926	Placebo ≥ 65 yrs	Placebo all pooled pts studies 1925 and 1926
Headache	2 (8%)	4 (2%)	3 (11%)	10 (4%)	2 (6%)	9 (4%)
URI	6 (23%)	3 (1%)	4 (14%)	2 (1%)	3 (10%)	4 (2%)
Epistaxis	1 (4%)	11 (5%)	3 (11%)	28 (13%)	2 (6%)	10 (4%)

COMMENT: *There is no suggestion that there was a significant difference in the type of adverse event or the frequency of adverse events in general or specific adverse events in patients 65 years of age and older compared to patients 18-64 years of age. Therefore, when reported adverse events are evaluated in regard to age, there is no evidence of any safety issue in patients 65 years of age and older.*

8.3.2. Gender:

Adverse events based on gender that occurred in 3 or more males/females who received Nasonex in studies 1925 and 1926 (v21, p113)

Adverse event	Nasonex 200 mcg QD	Nasonex 200 mcg bid	Placebo
Headache	16%F, 6%M	10%F, 10%M	18%F, 6%M
Pharyngitis	9%F, 3%M	2%F, 3%M	6%F, 2%M
URI	11%F, 14%M	14%F,10%	13%F, %10
Bronchitis	6%F, 3%M	2%F, 3%M	1%F, 1%M
Epistaxis	3%F, 8%M	11%F, 15%M	8%F, 3%M
Diarrhea	0F, 3%M	0F,1%M	1%F,1%M
Throat irritation	1%F, 0M	0F, 2%M	0F, 1%M
Toothache	0F, 2%M	1%F, 1%M	0F, 0M
Viral infection	0F, 3%M	1%F, 1%M	1%F, 0M
Sinusitis	1%F, 3%M	2%F, 4%M	6%F, 1%M
Overdose	3%F, 2%M	0F, 2%M	1%F, 3%M
Back pain	0F, 5%M	1%F, 2%M	2%F, 1%M
Cough	3%F, 1%M	1%F, 2%M	1%F, 1%M
Pruritis	3%F, 0M	0F, 2%M	0F, 0M

COMMENT: *Epistaxis and sinusitis occurred more frequently in males than in females who received either dose of Nasonex compared with the group that received placebo, in whom epistaxis and sinusitis occurred more frequently in females than males. The greater frequency of epistaxis and sinusitis in patients who received Nasonex than in patients who received placebo was not dose dependent and occurred with approximately equal frequency in those patients who received Nasonex 200 mcg once a day and patients who received Nasonex 200 mcg bid. There is no safety issue based on whether males or females received Nasonex.*

8.3.3. Race:

Adverse events based on race that occurred in at least 3 patients who received Nasonex in studies 1925 and 1926 (v21, p132)

Adverse events	Nasonex 200 mcg QD	Nasonex 200 mcg bid	Placebo
Number of Caucasian pts	N = 126	N = 131	N = 117
Number of Hispanic pts	N = 72	N = 75	N = 83
Number of other pts	N = 19	N = 18	N = 23
Headache			
Caucasian	10%	9%	8%
Hispanic	8%	13%	14%
Other	5%	6%	13%
Toothache			
Caucasian	2%	1%	0
Hispanic	0	1%	0
Other	0	0	0
Pharyngitis			
Caucasian	4%	3%	3%
Hispanic	3%	3%	4%
Other	16%	0	4%
Sinusitis			
Caucasian	2%	5%	2%
Hispanic	3%	1%	6%
Other	0	0	0
URI			
Caucasian	16%	15%	12%
Hispanic	10%	7%	13%
Other	5%	11%	0
Overdose			
Caucasian	3%	2%	1%
Hispanic	1%	1%	4%
Other	0	0	4%
Back pain			
Caucasian	4%	2%	2%
Hispanic	3%	1%	2%
Other	0	0	0
Bronchitis			
Caucasian	4%	3%	0
Hispanic	6%	1%	2%
Other	0	6%	0
Cough			
Caucasian	3%	1%	1%
Hispanic	0	3%	1%
Other	0	6%	4%
Epistaxis			
Caucasian	10%	18%	3%
Hispanic	1%	5%	7%
Other	0	11%	4%
Nasal irritation			
Caucasian	1%	2%	0
Hispanic	1%	0	4%
Other	0	0	9%

Rhinitis			
Caucasian	1%	2%	3%
Hispanic	1%	0	0
Other	0	6%	0

Comment: The small number of patients in the "other" category (non-Caucasian, non-Hispanic patients) make it difficult to draw any conclusions about the greater incidence after administration of Nasonex compared to placebo of pharyngitis, URI, bronchitis, or epistaxis in this group than was seen in Caucasians or Hispanics. The greater incidence overall of epistaxis after administration of Nasonex than after the administration of placebo was based on the much greater incidence of this adverse event in Caucasian patients than in Hispanic patients. There is no reason to expect that Caucasian patients receiving an intranasal corticosteroid would have a greater propensity for the development of epistaxis than would other racial groups.

8.4 Pediatrics

The applicant has requested a waiver for the assessment of the safety and efficacy of Nasonex in the treatment of nasal polyposis in patients less than 18 years of age. The applicant's rationale for requesting this waiver is based on the low occurrence of nasal polyposis in children and adolescents and the contention that Nasonex in this age group does not represent a meaningful therapeutic benefit over existing treatment, i.e. endoscopic surgery.

The data supplied by the applicant indicates that nasal polyposis occurs, although infrequently, in patients 6-17 years of age. The percentage of patients 6-17 years of age who have nasal polyps associated with cystic fibrosis or secondary to allergic rhinitis is not clear from the data that is provided. The labeling for beclomethasone nasal spray states that it is indicated for the prevention or recurrence of nasal polyps following surgical removal and is approved for patients 6 years of age and older. *Therefore, it is reasonable that the applicant study Nasonex for the treatment of nasal polyps in patients 6-17 years of age. In doing so, the applicant will have the opportunity to determine the appropriate dose for the treatment of nasal polyposis in this patient population. Therefore, the applicant's request for a waiver for the study of Nasonex in the treatment of nasal polyposis in patients less than 18 years of age is not granted.*

8.5 Advisory Committee Meeting

This Supplemental NDA was not presented to an Advisory Committee because there were no issues that needed input from outside experts.

8.6 Literature Review

A comprehensive review of the clinical literature was not performed because there were no questions raised by the data submitted by the sponsor that could have been answered by such a review. The references submitted by the sponsor that generally supported the use of intranasal corticosteroids in the treatment of nasal polyps were reviewed.

8.7 Postmarketing Risk Management Plan

A post-marketing risk management plan was not submitted by the sponsor and none is necessary.

8.8 Other Relevant Materials

This Supplemental NDA did not include any actual use, labeling comprehension or marketing studies. There were no consultations requested and no reviews from ODS.

9 OVERALL ASSESSMENT

9.1 Conclusions

The two efficacy studies (*studies 1925 and 1926*) submitted under this supplemental NDA were randomized, placebo-controlled, double-blind, parallel group multicenter studies and were designed by the sponsor with input from the Division (see discussion of study design and endpoints below). They were supported by *study Q99-925-01* which was a randomized, placebo-controlled, double-blind, parallel group, multicenter (12) study performed in Denmark, Finland, Norway and Sweden. There were two primary efficacy variables in *studies 1925 and 1926*: 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to endpoint in bilateral polyp grade. A statistically significant difference from placebo for both endpoints was required to demonstrate efficacy. In studies 1925 and 1926, two dosages of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray were evaluated and compared to placebo; 200 mcg once a day and 200 mcg bid (400 mcg per day). The primary efficacy variable in *study Q99-925-01* was the proportion of patients with improvement during the treatment period of 16 weeks in nasal congestion as evaluated by the investigator, with improvement being defined as a reduction in nasal congestion of at least one point. Assessment of polyp size was a secondary outcome variable in this study. Only a Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray dosage of 200 mcg once a day was evaluated in this study.

In *study 1925*, a statistically significant difference favoring Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray compared to placebo was seen for both nasal congestion/obstruction after one month of treatment and for reduction in polyp size at endpoint after both administration of 200 mcg once a day and 200 mcg bid. In addition, there was a statistically significant difference demonstrated between both dosages of Nasonex and placebo favoring Nasonex for all the secondary efficacy variables evaluated. *Therefore, the efficacy of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray for the treatment of nasal polyps was demonstrated in this study at both of the dosages evaluated.* In *study 1926*, both dosages of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray produced a statistically significantly greater improvement in nasal congestion/obstruction than was seen after administration of placebo. However, neither dosage produced a statistically significantly greater effect on polyp size than placebo using the pre-specified analysis, although the 200 mcg bid dosage showed greater improvement ($p=0.08$ compared to placebo) than did the 200 mcg once a day dosage ($p=0.62$ compared to placebo). The sponsor did a post-hoc analysis of reduction in polyp size using the baseline as a covariate and based on this analysis, there was a statistically

significant difference between Nasonex at a dose of 200 mcg bid and placebo, favoring Nasonex (p =0.05). Efficacy was demonstrated in this study for all secondary efficacy variables after administration of Nasonex 200 mcg bid but not after administration of Nasonex at a dosage of 200 mcg once a day. *Since the sponsor was able to show effectiveness in study 1926 for both primary outcome variables at a dosage of 200 mcg bid (400 mcg per day) using the post-hoc analysis for polyp size, this study can be used to demonstrate the effectiveness of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray at a dose of 200 mcg bid in the treatment of nasal polyps. The post-hoc analysis of polyp size in study 1926 is considered appropriate because of the importance of including baseline in this evaluation as demonstrated in study Q99-925-01.*

In study *Q99-925-01*, a statistically significant difference was shown between the group that received Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray and the group that received placebo for both the primary efficacy variable and reduction in polyp size. In addition, a statistically significant difference was shown between the group that received Nasonex and the group that received placebo, favoring the Nasonex group, for all of the other secondary efficacy variables. Reduction in polyp size was not specified as a primary outcome variable. *Although the design of the study in regard to the assessment of polyp size was different from that used in studies 1925 and 1926, it can be used to support the efficacy of a dosage of 200 mcg once a day for the proposed indication.*

In summary, the efficacy of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray at a dosage of 200 mcg twice a day was demonstrated in studies 1925 and 1926 for the treatment of nasal polyps in adult and adolescent patients 18 years and older". The efficacy of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray for the treatment of nasal polyps has been demonstrated in studies 1925 and Q99-925-01 at a dosage of 200 mcg once a day.

Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray has been shown in the data provided by the sponsor and based on previous use in the treatment of allergic rhinitis to be safe for administration at a dose of 200 mcg or 400 mcg per day. A higher incidence of epistaxis was noted after administration of a total daily dose of 400 mcg per day than was noted after administration of a total daily dose of 200 mcg per day or placebo, but was not unacceptably high or inconsistent with this effect seen after administration of other intranasal corticosteroids. There was no conclusive evidence of any significant systemic effect from the intranasal administration of mometasone at a dose of 400 mcg per day.

9.2 Recommendation on Regulatory Action

The efficacy of Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray for the treatment of nasal polyps (b) (4) in adult and adolescent patients 18 years of age and older has been demonstrated by the data provided by the applicant in this submission. Therefore, Nasonex Nasal Spray is approved for this indication. The safety data provided by the sponsor does not indicate any unacceptable risk associated with the administration of Nasonex Nasal Spray, the major adverse effect being epistaxis which is a recognized adverse event in patients receiving intranasal cortiosteroids. The

risk from the administration of this drug product is slight and acceptable for this type of drug product.

In regard to the labeling for this drug product the following comments were conveyed to the applicant on 23 November 2004.

1) Change (b) (4) (b) (4) to "nasal polyps" throughout the labeling for consistency.

2) Divide the Clinical Studies section into two sections, a section on allergic rhinitis and a section on nasal polyps to clarify if the data refers to studies in allergic rhinitis or studies in patients with nasal polyps. This should be done by inserting subheadings on line 130 under the heading "Clinical Studies" that reads "Allergic Rhinitis" and on line 171 prior to the discussion of the data from studies in patients with nasal polyposis that reads "Nasal Polyps".

3) Delete the entire first two new paragraphs in the Clinical Studies section on studies in patients with nasal polyps on lines 171-198 and replace those paragraphs with the following: "Two studies were performed to evaluate the efficacy and safety of Nasonex Nasal Spray in the treatment of nasal polyps. These studies involved 664 patients with nasal polyps, 441 of whom received Nasonex Nasal Spray. These studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in patients 18-86 years of age with bilateral nasal polyps. Patients were randomized to receive Nasonex Nasal Spray 200 mcg once daily, 200 mcg twice daily or placebo for a period of 4 months. The co-primary efficacy endpoints were 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of treatment as assessed by endoscopy. Efficacy was demonstrated in both studies at a dose of 200 mcg twice daily and in one study at a dose of 200 mcg once a day (see table below).

Effect of Nasonex Nasal Spray in two randomized, placebo-controlled trials in patients with nasal polyps

	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value for Nasonex 200 mcg qd vs placebo	P value for Nasonex 200 mcg bid vs placebo
Study 1	N = 112	N = 121	N = 114		
Baseline bilateral polyp grade *	4.21	4.27	4.25		
Mean change from baseline in bilateral polyp grade	- 1.13	- 0.95	- 0.49	< 0.001	0.01
Baseline nasal congestion **	2.29	2.35	2.28		
Mean change from baseline in nasal congestion	- 0.47	- 0.61	- 0.24	0.001	< 0.001
Study 2	N = 101	N = 101	N =100		
Baseline bilateral polyp grade *	4.00	4.10	4.17		
Mean change from	- 0.76	- 0.98	- 0.67	0.62	0.04

baseline in bilateral polyp grade					
Baseline nasal congestion **	2.23	2.20	2.18		
Mean change from baseline in nasal congestion	- 0.42	- 0.66	- 0.23	0.01	< 0.001

* polyps were graded by the investigator based on endoscopic visualization, using a scale of 0-3 where 0 = no polyps, 1 = polyps in the middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the midlle turninate but not the inferior border of the inferior turbinate; 3 = polyps reaching to or below the lower border of the inferior turbinate, or polyps medial to the middle turbinate.

** nasal congestion/obstruction was scored daily by the patient using a 0-3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms

These changes provide the reader with a more concise description of the results of the two key studies that provide data on the treatment of nasal polyps.

4. In the Indications and Usage section, delete (b) (4) on line 214 in the second paragraph in this section.

5. Divide the Adverse Reactions section into two sections, a section on allergic rhinitis and a section on nasal polyps to clarify if the data refers to studies in allergic rhinitis or studies in patients with nasal polyps. This should be done by inserting subheadings on line 429 under the heading "Adverse Reactions" that reads "Allergic Rhinitis" and on line 492 prior to the discussion of the data from studies in patients with nasal polyps that reads "Nasal Polyps".

6. In the new paragraph on lines 492-497 under the Adverse Reactions section, dealing with adverse events in patients with nasal polyposis, insert an additional sentence at the end of the paragraph that reads, "The incidence of epistaxis was greater in patients who received Nasonex Nasal Spray compared to placebo". *The higher dose-related incidence of epistaxis seen in patients who received Nasonex Nasal Spray needs to be mentioned in the labeling since it is recognized that intranasal corticosteroid sprays can produce this adverse event. Combine the data from studies 1925, 1926 and Q99-925-01 in regard to the incidence of epistaxis in patients who received each dose of Nasonex and patients who received placebo and provide those data in parentheses arfter the above sentence.*

7. The new 5th paragraph on lines 541-547 under the Dosage and Administration section should be deleted and replaced with the following: "The recommended dose for nasal polyps is two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg). A dose of two sprays (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 mcg) is also effective in some patients."

8. Under Patients Instructions for Use, under the Caution section on lines 639-653, in the last sentence of the first paragraph on line 645 add "helps to" after "50 mcg" and before "control".

9. At the end of the second paragraph on line 653 in the Patients Instructions for Use section, add the sentence "Side effects were generally mild and included headache, viral infection, sore throat, nosebleeds, and coughing."

The applicant responded to these comments on 30 November 2004 by revising the labeling. The Division's comments, the sponsor's revisions and this reviewer's comments *in italics* on 2 December 2004 are as follows:

1. Division comment: Change (b) (4) (b) (4) to "nasal polyps" throughout the labeling for consistency. *The applicant has made this change*.

2. Division comment: Divide the Clinical Studies section into two sections, a section on allergic rhinitis and a section on nasal polyps to clarify if the data refers to studies in allergic rhinitis or studies in patients with nasal polyps. This should be done by inserting subheadings on line 130 under the heading "Clinical Studies" that reads "Allergic Rhinitis" and on line 171 prior to the discussion of the data from studies in patients with nasal polyposis that reads "Nasal Polyps". *The applicant has made this change*.

3. Division comment: Delete the entire first two new paragraphs in the Clinical Studies section on studies in patients with nasal polyps on lines 171-198 and replace those paragraphs with the following: "Two studies were performed to evaluate the efficacy and safety of Nasonex Nasal Spray in the treatment of nasal polyps. These studies involved 664 patients with nasal polyps, 441 of whom received Nasonex Nasal Spray. These studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in patients 18-86 years of age with bilateral nasal polyps. Patients were randomized to receive Nasonex Nasal Spray 200 mcg once daily, 200 mcg twice daily or placebo for a period of 4 months. The co-primary efficacy endpoints were 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of treatment as assessed by endoscopy. Efficacy was demonstrated in both studies at a dose of 200 mcg twice daily and in one study at a dose of 200 mcg once a day (see table below).

Effect of Nasonex Nasal Spray in two randomized, placebo-controlled trials in patients with nasal polyps

(b) (4)

(b) (4)

Reviewer comment: *The applicant has modified the third sentence to read, "These studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in patients 18-86 years of age with bilateral polyps.", by deleting* (b) (4) *before "bilateral" and "nasal" before "polyps". Moreover, the applicant has left in the sentence that reads,* (b) (4) *In addition, the applicant has modified the description under the table about polyp grade by adding "in each nasal fossa" and "(score reflects sum of left and right nasal fossa grades)". The statement about* (b) (4) *should be deleted from this section. Improvement in these symptoms was not consistently seen across all time points in one of the key studies and these are only some of the symptoms that can be demonstrated in patients with nasal polyps. To emphasize these symptoms to the exclusion of others associated with nasal polyps does not provide the practicing physician with an adequate picture of response in patients with nasal polyps to the administration of Nasonex. The other changes proposed by the applicant are acceptable.*

4. Division comment: In the Indications and Usage section, delete (b) (4) on line 214 in the second paragraph in this section. *The applicant has made this change.*

5. Division comment: Divide the Adverse Reactions section into two sections, a section on allergic rhinitis and a section on nasal polyps to clarify if the data refers to studies in allergic rhinitis or studies in patients with nasal polyps. This should be done by inserting subheadings on line 429 under the heading "Adverse Reactions" that reads "Allergic Rhinitis" and on line 492 prior to the discussion of the data from studies in patients with nasal polyps that reads "Nasal Polyps". *The applicant has made this change.*

6. Division comment: In the new paragraph on lines 492-497 under the Adverse Reactions section, dealing with adverse events in patients with nasal polyposis, insert an additional sentence at the end of the paragraph that reads, "The incidence of epistaxis was greater in patients who received Nasonex Nasal Spray compared to placebo". The applicant has changed the last sentence in this section to read, "The overall incidence of adverse events for patients treated with Nasonex Nasal Spray, 50 mcg was comparable to patients treated with the placebo except for epistaxis/ (b) (4) which was 9% for 200 mcg once daily; 13% for 200mcg twice daily and 5% for placebo." *These additions by the applicant are exceptable. The applicant correctly indicates that the vast majority of reported cases of epistaxis were not frank bleeding but reflected* (b) (4) *as indicated in the CRFs.*

7. Division comment: The new 5th paragraph on lines 541-547 under the Dosage and Administration section should be deleted and replaced with the following: "The recommended dose for nasal polyps is two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg). A dose of two sprays (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 mcg) is also effective in some patients." *The applicant has made this change.*

8. Division comment: Under Patients Instructions for Use, under the Caution section on lines 639-653, in the last sentence of the first paragraph on line 645 add "helps to" after "50 mcg" and before "control". *The applicant has made this change.*

9. Division comment: At the end of the second paragraph on line 653 in the Patients Instructions for Use section, add the sentence "Side effects were generally mild and included headache, viral infection, sore throat, nosebleeds, and coughing." *The applicant has made this change. NOTE: DDMAC asked the Division to reconsider their recommendation that the Patient Instruction for Use section include the approved indication for Nasonex. The Division recommends that the applicant either delete the section from line 632 to line 642 on page 23 of the labeling submitted on 30 November 2004 or put into lay language in this section the indications for Nasonex.*

A conference call was held on 3 December 2004 with the applicant to discuss specific aspects of the labeling. (b) (4)

The Division also stated that the applicant should either delete the part at the end of the Patient Instructions for Use section of the labeling under "Caution" that states "Nasonex Nasal Spray, 50 mcg, helps to control the underlying disorders responsible……..Based on single-day studies……nosebleeds and coughing.", or replace it with lay language.

9.3 Recommendation on Postmarketing Actions

The sponsor has been told to submit a pediatric drug development plan for the study of Nasonex Nasal Spray in the treatment of nasal polyposis since a waiver was not granted for pediatric patients 6-17 years of age with this condition.

9.3.1 Risk Management Activity

No post-marketing risk management activity has been discussed with the sponsor or is required.

9.3.2 Required Phase 4 Commitments

The sponsor has a commitment to submit a drug development plan for the study of Nasonex Nasal Spray for the treatment of nasal polyposis in patients 6-17 years of age.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

Based on the data from these studies the clinical Pharmacology, Indications and Usage, Precautions, Adverse Reactions, and Dosage and Administration sections of the labeling have been modified. In the Pharmacodynamics section, there is a new paragraph describing a study assessing adrenal function in 213 patients with nasal polyposis before and after 4 months of treatment based on 24 hour urinary free cortisol levels. In the Clinical Studies section there is a description of the studies performed to support a claim for treatment of nasal polyps. Under the Indications and Usage section, an additional paragraph has been added that states, (b) (4)

n the Adverse Reactions section there is a new paragraph reflecting the safety data form the studies on nasal polyposis. Under the Dosage and Administration section, there is a new paragraph indicating the dosage that should be used for the treatment of nasal polyps. Other changes in the labeling are relatively minor and generally are changed based on the data from the studies on nasal polyposis.

9.5 Comments to Applicant:

See 9.2., Recommendations on Regulatory Action above.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1. Study 1925 (v3-6): There were 44 centers in this study in 10 countries, 22 in the US and 22 outside the US.

10.1.1.1. Study Design: Study 1925 was a randomized, double-blind, placebo-controlled, parallel group, multicenter study in which patients received either 200 mcg Nasonex once a day, 200 mcg Nasonex bid or placebo for 4 months. There was a 14 days single-blind placebo run-in period and 4 months of randomized treatment.

10.1.1.2. Patient Population: For entry into the study, patients had to have a nasal congestion score of 2 or greater for each of the last 7 days of the run-in period. Patients with SAR were excluded to ensure that the symptom scoring was consistent throughout the 4 month treatment period. Patients with glaucoma or sub-capsular cataracts were excluded since corticosteroids have been associated with the development of these conditions. Patients were also excluded if they had had sinus or nasal surgery within the previous 6 months, 3 or more nasal surgeries at any time in the past, previous surgery that would make accurate grading of polyps impossible or complete nasal obstruction. Patients had bilateral nasal polyps and clinically significant nasal congestion/obstruction with an AM instantaneous score of 2 or greater for each of the last 7 days of the 2 week run-in period. Randomization was stratified by the presence or absence of concomitant asthma. Patients with asthma could be entered into the study if they had an FEV-1 of 80% or greater and no recent exacerbation. If a patient was receiving inhaled corticosteroids the dose could not exceed 840 mcg per day of beclomethasone or an equivalent dose of another corticosteroid (up to 600 mcg per day of budesonide, up to 2000 mcg per day of flunisolide, up to 660 mcg per day of fluticasone and up to 1000 mcg per day of triamcinolone) for at least one month prior to screening and had to remain stable throughout the study. The patient population was a mixed population with mild to severe nasal polyposis, except for nasal congestion and loss of smell, which were moderate to severe. There were 354 patients randomized; 115 of whom received 200 mcg once a day of Nasonex, 122 of whom received 200 mcg bid of Nasonex and 117 who received placebo. There were 221 males and 133 females between the ages of 18-81 years of age.

10.1.1.3. Parameters evaluated: The co-primary endpoints which were pre-specified were: 1) change from baseline (average of the last 7 days of the placebo run-in plus the baseline visit) in congestion/obstruction averaged over the first month of treatment using a 0-3 categorical scale; and 2) change from baseline to last assessment (endpoint) (at 4 months or the last visit carried forward) in bilateral polyp grade (sum of the scores of the polyps from the left and from the right side) during the entire 4 months of the studies as graded by investigator visual assessment by nasal endoscopy. Grading of polyps was done using a 0-3 scale, where 0 = no polyps, 1 = polyps in the middle meatus not reaching below the inferior border of the middle turbinate, 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate, and 3 + large polyps reaching to or below the lower border of the inferior turbinate or polyps medial to the middle turbinate. Both primary endpoints were required to be statistically significant for the 200 mcg bid dose of Nasonex in order to proceed to the testing of

the 200 mcg once a day dose compared to placebo. Secondary endpoints included evaluation of loss of smell, peak nasal inspiratory flow (PNIF), rhinorrhea and % responders. Loss of smell was pre-defined and designated a "key" secondary variable. Once the two primary outcome variables had been shown to be statistically significant, loss of smell was tested. Polyps were evaluated using nasal endoscopy. Symptoms were scored by the patient every morning prior to drug administration and were instantaneous. Congestion/obstruction was graded using a 0-3 categorical scale where 0 = normal breathing through the nose, no congestion present, 1 = mild congestion, breathing through the nose slightly altered but little or no discomfort, 2 = moderate congestion, breathing through the nose moderately altered, annoying and caused discomfort, and 3 = severe congestion, breathing through the nose was severely altered, interfered with daily activities and/or sleep. A "key" secondary efficacy variable was the change from baseline averaged over the first month of treatment in loss of smell. Improvement was pre-defined as a decrease in bilateral polyp grade from baseline of 1.0 or more (a scale of 0-6 for polyps on the right + polyps on the left) and a decrease in nasal congestion/obstruction from baseline to an average of the last 8 days of the study of 0.5 or more, using a categorical scale of 0-3 (v3, p57). Health-related quality of life (QOL) was evaluated using the SF-36 scales, a Work Productivity and Activity Inventory and a generic treatment satisfaction questionnaire (v3, p95). Physical examination was performed at screening and at the conclusion of the study. Nasal endoscopy was performed at screening, baseline, and after 1-4 months of treatment. Vital signs were measured at each visit. Laboratory tests were done at screening and at the conclusion of the study. 24 hour urinary free cortisol levels were obtained at baseline and at the conclusion of the study. PNIF was measured at each visit.

10.1.1.4. Drug administration: Nasonex was administered as 2 sprays of a 50 mcg/spray concentration in each nostril either once daily (200 mcg once daily) or twice daily (200 mcg bid).

10.1.1.5. Periods of evaluation:

Study visits were at screening (visit 1), at baseline (visit 2) and on day 8 and after 1, 2, 3, and 4 months of treatment (visits 3-7).

10.1.1.6. Data Analysis:

Analyses were based on all patients randomized to the study (ITT population). A confirmatory analysis of the primary efficacy variables was done on all randomized patients who met key eligibility and evaluability criteria, which were established prior to un-blinding the study. Consistency of results across centers was assessed for both primary efficacy outcome variables based on ANOVA, which included sources of variability due to treatment, center, asthma status and treatment-by-center interaction. For this assessment, smaller centers were combined to form large composite centers. The primary comparison was Nasonex 200mcg bid vs placebo. If this comparison showed a statistically significant difference for both endpoints, Nasonex 200 mcg once a day was compared to placebo. With a sample size of 100 patients per treatment group, the study had 90% power to detect at least 0.37 points in change from baseline over the first month of treatment in average congestion/obstruction assuming a standard deviation of 0.8 and at least 1.0 point in change from baseline to month 4 in bilateral polyp grade assuming a standard deviation of 1.44. With 100 patients per treatment group, a difference of 0.66 in bilateral polyp

grade would be detectable with 90% individual power. With 30 patients per treatment group, difference between treatment means of 32.3 in urinary free cortisol levels would be detectable with 90% power assuming a standard deviation of 37.9.

Two centers (centers 8 and 31) were terminated due to significant departure from GCP. The data from these two centers was excluded from the efficacy and safety analysis. The sponsor was asked to analyze the data including as well as excluding the data from these two sites. Excluding these two sites, there were 354 patients randomized to treatment at 44 centers in 10 countries. There were 115 patients who received Nasonex 200 mcg qd, 122 patients who received Nasonex 200 mcg bid and 117 patients who received placebo. There were 101 (88%) of patients who received Nasonex 200 mcg once a day, 109 (89%) of patients who received Nasonex 200 mcg bid and 95 (81%) of patients who received placebo who completed 4 months of treatment. At one site, there were 12 patients (4 in each of the three treatment groups) who received an expired batch of mometasone nasal spray for 1-3 days. Retained samples from this batch were tested and found to be within specifications.

10.1.1.7. Patient Disposition:

There were 14 discontinuations in the Nasonex 200 mcg qd group, 13 discontinuations in the Nasonex 200 mcg bid group, and 22 discontinuations in the placebo group. Adverse events were the reason for discontinuation in 2 patients in the Nasonex 200 mcg qd group, 4 patients in the Nasonex 200 mcg bid group and 4 patients in the placebo group (v3, p68, t8). There were 23 patients in the Nasonex 200 mcg qd group, 17 patients in the Nasonex 200 mc bid group and 27 patients in the placebo group who were excluded from the efficacy-evaluable data set because of protocol deviations (see table below)(v3, p69, t9).

Patient disposition in study 1925

	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo
Number of patients randomized	115	122	117
Efficacy evaluable subset of patients	92 (80%)	105 (86%)	90 (77%)
Excluded from evaluable analysis	23 (20%)	17 (14%)	27 (23%)
Non-compliance with study medications	5 (4%)	6 (5%)	12 (10%)
Unacceptable concomitant medications	6 (5%)	3 (2%)	1 (1%)
Insufficient washout	2 (2%)	1 (1%)	1 (1%)
Did not meet other evaluation criteria	15 (13%)	11 (9%)	22 (19%)

The 67 patients who were excluded from the efficacy-evaluable data analysis were included in the ITT analysis upon which the efficacy conclusions were based. There were two data sets used for evaluation and analysis: 1) all randomized patients; and 2) evaluable patients, i.e. all randomized patients who met key eligibility and evaluability criteria which were established prior to the un-blinding of the study. Analysis for treatment by center interaction did not reveal any such interaction.

10.1.1.8. Compliance:

Non-compliance was defined as the use of < 59% or > 138% of the study drug bottle weight. Since this study used a reference study drug bottle weight that could vary by 15%, the range was increased from the usual 70-120%. Patients were expected to use 800 mcg per day multiplied by the number of days the study drug was used and an additional factor to account for priming. Compliance, or lack thereof, was then confirmed by diary data where compliance was defined as at least 80% of the proposed doses being taken by the patient. Compliance with the dosing regimen occurred in 94% of patients (see table below). Patients who were non-compliant were included in the ITT analysis but not the efficacy-evaluable analysis (v3, p73).

Compliance with the dosing regimen in study 1925

Amount of drug taken	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo
< 59%	3 patients	5 patients	9 patients
>138%	2 patients	1 patient	3 patients

COMMENT: *The sponsor's approach to assessing compliance is reasonable and acceptable.*

10.1.1.9. Efficacy:

The treatment groups were comparable at entry in terms of demographic and disease characteristics. Baseline symptom scores were similar across the three treatment groups. There were similar numbers of patients in each treatment group who were less than 65 years of age and who were 65 years of age and older. Caucasians comprised 43-54% of the patients in the three treatment groups while Hispanics comprised 38-45%. The majority of patients had no history of asthma (79-82%). See the table below for baseline demographics.

Baseline demographics in study 1925

Study	Rx	Age (yrs) (mean)	Age 18-64	Age ≥65	Female/ Male %	Caucasian/ Black/ Asian/ Hispanic	Hx asthma %	Hx PAR %
1925 (v3, p72, t10)								
N=115	200 mcg qd	46.7	86%	14%	34/66	62/4/5/44	18	20
N=122	200 mcg bid	48.3	85%	15%	39/61	66/6/2/47	21	25
N=117	Placebo	47.5	87%	13%	39/61	50/11/0/53	21	17
1926								
N=102	200 mcg qd	47.2	90%	10%	30/70	64/0/7/28	15	14
N=102	200 mcg bid	47.6	90%	10%	38/62	65/1/8/28	19	18
N=106	Placebo	50.9	85%	15%	35/65	67/0/8/28	16	21
1925/1926								
N=217	200 mcg qd	46.9	88%	12%	32/68	126/4/12/72	17	17
N=224	200 mcg bid	48	88%	12%	39/61	131/7/10/75	20	21
N=223	Placebo	49.1	86%	14%	37/63	117/11/8/83	19	19

The number (%) of patients who received treatment for various durations (v5, p782)

Duration of treatment	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo
Number randomized	115	122	117
Any treatment	115	121	116
8 days of more	113	121	114
30 days or more	109	120	110
60 days or more	105	112	101
90 days or more	102	111	97
120 days or more	69	81	71
Randomized, not treated	0	0	1

10.1.1.9. Mean change from baseline in bilateral polyp grade using the ITT population (v3, p75, t11, p170):

Mean change from baseline in bilateral polyp grade was a co-primary efficacy variable. A reduction in mean bilateral polyp grade from baseline was seen in all treatment groups (see table below). There was a greater reduction seen after the administration of Nasonex 200 mcg once a day than after the administration of Nasonex 200 mcg bid. There was a statistically significantly greater decrease in bilateral polyp grade seen after administration of either dosage of Nasonex at all time points over the 4 months of treatment than was seen in the placebo group, despite the fact that a considerable placebo effect was seen. There was no significant difference in the results based on analysis of the efficacy-evaluable population (v3, p172) or based on age (v3, p174-175), gender (v3, p176177) or race (v3, p178, 179). The relatively small number of patients > 65 years of age and the small number of patients with asthma prevent make it difficult to draw any meaningful conclusions about efficacy in these subsets of patients (v3, p174) (v3, p181, p182).

Mean change from baseline in bilateral polyp grade using the ITT population in Study 1925

Visit	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value Nasonex 200 mcg qd vs placebo	P value Nasonex 200 mcg bid vs placebo
Baseline	4.21 (n=112)	4.27 (n=121)	4.25 (n=114)		
Month 1	-0.57 (n=111)	- 0.61 (n=119)	-0.33 (n=114)	0.05	0.02
Month 2	-0.87 (n=107)	-0.83 (n=114)	- 0.52 (n=104)	0.04	0.06
Month 3	-1.10 (n=102)	-0.93 (n=111)	- 0.56 (n=99)	0.003	0.04
Month 4	-1.20 (n=102)	-1.14 (n=108)	- 0.63 (n=94)	0.005	0.01
Endpoint	-1.13 (n=112)	-0.95 (n=121)	- 0.49 (n=114)	< 0.001	0.01

COMMENT: *A greater mean change from baseline in bilateral polyp grade was seen after a lower dose of Nasonex, i.e. 200 mcg once a day, compared with 200 mcg bid. However, both doses of Nasonex produced a statistically significantly greater mean decrease in polyp grade than did placebo, although there was a mean reduction in polyp grade seen in patients who received placebo as well as patients who received Nasonex. The effectiveness of Nasonex in polyp reduction has been demonstrated in this study. The data from this study would support a dosage of Nasonex 200 mcg once a day in addition to a dosage of 200 mcg bid in the treatment of nasal polyposis.*

10.1.1.9. Congestion/obstruction symptom scores (v3, p78, t12, p184):

A statistically significant mean decrease in nasal congestion/obstruction was seen with both doses of Nasonex compared to placebo in a dose-dependent fashion at all time points throughout the study. Mean change in congestion/ obstruction was a co-primary efficacy variable. The results were not significantly different when analyzed using the efficacy-evaluable data (v3, p186), or when analyzing the results in terms of presence of asthma (v3, p195, 196), age (v3, p188, 189), gender (v3, p190, 191) or race (v3, p192, 193).

Mean change in congestion/obstruction analyzed using the ITT population in study 1925

Time-point	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value Nasonex 200 mcg qd vs placebo	P value Nasonex 200 mcg bid vs placebo
Baseline	2.29 (n=113)	2.35 (n=122)	2.28 (n=114)		
Week 1	-0.24 (n=113)	-0.37 (n=122)	-0.16 (n=114)	0.20	0.001
Week 2	-0.49 (n=113)	-0.57 (n=121)	-0.20 (n=111)	< 0.001	< 0.001
Week 3	-0.55 (n=111)	-0.72(n=121)	-0.28 (n=110)	0.002	< 0.001
Week 4	-0.58 (n=110)	-0.76 (n=121)	-0.32 (n=109)	0.002	< 0.001
Month 1 **	-0.47 (n=113)	-0.61 (n=122)	-0.24 (n=114)	0.001	< 0.001
Month 2	-0.68 (n=109)	-0.83 (n=119)	-0.32 (n=107)	< 0.001	< 0.001
Month 3	-0.78 (n=104)	-1.01 (n=112)	-0.48 (n=101)	0.004	< 0.001
Month 4	-0.86 (n= 102)	-1.10 (n=109)	-0.50 (n=96)	0.001	< 0.001
Months 1-2	-0.57 (n=113)	-0.72 (n=122)	-0.28 (n=114)	< 0.001	< 0.001
Months 3-4	-0.83 (n=104)	-1.07 (n=112)	-0.48 (n=101)	< 0.001	< 0.001

** Specified as time point for analysis in comparison with placebo.

COMMENT: *There was a statistically significantly greater mean reduction in nasal congestion/obstruction after administration of Nasonex in a dose-dependent manner than was seen after the administration of placebo. This is consistent with the demonstrated effectiveness of Nasonex on nasal symptoms in the data submitted for approval of this drug product for allergic rhinitis. Over the last two months of treatment, the improvement of 0.83 after 200 mcg once a day and 1.07 after 200 mcg bid represents a clinically significant effect as well. After one month of treatment, the effect size of 0.47 in the 200 mcg once a day group and 0.62 in the 200 mcg bid group is consistent with what has been demonstrated in other studies with intranasal cortico-steroids and is considered to represent a change that is consistent with clinical efficacy. Based on the data in this study, Nasonex is effective for reduction in nasal congestion/ obstruction in patients who have bilateral nasal polyposis. The number of patients in this study who had documented evidence of allergic rhinitis is not stated. It is, therefore, unclear if exclusion of such patients from the data analysis would produce any different result in the comparison between treatment groups.*

10.1.1.9. Loss of smell:

Loss of smell was considered a "key" secondary efficacy variable. At baseline, moderate-severe loss of smell was reported by > 70% of patients in this study. For change from baseline, see table below (v3, p81, t13, p198). Loss of smell was assessed using a categorical scale of 0-3, with 0 = normal sense of smell, 1 = sense of smell mildly lost with no perception of subtle odors, e.g.

strawberry, orange, lemon, 2 = sense of smell moderately lost with no perception of more characteristic odors, e.g. garlic, onion, coffee, and 3 = sense of smell totally lost, patient could not smell anything. The analytical approach for improvement in smell was pre-specified by the applicant.

Change from baseline in loss of smell in study 1925

Time-point	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value N 200 qd vs placebo	P value N 200 bid vs placebo
Baseline	2.27 (n=113)	2.14 (n=122)	2.32 (n=114)		
Week 1	-0.20 (n=113)	-0.14 (n=122)	-0.05 (n=114)	0.02	0.17
Week 2	-0.33 (n=113)	-0.21 (n=121)	-0.04 (n=111)	< 0.001	0.04
Week 3	-0.47 (n=111)	-0.31 (n=121)	-0.12 (n=110)	< 0.001	0.03
Week 4	-0.48 (n=110)	-0.31 (n=121)	-0.16 (n=109)	< 0.001	0.09
Month 1 **	-0.37 (n=113)	-0.24 n=122)	-0.09 (n=114)	< 0.001	0.04
Month 2	-0.42 (n=109)	-0.39 (n=119)	-0.18 (n=107)	0.01	0.03
Month 3	-0.49 (n=104)	-0.52 (n=112)	-0.23 (n=101)	0.02	0.006
Month 4	-0.60 (n=102)	-0.54 (n=109)	-0.27 (n=96)	0.004	0.02
Months 1-2	-0.41 (n=113)	-0.32 (n=122)	-0.14 (n=114)	< 0.001	0.03
Months 3-4	-0.56 (n=104)	-0.55 (n=112)	-0.25 (n=101)	0.003	0.004

** pre-specified evaluation timepoint

COMMENT: *Although both doses of Nasonex were statistically significantly greater at most time points compared to placebo, a greater effect was seen with 200 mcg once a day than was seen with 200 mcg bid.* (b) (4)

10.1.1.9. Other symptoms and PNIF (v3, pgs82-87, t14-16, p200,202,204):

Consistently across all secondary parameters, there was a statistically significantly greater improvement from baseline after treatment with either dose of Nasonex compared to treatment with placebo at all time points except week 1 with the lower dose of Nasonex in regard to PNIF. Rhinorrhea was evaluated using a 0-3 categorical scale where 0 = none, 1 = mild requiring blowing of nose with little or no discomfort, 2 = moderate requiring frequent blowing of the nose, annoying and caused discomfort, and 3 = severe, consistent blowing of the nose, interfered with daily activities and/or sleep. PND was evaluated using a 0-3 categorical scale where 0 = none, 1 = mild, causing little or no discomfort, 2 = moderate, annoying, causing discomfort, and 3 = severe, interfered with daily activities and/or sleep. PNIF was obtained using a nasal peak flow meter. Patients measured PNIF each morning right after assessment of symptoms and before drug administration testing 3 times and recording the highest result.

Change in secondary endpoints in study 1925

Time-point	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value N 200 mcg qd vs placebo	P value N 200 mcg bid vs placebo
Rhinorrhea					
Baseline	1.66 (n=113)	1.62 (n=122)	1.58 (n=114)		
Month 1	-0.29 (n=113)	-0.42 (n=122)	-0.03 (n=114)	< 0.001	< 0.001
Months 3-4	-0.50 (n=104)	-0.70 (n=112)	-0.24 (n=101)	0.01	< 0.001
Post-nasal drip					
Baseline	1.55 (n=113)	1.43 (n=122)	1.48 (n=114)		
Month 1	-0.36 (n=113)	-0.24 (n=122)	-0.01 (n=114)	< 0.001	0.001
Months 3-4	-0.54 (n=104)	-0.48 (n=112)	-0.11 (n=101)	< 0.001	< 0.001
PNIF					
Baseline	87.6 L/min (n=113)	92.7 L/min (n=121)	83.9 L/min (n=114)		
Month 1	21.1 (n=113)	25.1 (n=121)	10.3 (n=114)	0.003	< 0.001
Months 3-4	39.1 (n=104)	43.5 (n=112)	14.6 (n=101)	< 0.001	< 0.001

COMMENT: *The secondary parameters evaluated during this study support the efficacy of Nasonex at a dose of 200 mcg once a day and a dose of 200 mcg bid in the treatment of* (b) (4) *nasal* (b) (4) (b) (4)

10.1.1.9. Percentage of patients with improvement (v3, p88, t17, p206):

Improvement was defined as a decrease in bilateral polyp grade of 1.0 or more from baseline to the last visit and a decrease in congestion /obstruction score of 0.5 or more from baseline to the average of the last 8 days of the study. Using this definition, 43% (48/111) patients who received Nasonex 200 mcg once a day and 57% (68/119) of patients who received Nasonex 200 mcg bid improved compared to 34% (38/112) of patients who received placebo. There was a statistically significant difference between the 200 mcg bid dose of Nasonex and placebo (p <0.001) but not between the 200 mcg once a day dose of Nasonex and placebo (p=0.16).

10.1.1.9. Individual patient improvement in polyp grade and congestion/obstruction *based on a one point or greater reduction from baseline to endpoint* can be seen in the table below (v3, p146-166)

Number of patients (%) who had improvement from baseline in polyp grade, congestion/obstruction and/or both

Treatment	↓ polyp grade ≥ 1	↓ congestion ≥ 1	↓ both polyp grade and congestion ≥ 1
Nasonex 200 mcg qd	73/112 (65%)	59/113 (52%)	44/112 (39%)
Nasonex 200 mcg bid	80/121 (66%)	77/122 (63%)	59/121 (49%)
Placebo	53/114 (47%)	38/114 (33%)	26/114 (23%)

10.1.1.9. Investigator's assessment of therapeutic response (v3, p89, t18, p 211):

This assessment used a categorical scale of 0 = complete relief, virtually no symptoms present, 1 = marked relief, symptoms greatly improved, 2 = moderate relief, symptoms present, but noticeably improved, 3 = slight relief, symptoms present and only minimal improvement and 4 = no relief, symptoms unchanged or worse than baseline. There was a statistically significantly greater improvement based on this global assessment at endpoint in the patients who received either dose of Nasonex compared to placebo ($p < 0.001$).

EFFICACY CONCLUSIONS: The efficacy of Nasonex Nasal Spray was demonstrated in study 1925. There was a statistically significant difference between both dosages of Nasonex and placebo for both of the co-primary endpoints and most of the secondary endpoints. It should be noted that for reduction in polyp size, a dose response was not seen, i.e. a greater reduction was seen with the lower dosage (200 mcg once a day).

10.1.1.10. Safety:

More than 89% of the patients who received Nasonex and 83% of the patients who received placebo took the study drug for at least 90 days. At least 60% of patients in each treatment group took study drug for at least the pre-specified 120 days (v3, p 98, t20).

10.1.1.10. Adverse events:

Treatment-emergent adverse events were defined as those adverse events that began while the patient was receiving treatment or began prior to treatment but increased in severity while receiving treatment. Overall the incidence of adverse events was 49% in the group that received 200 mcg per day of Nasonex, 49% in the group that received 200 mcg bid and 55% of the patients who received placebo. There were 3 patients (3%) in the Nasonex once a day group who had a *severe* adverse event (headache, tooth abscess associated with an URI and sinusitis, and back pain) compared to 7 (6%) in the Nasonex 200 mcg bid group (headache, migraine, appendicitis, viral infection, joint sprain, alcoholism, and dyspnea) and 5 (4%) in the placebo group (headache, loss of consciousness, epistaxis aggravated, rhinorrhea associated with sneezing and dental procedure)(v3, pgs 222-245). There were no severe adverse events that occurred in more than one patient or that were considered related to the study drug (v3, p106, t23). There were 2 *serious* adverse events recorded, one in the 200 mcg bid group and one in the placebo group. The patient who had received Nasonex developed appendicitis. There were 10 *discontinuations* due to adverse events, 2 of which were in the Nasonex once a day group, 4 of which were in the Nasonex bid group and 4 of which were in the placebo group. The two patients in the Nasonex 200 mcg bid group were discontinued because of an unlikely-related increase in free cortisol in the urine and moderate possibly related urticaria. The four patients in the Nasonex 200 mcg bid group were discontinued because of moderately severe probably related headache, unlikely related mild-moderate sinusitis (2) and unlikely related moderate panic attack. The patients in the placebo group who were discontinued were discontinued because of unlikely related moderate sinusitis, possibly related severe nasal burning, mild unlikely related nightmares and possibly related "aggravated" epistaxis (v3, pgs 327-329). There were 7 patients who *interrupted treatment* because of an adverse event, 2 in the Nasonex 200 mcg once a day group, 3 patients in the Nasonex 200 mcg bid group and 2 patients in the placebo group. Treatment interruption occurred because of severe unlikely related tooth abscess and URI

in one patient and moderate possible alopecia in another patient in the Nasonex 200 mcg qd group, severe unlikely related appendicitis, mild unlikely related constipation as well as mild probably related epistaxis and nasal irritation in one patient in the Nasonex 200 mcg bid group and moderate somnolence and severe unlikely related loss of consciousness in one patient and moderate unlikely URI in another patient in the placebo group (v3, pgs 338-340). *Epistaxis* was reported more frequently after the use of Nasonex than after the use of placebo. All reports of epistaxis were mild-moderate in severity. However, one patient who received placebo, developed severe epistaxis considered to be related to the study drug and resulted in discontinuation, one patient interrupted study treatment due to epistaxis and one patient required additional treatment. Epistaxis was reported by 17% of Caucasian patients who received Nasonex 200 mcg bid compared to 11% of Caucasian patients who received Nasonex 200 mcg once a day and 4% of Caucasian patients who received placebo (v3, p296). By comparison in Hispanic patients, 6% of both the Nasonex 200 mcg bid and placebo groups developed epistaxis compared to 2% of patients who received Nasonex 200 mcg once a day (v3, p391).

Adverse events (considered related and unrelated to administration of the study drug) occurring in at least 3% of patients in any treatment group in study 1925 (v3, p101-102, t21)

Adverse events	Nasonex 200 mcg QD N=115	Nasonex 200 mcg bid N=122	Placebo N=117
Dizziness	0	1(1%)	3 (3%)
Headache	9 (8%)	10 (8%)	14 (12%)
Hypertension	1 (1%)	0	4 (3%)
Viral infection	3 (3%)	3 (2%)	1 (1%)
Pharyngitis	6 (5%)	3 (2%)	3 (3%)
Sinusitis	4 (3%)	4 (3%)	6 (5%)
URI	12 (10%)	13 (11%)	12 (10%)
Overdose	3 (3%)	1 (1%)	5 (4%)
Back pain	4 (3%)	2 (2%)	2 (2%)
Bronchitis	6 (5%)	3 (2%)	2 (2%)
Epistaxis	8 (7%)	15 (12%)	6 (5%)
Nasal dryness	2 (2%)	2 (2%)	3 (3%)

There were 28 patients (24%) of the placebo patients who had an adverse event that was considered related to the study drug compared with 19 (17%) of the Nasonex 200 mcg once a day and 31 (25%) of the Nasonex 200 mcg bid groups who had treatment-related adverse events. The only treatment-related adverse event that occurred with an incidence greater than 1% and a higher incidence in patients who received Nasonex than in patients who received placebo was throat irritation (2% of the Nasonex 200 mcg bid group compared with none in the other two groups)(v3, p104, t22). There were 14% (16/115) of the patients in the Nasonex 200 mcg qd group, 15% (18/122) of the patients in the Nasonex 200 mcg bid group and 13% (15/117) of the patients in the placebo group who were 65 years of age and older.

None of the adverse events reported occurred significantly more frequently based on gender (v3, pgs266-277) in the active treatment groups than in the placebo groups, with the exception of epistaxis (v3, p276) that occurred in males more frequently. There were no adverse events that

occurred with a significantly greater frequency in patients 18-64 years of age compared to patients 65 years and older, although the small number of patients 65 years of age and older in each treatment group (16 received Nasonex 200 mcg once a day, 18 received Nasonex 200 mcg bid and 15 received placebo) make any comparisons between these two age groups difficult (v3, p289).

COMMENT: *There was no indication from the adverse events reported in this study that there should be any safety concern related to the administration of Nasonex Nasal Spray. Epistaxis is a recognized adverse effect that can occur from administration of corticosteroid nasal sprays and even though there was an increased incidence of epistaxis in the higher dose Nasonex group, there was no patient receiving Nasonex who developed severe or serious epistaxis. Bronchitis and pharyngitis were seen more frequently in patients who received Nasonex but were not dose-related and in all likelihood occurred spontaneously without relationship to the study drug.*

10.1.1.10. Laboratory tests:

Laboratory tests were obtained at baseline and at visit 7. Median, minimum and maximum values at baseline and endpoint in regard to changes from baseline by treatment for routine laboratory tests were evaluated. Changes noted after administration of Nasonex at the two dosage levels was evaluated first and then compared with the change seen after administration of placebo if there was a significant change seen in the Nasonex groups. No significant changes were seen in hematology or blood chemistry values when all patients were included in the analysis (v4, pgs368-426). Then laboratory results were evaluated in terms of gender (v4, pgs428-503), age (18-64 vs 65 years and older) (v4, pgs505-580) and race (v4, pgs 582-694). See table below for number (%) of patients with a shift from a normal baseline value to a value outside the normal reference range for selected lab tests. These were lab tests where the incidence of such a change was greater in one or both of the Nasonex groups than in the placebo group.

Laboratory test	N	Baseline normal Outside normal reference range after treatment
Hematocrit		Low
Nasonex 200 mcg qd	96	2 (2%)
Nasonex 200 mcg bid	98	0
Placebo	90	0
Glucose		High
Nasonex 200 mcg qd	100	4 (4%)
Nasonex 200 mcg bid	105	5 (5%)
Placebo	97	1 (1%)

SGOT		High
Nasonex 200 mcg qd		6 (6%)
Nasonex 200 mcg bid		8 (8%)
Placebo		2 (2%)
SGPT		High
Nasonex 200 mcg qd	102	2 (2%)
Nasonex 200 mcg bid	107	9 (8%)
Placebo	97	1 (1%)

COMMENT: Intranasal corticosteroids are metabolized in the liver. Mometasone undergoes extensive metabolism to metabolites regulated by the cytochrome P-450 3A4 enzyme system. Liver mixed-function oxidases and glucuronyl transferases are important in the metabolism of many glucocorticosteroids. As a result, liver disease, drugs and other chemical that modify liver function can affect the biologic half-life of glucocorticosteroids. However, intranasal corticosteroids have not been reported to produce an increase in liver enzymes and there is nothing unique about this drug product that would support any concern about its hepatic effect. The greater incidence of elevated glucose levels in patients who received Nasonex was not seen in study 1926 described below, but could represent a systemic effect from intranasal mometasone in some patients. Overall, the sponsor has demonstrated the safety of Nasonex at a dosage of 200 mcg once a day and a dosage of 200 mcg bid.

There was one patient (pt 700), a 33 year old male who received Nasonex 200 mcg once a day who had an elevated SGPT at baseline (134 U/L)(normal range 6-43 u/L) but was included in the study because the patient appeared to be in good health and did not have symptoms or signs of liver disease. The patient had a further increase in SGPT after treatment with Nasonex to 235 U/L on day 8 (visit 3) that was repeated and was 240 U/L. The patient had an associated increase in SGOT to 90 U/L. The patient was referred to a hepatologist and found to have inflammatory hepatopathy on hepatic ultrasound. Subsequently, these tests were repeated and the SGPT was 26 U/L and the SGOT was 23 U/L. During the period when the liver enzymes were elevated the patient was asymptomatic. There was another patient (pt 548) who received

Nasonex 200 mcg once a day who had an SGOT at baseline of 97 U/L that was 35 U/L at the end of the study and had no adverse event during the study (v3, p115, t27).

COMMENT: *The patient who was entered into the study with an elevation in SGPT could have experienced a further elevation in SGPT because of a continuation of the process that caused the elevation in SGPT at baseline or because of an effect of the study drug. It is possible therefore that Nasonex had an effect on liver enzymes. However, liver enzymes returned to normal and there was no further assessment of liver histopathology. Therefore, this finding should be considered in conjunction with the effect, if any, in other studies of Nasonex on liver function.*

24 hour urinary free cortisol levels: Samples were collected starting from the morning prior to visit 1 and visit 7 or upon early termination. There were 164 patients from 28 sites who had baseline 24 hour urinary free cortisol levels and at least one post-baseline value, and who were included in the analysis. Although the protocol only required 90 patients to be tested, by the time that the sites were notified that the accrual target had been reached, 213 patients had been tested. For mean changes from baseline in the three treatment groups and pair-wise p values comparing the treatment groups, see the table below (v3, p118, t28). One patient (#43-643) who received 200 mcg bid of Nasonex had a baseline value of 18.1 nmol/mmol and an endpoint value of 74.3 nmol/mmol. There were 18% of the Nasonex 200 mcg qd group, 5% of the Nasonex bid group and 11% of the placebo group who had values above the level of quantitation at baseline and below the level of quantitation at endpoint.

24 hour urinary free cortisol corrected for creatinine – nmol/mmol (patients without missing values at both visits) – study 1925

Time-point	Nasonex 200 mcg QD (n=49)	Nasonex 200 mcg bid (n=59)	Placebo (n=56)	P value comparison of Nasonex 200 mcg qd and placebo	P value comparison of Nasonex 200 mcg bid and placebo
Baseline (nmol/mmol)	5.1	5.9	5.3	0.86	0.34
End-point (nmol/mmol)	4.0	7.2	4.4	0.82	0.03
Change from baseline (nmol/mmol)	-1.1	1.2	-0.9	0.89	0.09

COMMENT: The data from this subset of patients reinforced by data obtained from clinical pharmacology studies in patients with allergic rhinitis gives no indication that there is any clinically significant effect on HPA axis in patients receiving Nasonex Nasal Spray.

10.1.1.10. Vital signs (v4, pgs 717-728):

Vital signs were obtained at each visit and included blood pressure, pulse rate and respiratory rate. No clinically significant changes in median, minimum or maximum values were seen in any of the treatment groups for systolic blood pressure, diastolic blood pressure, pulse rate or respiratory rate. There were no clinically significant median changes in vital signs based on gender (v4, pgs720-723), age (patients 18-64 vs patients 65 years of age and older) (v4, pgs725-728) or race (v5, pgs730-735). There were 3 patients (2%) in the 200 mcg once a day group who had an increase in systolic blood pressure of greater than 30%, whereas there were no patients in

the other two treatment groups who had such an increase (see table below; v5, p737). There was no clinically significant difference in terms of change in diastolic blood pressure between the three treatment groups.

Incidence of percentage change in vital signs in study 1925

Systolic blood pressure	> 30% ↓	11- 30 % ↓	10-30% ↑	> 30% ↑
Nasonex 200 mcg qd	0	14 (13%)	8 (7%)	0
Nasonex 200 mcg bid	0	10 (8%)	11 (9%)	3 (2%)
Placebo	0	7 (6%)	11 (9%)	0
Diastolic blood pressure				
Nasonex 200 mcg qd	0	27 (24%)	18 (16%)	1 (1%)
Nasonex 200 mcg bid	1 (1%)	24 (20%)	23 (19%)	3 (2%)
Placebo	1 (1%)	22 (19%)	22 (19%)	6 (5%)
Pulse rate				
Nasonex 200 mcg qd	0	21 (19%)	43 (39%)	2 (2%)
Nasonex 200 mcg bid	0	24 (29%)	48 (39%)	4 (3%)
Placebo	0	17 (15%)	47 (41%)	6 (5%)

COMMENT: Based on the data in this study, no safety concerns are raised about the administration of Nasonex Nasal Spray at either a dose of 200 or 400 mcg per day.

CONLUSION: The data from this study supports the efficacy and safety of Nasonex at a dose of 200 mcg once a day and a dose of 200 mcg twice a day in the treatment of nasal polyps.

10.1.2. Study 1926 (v8-11):

Study 1926 was identical in design to study 1925 except that 24 urinary free cortisol was not evaluated in a subset of patients and QOL assessment was done.

10.1.2.1 Study Characteristics:

There were 24 centers in this study in 17 countries, in the US and outside the US. The study was a multicenter, randomized, double-blind, placebo-controlled, parallel group study with a 14 days single-blind placebo run-in period and 4 months of randomized treatment. Randomization was stratified by the presence or absence of concomitant asthma. There were 310 patients randomized; 102 of whom received 200 mcg once a day of Nasonex, 102 of whom received 200 mcg bid of Nasonex and 106 who received placebo. There were 221 males and 133 females between the ages of 18-86 years of age. Patients had bilateral nasal polyps and clinically significant nasal congestion/obstruction with an AM instantaneous score of 2 or greater for each of the last 7 days of the 2 week run-in period. Patients with asthma could be entered into the study if they had an FEV-1 of 80% or greater and no recent exacerbation. If a patient was receiving inhaled corticosteroids the dose could not exceed 840 mcg per day of beclomethasone or an equivalent dose of another corticosteroid (up to 600 mcg per day of budesonide, up to 2000

mcg per day of flunisolide, up to 660 mcg per day of fluticasone and up to 1000 mcg per day of triamcinolone) for at least one month prior to screening and had to remain stable throughout the study.

Nasonex was administered as 2 sprays of a 50 mcg/spray concentration in each nostril either once daily (200 mcg once daily) or bid (200 mcg bid). There were two primary efficacy variables: 1) change from baseline (the average of the last 7 days of the baseline period plus the day of the baseline visit) in congestion/obstruction averaged over the first month of the treatment period; and 2) change from baseline to endpoint (at 4 months or the last visit carried forward) in the bilateral polyp grade (sum of the scores of the polyps from the left and from the right side). Polyps were evaluated using nasal endoscopy. Grading of polyps was done using a 0-3 scale, where 0 = no polyps, 1 = polyps in the middle meatus not reaching below the inferior border of the middle turbinate, 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate, and 3 + large polypos reaching to or below the lower border of the inferior turbinate or polyps medial to the middle turbinate. Symptoms were scored by the patient every morning prior to drug administration and were instantaneous. Congestion/obstruction was graded using a 0-3 categorical scale where 0 = normal breathing through the nose, no congestion present, 1 = mild congestion, breathing through the nose slightly altered but little or no discomfort, 2 = moderate congestion, breathing through the nose moderately altered, annoying and caused discomfort, and 3 = severe congestion, breathing through the nose was severely altered, interfered with daily activities and/or sleep. A "key" secondary efficacy variable was the change from baseline averaged over the first month of treatment in loss of smell which was evaluated by a pre-specified analytical approach. Improvement was pre-defined as a decrease in bilateral polyp grade from baseline of 1.0 or more (a scale of 0-6 for polyps on the right + polyps on the left) and a decrease in nasal congestion/obstruction from baseline to an average of the last 8 days of the study of 0.5 or more, using a categorical scale of 0-3 (v3, p57). Health-related quality of life (QOL) was evaluated using the SF-36 scales, a Work Productivity and Activity Inventory and a generic treatment satisfaction questionnaire (v3, p95). Study visits were at screening (visit 1), at baseline (visit 2) and on day 8 and after 1, 2, 3, and 4 months of treatment (visits 3-7). Physical examination was performed at screening and at the conclusion of the study. Nasal endoscopy was performed at screening, baseline, and after 1-4 months of treatment. Vital signs were measured at each visit. Laboratory tests were done at screening and at the conclusion of the study. 24 hour urinary free cortisol levels were obtained at baseline and at the conclusion of the study. PNIF was measured at each visit. QOL was obtained at baseline and after 1 and 4 months of treatment.

Analyses were based on all patients randomized to the study (ITT population). A confirmatory analysis of the primary efficacy variables was done on all randomized patients who met key eligibility and evaluability criteria, which were established prior to un-blinding the study. Consistency of results across centers was assessed for both primary efficacy outcome variables based on ANOVA, which included sources of variability due to treatment, center, asthma status and treatment-by-center interaction. For this assessment, smaller centers were combined to form large composite centers. The primary hypothesis was that a dosage of 200 mcg bid was effective relative to placebo in the treatment of nasal polyps and the secondary hypothesis was that a dosage of 200 mcg once a day in the AM was effective relative to placebo in terms of the treatment of nasal polyps. Each of these hypotheses was expressed as a composite of change in

bilateral nasal polyp grade from baseline to the last visit at month 4 (sum of left and right nasal cavity grades) and change from baseline in congestion score averaged over the first month of treatment (v10, p1085). Two subsets of patients were analyzed, all randomized patients and evaluable patients, i.e. patients who met key eligibility and evaluability criteria.

The primary comparison was Nasonex 200mcg bid vs placebo. If this comparison showed a statistically significant difference for both endpoints, Nasonex 200 mcg once a day was compared to placebo. With a sample size of 100 patients per treatment group, the study had 90% power to detect at least 0.37 points in change from baseline over the first month of treatment in average congestion/obstruction assuming a standard deviation of 0.8 and at least 1.0 point in change from baseline to month 4 in bilateral polyp grade assuming a standard deviation of 1.44. With 100 patients per treatment group, a difference of 0.66 in bilateral polyp grade would be detectable with 90% individual power. With 30 patients per treatment group, difference between treatment means of 32.3 in urinary free cortisol levels would be detectable with 90% power assuming a standard deviation of 37.9.

10.1.2.2 Patient Disposition:

Number (%) of randomized patients who completed randomized treatment, number (%) who discontinued and reasons for discontinuation in study 1926 (v8, p61, t8)

Category	Nasonex 200 mcg qd	Nasonex 200 mcg bid	placebo
Patients randomized	102	102	108
Patients completed study	94 (92%)	93 (91%)	87 (82%)
Patients discontinued	8 (8%)	9 (9%)	19 (18%)
d/c due to adverse event	0	0	1 (1%)
d/c due to treatment failure	1 (1%)	3 (3%)	5 (5%)
d/c lost to follow-up	0	0	2 (2%)
d/c did not wish continue	3 (3%)	1 (1%)	4 (4%)
d/c non-compliance	2 (2%)	3 (3%)	1 (1%)
d/c did not meet entry criteria	2 (2%)	2 (2%)	6 (6%)

Patients who were excluded from the efficacy-evaluable data set because of protocol deviations in study 1926 (see table below) (v8, p62, t9).

	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo
Number of patients randomized	102	102	106
Efficacy evaluable subset of patients	79 (7%)	78 (76%)	76 (72%)
Excluded from evaluable analysis	23 (23%)	24 (24%)	30 (28%)
Non-compliance with study medications	8 (8%)	12 (12%)	8 (8%)
Unacceptable concomitant medications	5 (5%)	3 (3%)	6 (6%)
Insufficient washout	2 (2%)	1 (1%)	2 (2%)
Did not meet other evaluation criteria	13 (13%)	14 (14%)	21 (20%)

Study compliance was defined as the use of 59%-138% of the reference study drug bottle weight. The number of patients in each treatment group who were non-compliant can be seen in the table below (v8, p66).

Amount of drug taken	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo
< 59%	6 patients	10 patients	5 patients
>138%	2 patients	2 patient	3 patients

10.1.2.3. Efficacy:

The treatment groups were comparable at entry in terms of demographic and concomitant disease characteristics, e.g. history of asthma. Baseline symptom scores were similar across the three treatment groups. There were similar numbers of patients in each treatment group who were less than 65 years of age and who were 65 years of age and older. Caucasians comprised 64-67% of the patients in the three treatment groups while Hispanics comprised 28%. The majority of patients had no history of asthma (81-85%).

10.1.2.4. Mean change from baseline in bilateral polyp grade using the ITT population (v8, p69, t11, p141): A reduction in mean bilateral polyp grade from baseline was seen in all treatment groups (see table below). Mean change from baseline in bilateral polyp grade was a co-primary efficacy variable. There was a greater reduction seen after the administration of Nasonex 200 mcg bid than after the administration of Nasonex 200 mcg once a day, although the improvement after 200 mcg bid was not statistically significantly different than placebo (p=0.08). A considerable placebo effect was seen. There was no significant mean difference in the results based on analysis of the efficacy-evaluable population (v8, p143). On the other hand, mean improvement in patients who received 200 mcg once a day was less than or essentially the same in patients who received placebo if patients were younger than 65 years of age (n=92)(v8, p145-146), males (n=70) (v8, p147-148) or non-Caucasians (n=38) (v8, p149-150). Patients 65 years of age and older (n=9), females (n=31) and Caucasians (n=63) had a greater decrease after 200 mcg once a day than after placebo. The relatively small number of patients > 65 years of age and the small number of patients with asthma prevent, according to the sponsor, any meaningful conclusions with respect to the impact of these elderly age (v8, p145) or asthma on reduction in polyp grade (v8, p152,153). There was a slight imbalance in baseline polyp grade. When baseline polyp grade was added as a covariate in the analysis, there was a statistically significant difference between the change seen in the Nasonex 200 mcg bid group and the placebo group at endpoint. This analysis was not pre-specified. *However, this post-hoc analysis is justified based on the importance of including baseline as a covariate which was demonstrated in study Q99-925-01.*

Mean change from baseline in bilateral polyp grade using the ITT population in Study 1926

Visit	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value Nasonex 200 mcg qd vs placebo	P value Nasonex 200 mcg bid vs placebo
Baseline	4.00 (n=101)	4.10 (n=101)	4.17 (n=100)		
Month 1	-0.36 (n=100)	- 0.51 (n=100)	-0.34 (n=97)	0.91	0.23
Month 2	-0.52 (n=96)	-0.88 (n=97)	- 0.56 (n=93)	0.81	0.06
Month 3	-0.61 (n=97)	-0.89 (n=96)	- 0.56 (n=89)	0.77	0.07
Month 4 **	-0.81 (n=93)	-0.98 (n=93)	- 0.78 (n=88)	0.88	0.27
Endpoint	-0.76 (n=101)	-0.98 (n=101)	- 0.67 (n=100)	0.62	0.08

** specified as time point for analysis in comparison with placebo

COMMENT: A greater mean change from baseline in bilateral polyp grade was seen after administration of Nasonex 200 mcg bid compared with 200 mcg once a day. However, neither dosage of Nasonex produced a statistically significantly greater mean decrease in polyp grade than did placebo, although there was a mean reduction in polyp grade seen in patients who received placebo as well as patients who received Nasonex. Although there is a strong trend favoring the Nasonex 200 mcg bid dosage over placebo, there was not a statistically significant difference between either dosage of Nasonex and placebo in terms of mean polyp grade unless the analysis included baseline as a co-variate. When this re-analysis was done, there was a statistically significant difference between Nasonex 200 mcg bid and placebo (p = 0.05). Given the importance of baseline balance in terms of polyp size as demonstrated in study Q99-925-01 (see discussion below), this re-analysis can be accepted as demonstrating the effectiveness of Nasonex at at dosage of 200 mcg bid in reducing polyp size and supports the findings in study 1925.

10.1.2.4. Congestion/obstruction symptom scores (v8, p71, t12, p): A statistically significant mean decrease in nasal congestion/obstruction was seen with both doses of Nasonex compared to placebo in a dose-dependent fashion at most time points throughout the study. Mean change in congestion/ obstruction was a co-primary efficacy variable. Average change from baseline was taken over each of the four months and over each of the first four weeks. The results were not significantly different when analyzed using the efficacy-evaluable data (v8, p157), or when analyzing the results in terms of presence of asthma (v8, p166, 167), age (v8, p159, 160), gender (v8, p161, 162) or race (v8, p163, 164).

Mean change from baseline in nasal congestion/obstruction using the ITT population in Study 1926

Time-point	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value Nasonex 200 mcg qd vs placebo	P value Nasonex 200 mcg bid vs placebo
Baseline	2.23 (n=101)	2.20 (n=100)	2.18 (n=104)		
Week 1	-0.25 (n=101)	-0.38 (n=100)	-0.12 (n=104)	0.07	< 0.001
Week 2	-0.43 (n=100)	-0.65 (n=99)	-0.22 (n=99)	0.01	< 0.001
Week 3	-0.48 (n=99)	-0.81(n=98)	-0.30 (n=96)	0.04	< 0.001
Week 4	-0.54 (n=99)	-0.83 (n=98)	-0.36 (n=95)	0.05	< 0.001
Month 1 **	-0.42 (n=101)	-0.66 (n=100)	-0.23 (n=104)	0.01	< 0.001
Month 2	-0.66 (n=98)	-0.90 (n=96)	-0.43 (n=95)	0.02	< 0.001
Month 3	-0.74 (n=97)	-1.04 (n=94)	-0.58 (n=88)	0.14	< 0.001
Month 4	-0.86 (n= 95)	-1.09 (n=92)	-0.61 (n=87)	0.02	< 0.001
Months 1-2	-0.53 (n=101)	-0.76 (n=100)	-0.31(n=104)	0.005	< 0.001
Months 3-4	-0.78 (n=97)	-1.05 (n=94)	-0.59 (n=88)	0.06	< 0.001

** specified as the time point for analysis in comparison with placebo

COMMENT: *The finding of a statistically significantly greater mean reduction in nasal congestion/ obstruction after administration of Nasonex in a dose-dependent manner than after administration of placebo is consistent with the demonstrated effectiveness of Nasonex on nasal symptoms in the data submitted for approval of this drug product for allergic rhinitis. Over the last two months of treatment, the improvement of 0.78 after 200 mcg once a day and 1.05 after 200 mcg bid represents a clinically significant effect as well. The improvement of 0.42 and 0.66 after the administration of Nasonex 200 mcg once a day and Nasonex 200 mcg bid, respectively, is also consistent with the effect shown with other intranasal corticosteroids and considered to represent efficacy. Based on this data, Nasonex is effective for reduction in nasal congestion/obstruction in patients who have bilateral nasal polyposis.*

10.1.2.4. Loss of smell:

Loss of smell was considered by the applicant a "key" secondary efficacy variable. The analysis for this endpoint was pre-specified by the applicant. At baseline, moderate-severe loss of smell was reported by > 60% of patients in this study. For change from baseline, see table below (v8, p73, t13, p169). Loss of smell was assessed using a categorical scale of 0-3, with 0 = normal sense of smell, 1 = sense of smell mildly lost with no perception of subtle odors, e.g. strawberry, orange, lemon, 2 = sense of smell moderately lost with no perception of more characteristic odors, e.g. garlic, onion, coffee, and 3 = sense of smell totally lost, patient could not smell anything.

Mean improvement in sense of smell (decrease in loss of smell) in the ITT population in study 1926

Time-point	Nasonex 200 mcg qd AM	Nasonex 200 mcg bid	Placebo	P value N 200 qd vs placebo	P value N 200 bid vs placebo
Baseline	2.03 (n=101)	1.94 (n=100)	1.96 (n=104)		
Week 1	-0.03 (n=101)	-0.03 (n=100)	-0.03 (n=104)	0.94	0.96
Week 2	-0.09 (n=100)	-0.18 (n=99)	-0.06 (n=99)	0.66	0.12
Week 3	-0.06 (n=99)	-0.22 (n=98)	-0.03 (n=96)	0.74	0.03 •
Week 4	-0.05 (n=99)	-0.26 (n=98)	-0.03 (n=95)	0.77	0.009 •
Month 1 **	-0.06 (n=101)	-0.18 n=100)	-0.05 (n=104)	0.85	0.05 •
Month 2	-0.16 (n=98)	-0.30 (n=96)	-0.12 (n=95)	0.70	0.08
Month 3	-0.26 (n=97)	-0.36 (n=94)	-0.26 (n=88)	0.98	0.37
Month 4	-0.33 (n=95)	-0.40 (n=92)	-0.23 (n=87)	0.37	0.11
Months 1-2	-0.11 (n=101)	-0.24 (n=100)	-0.10 (n=104)	0.83	0.06
Months 3-4	-0.29 (n=97)	-0.38 (n=94)	-0.24 (n=88)	0.67	0.21

** specified as the time point for analysis in comparison with placebo

COMMENT: *A dose of 200 mcg once a day of Nasonex is not effective in improving sense of smell in patients with bilateral nasal polyposis. A dose of 200 mcg bid is not effective in improving a sense of smell beyond a period of one month.* (b) (4) (b) (4)

10.1.2.4. Other symptoms and PNIF (v8, pgs74-78, t14-16, pgs171-175): Rhinorrhea was evaluated using a 0-3 categorical scale where 0 = none, 1 = mild requiring blowing of nose with little or no discomfort, 2 = moderate requiring frequent blowing of the nose, annoying and caused discomfort, and 3 = severe, consistent blowing of the nose, interfered with daily activities and/or sleep. PND was evaluated using a 0-3 categorical scale where 0 = none, 1 = mild, causing little or no discomfort, 2 = moderate, annoying, causing discomfort, and 3 = severe, interfered with daily activities and/or sleep. PNIF was obtained using a nasal peak flow meter. Patients measured PNIF each morning right after assessment of symptoms and before drug administration testing 3 times and recording the highest result. Average change from baseline was taken over each of the four months and over each of the first four weeks, except for peak nasal inspiratory flow where averages were taken as well over each two month interval.

Mean change from baseline for secondary outcome variables in study 1926

Time-point	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value N 200 mcg qd vs placebo	P value N 200 mcg bid vs placebo
Rhinorrhea					
Baseline	1.53 (n=101)	1.58 (n=100)	1.57 (n=104)		
Month 1	-0.28 (n=101)	-0.47 (n=100)	-0.11 (n=104)	0.02	< 0.001
Months 3-4	-0.58 (n=97)	-0.73 (n=94)	-0.38 (n=88)	0.07	0.001
Post-nasal drip					
Baseline	1.47 (n=101)	1.46 (n=100)	1.41 (n=104)		
Month 1	-0.19 (n=101)	-0.38 (n=100)	-0.10 (n=104)	0.23	< 0.001
Months 3-4	-0.47 (n=97)	-0.60 (n=94)	-0.36 (n=88)	0.32	0.04
PNIF					
Baseline	102 L/min (n=101)	95.4 L/min (n=100)	97.7 L/min (n=104)		
Month 1	16.7(n=101)	25.6 (n=100)	5.4 (n=104)	< 0.001	< 0.001
Months 3-4	31.7 (n=96)	44.9 (n=94)	13.3 (n=88)	< 0.001	< 0.001

COMMENT: The secondary parameters evaluated during this study support the efficacy of Nasonex at a dose of 200 mcg bid in the treatment of (b) (4) *nasal polyps* (b) (4) *Nasonex at a dosage of 200 mcg once a day had a statistically significant effect only in terms of rhinorrhea after one month of treatment, and* (b) (4)

10.1.2.4. Percentage of patients with improvement (v8, p79, t17, p177): improvement was defined as a decrease in bilateral polyp grade of 1.0 or more from baseline to the last visit and a decrease in congestion /obstruction score of 0.5 or more from baseline to the average of the last 8 days of the study. Using this definition, 34% (34/101) patients who received Nasonex 200 mcg once a day and 49% (49/100) of patients who received Nasonex 200 mcg bid improved compared to 25% (24/98) of patients who received placebo. There was a statistically significant difference between the 200 mcg bid dose of Nasonex and placebo ($p < 0.001$) but not between the 200 mcg once a day dose of Nasonex and placebo ($p=0.16$).

10.1.2.4. Individual patient improvement in polyp grade and congestion/obstruction *based on a one point or greater reduction from baseline to endpoint* can be seen in the table below (v8, p120-137)

Number of patients (%) who had improvement from baseline in polyp grade, congestion/obstruction and/or both in study 1926

Treatment	↓ polyp grade ≥ 1	↓ congestion ≥ 1	↓ both polyp grade and congestion ≥ 1
Nasonex 200 mcg qd	52/101 (52%)	30/101 (30%)	18/101 (18 %)
Nasonex 200 mcg bid	60/101 (60%)	48/100 (48%)	28/100 (28%)
Placebo	49/100 (49%)	18/104 (18%)	6/100 (6%)

10.1.2.4. Investigator's assessment of therapeutic response (v8, p80, t18, p182): This assessment used a categorical scale of 0 = complete relief, virtually no symptoms present, 1 = marked relief, symptoms greatly improved, 2 = moderate relief, symptoms present, but noticeably improved, 3 = slight relief, symptoms present and only minimal improvement and 4 = no relief, symptoms

unchanged or worse than baseline. There was a statistically significantly greater improvement based on this global assessment at endpoint in the patients who received either dose of Nasonex compared to placebo ($p < 0.001$).

10.1.2.4. Health-Related Quality of Life (QOL) (v8, p86, t19): The QOL was evaluated using the SF-36 scales, Work Productivity and Activity Inventory (WPAI-SHP) and the generic treatment satisfaction questionnaire. The SF-36 and WPAI-SHP were collected at baseline, month 1, month 4, and at discontinuation. The generic treatment satisfaction questionnaire was collected at month 4 or at the time of discontinuation. There were 295/310 patients (95%) who completed the SF-36 at both baseline and endpoint and 283/310 patients (91%) who completed the SPAI-SHP. The SF-36 assessed 8 domains of health over the previous week. Domains included: 1) physical functioning; 2) role physical; 3) bodily pain; 4) general health; 5) vitality; 6) social functioning; 7) role emotional; and 8) mental health. Two additional summary measures of physical (PCS) and mental (MCS) were constructed based on all the eight domains of the SF-36. The SF-36 is scored from 0-100 with the lower score indicating greater disease burden. Since the mean baseline scores for all domains of the SF-36 showed that the QOL in the study population was similar to that in the general population in the US, no specific QOL burden was evident in the study population. The mean baseline scores for the SF-36 domains were similar across treatment group. At endpoint, there was no statistically significant difference between either the Nasonex 200 mcg once a day or the Nasonex 200 mcg bid treatment group and placebo were noted for the vitality domain, which was the pre-specified primary domain. Since there was no significant difference between active treatment and placebo for the primary domain, no further analysis of the data was done. Neither active treatment group showed any increase in work productivity over that seen in the placebo group. In addition, the generic treatment satisfaction data did not show any clear benefit of treatment.

10.1.2.5. Safety:

More than 93% of the patients who received Nasonex and 84% of the patients who received placebo took the study drug for at least 90 days. At least 50% of patients in each treatment group took study drug for at least the pre-specified 120 days (v8, p 88, t20).

10.1.2.5. Adverse events:

Treatment-emergent adverse events were defined as those adverse events that began while the patient was receiving treatment or began prior to treatment but increased in severity while receiving treatment. Overall the incidence of adverse events was 53% in the group that received 200 mcg per day of Nasonex, 56% in the group that received 200 mcg bid and 51% of the patients who received placebo. The most frequently reported adverse events were headache (11%, 13% and 9% in the Nasonex 200 mcg qd, Nasonex 200 mcg bid and placebo treatment arms), URI (16%, 13% and 12% in the Nasonex 200 mcg qd, Nasonex 200 mcg bid and placebo groups) and epistaxis (6%, 15% and 5% in the Nasonex 200 mcg qd, Nasonex 200 mcg bid and placebo treatment arms). There were 4 patients (4%) in the Nasonex once a day group who reported 8 *severe* adverse event (headache, dizziness, toothache, atrial flutter and fibrillation, upper respiratory infection, arthralgia and back pain) compared to 2 (2%) in the Nasonex 200 mcg bid group (eye pain and asthma) and 5 (5%) in the placebo group who reported 6 severe

adverse events (headache, allergy, arrhythmia, pneumonia, pleurisy and loss of taste)(v8, pgs 88-98). There were no severe adverse events that occurred in more than one patient or that were considered related to the study drug (v8, p93, t23). There were 6 *serious* adverse events recorded, one in the Nasonex 200 mcg once a day group, 2 in the Nasonex 200 mcg bid group and three in the placebo group. A 55 year old Caucasian male who had received Nasonex 200 mcg once a day for 29 days developed atrial flutter and fibrillation for which the patient was hospitalized and treated (v8, p261). The patient had a history of atrial fibrillation and screening ECG showed sinus bradycardia and prolonged QT interval (v8, p276). Three serious adverse events were reported for 2 patients in the Nasonex 200 mcg bid group: 1) coronary artery stenosis in a 58 year old Caucasian male which was noted on the screening ECG, 7 days prior to initiation of treatment. The patient was randomized into the study but the ECG findings were confirmed after one month of treatment with the study drug for which the patient was hospitalized and had cardiac catherization (procedure) (v8, p262, 272); and 2) choroidal neovascularization in a 27 year old Asian male which began after 65 days of treatment and for which treatment was interrupted (v8, p262). This event was considered by an ophthalmologist to be a consequence of the patient's pre-existing myopia (v8, p271) Four serious adverse events were reported for 3 patients in the placebo group: 1) an arrhythmia in a 42 year old Hispanic male that began on the 72nd day of treatment for which the patient was hospitalized and treatment with the study drug interrupted (v8, p275); 2) pneumonia and pleurisy in a 57 year old Caucasian male that occurred after 47 days of treatment for which the patient was hospitalized and treated (v8, p274); and 3) edema of the tongue in a 43 year old Caucasian female that began after 106 days of treatment, was moderate in severity and required interruption of study treatment (v8, p273). There was 1 *discontinuation* due to an adverse event, a 68 year old Caucasian male in the placebo group who developed severe loss of taste after 15 days of treatment considered unrelated to the study drug (v8, p97, 265). There were 7 patients who *interrupted treatment* because of an adverse event: an 80 year old Caucasian female in the Nasonex 200 mcg once a day group who developed a URI after 115 days of treatment (v8, p267); 3 patients in the Nasonex 200 mcg bid group (a 27 year old Asian male who developed retinal neovascularization, a 31 year old Caucasian male who developed influenza-like symptoms after 105 days of treatment and a 54 year old Caucasian male who developed a URI after 71 days of treatment)(v8, p268);and 3 patients in the placebo group (a 60 year old Caucasian male who had an inguinal hernia repair after 55 days of treatment, a 43 year old Caucasian female who developed edema of the tongue after 106 days of treatment and a 42 year old Hispanic male who developed an arrhythmia after 72 days of treatment (v8, p269). Treatment interruption occurred because of an URI in the one patient in the Nasonex 200 mcg qd group, influenza-like symptoms, retinal neovascularization and URI in the three patients in the Nasonex 200 mcg bid group and arrhythmia, tongue edema and a procedure (without adverse event) in the three patients in the placebo group (v8, p98, t25). *Epistaxis* was reported more frequently after the use of Nasonex 200 mcg bid (13%)) compared to use of Nasonex 200 mcg qd (4%) and the administration of placebo (5%). All reports of epistaxis were mild-moderate in severity. Epistaxis was reported by 20% of Caucasian patients who received Nasonex 200 mcg bid compared to 9% of Caucasian patients who received Nasonex 200 mcg once a day and 3% of Caucasian patients who received placebo (v8, p230). By comparison in Hispanic patients (n=28), 4% of the Nasonex 200 mcg bid, 10% of the placebo group and none of the Nasonex 200 mcg qd group developed epistaxis (v8, p237).

Adverse events (considered related and unrelated to administration of the study drug) occurring in at least 3% of patients in any treatment group or 2% in either or both active treatment groups and none in the placebo group in study 1926 (v8, p90-91, t21)

Adverse events	Nasonex 200 mcg QD N=102	Nasonex 200 mcg bid N=102	Placebo N=106
Dizziness	2 (2%)	1(1%)	0
Headache	11 (11%)	13 (13%)	10 (9%)
Abdominal pain	0	1 (1%)	3 (3%)
Arthrosis	1 (1%)	2 (2%)	0
Pharyngitis	4 (4%)	3 (3%)	5 (5%)
Sinusitis	1 (1%)	3 (3%)	1 (1%)
URI	16 (16%)	13 (13%)	13 (12%)
Overdose *	2 (2%)	2 (2%)	0
Back pain	3 (3%)	2 (2%)	2 (2%)
Bronchitis	3 (3%)	3 (3%)	0
Coughing	3 (3%)	4 (4%)	3 (3%)
Epistaxis	6 (6%)	15 (15%)	5 (5%)
Nasal burning	1 (1%)	2 (2%)	0
Nasal irritation	0	1 (1%)	3 (3%)
Pruritis	2 (2%)	1 (1%)	0

* None of the 4 patients who took more than the recommended dose of Nasonex had any adverse events considered to be related to overdose of this medication (v8, pgs278-281).

There were 17 patients (16%) of the placebo patients who had an adverse event that was considered related to the study drug compared with 11 (11%) of the Nasonex 200 mcg once a day and 25 (25%) of the Nasonex 200 mcg bid groups who had treatment-related adverse events. The only treatment-related adverse events that occurred with an incidence greater than 1% and a higher incidence in patients who received Nasonex than in patients who received placebo were headache (5% of the Nasonex 200 mcg bid group compared with 2% in the placebo group), pharyngitis (2% of the Nasonex 200 mcg bid group compared with 1% of the placebo group), overdose (2% of both Nasonex groups and none in the placebo group), epistaxis (13% in the Nasonex 200 mcg bid group and 5% in the placebo group), and nasal burning (2% of the Nasonex 200 mcg bid group, 1% of the Nasonex qd group and none of the placebo group)(v8, p92, t22).

None of the adverse events reported occurred significantly more frequently based on gender (v8, pgs202-212) in the active treatment groups than in the placebo groups, with the exception of epistaxis (v8, p204) that occurred in 5% of male patients who received Nasonex 200 mcg once a day, 11% of male patients who received Nasonex 200 mcg bid and 6% of the male placebo patients but occurred in 21% of the female patients who received 200 mcg bid compared to 3% in the other treatment groups (*note: in study 1925, epistaxis occurred more frequently in males*). There were no adverse events that occurred with a significantly greater frequency in patients 18-64 years of age compared to patients 65 years and older, although the small number of patients 65 years of age and older in each treatment group (10 received Nasonex 200 mcg once a day, 10 received Nasonex 200 mcg bid and 16 received placebo) make any comparisons between these two age groups difficult (v8, pgs223-224).

COMMENT: *There was no indication from the adverse events reported in this study that there should be any safety concern related to the administration of Nasonex Nasal Spray. Epistaxis is a recognized adverse effect that can occur from administration of corticosteroid nasal sprays but there was no patient receiving Nasonex who developed severe or serious epistaxis. Bronchitis, pruritis, dizziness, sinusitis and arthrosis were seen more frequently in patients who received Nasonex but for bronchitis, dizziness and prurutis were not dose-related and in all likelihood occurred spontaneously without relationship to the study drug.*

10.1.2.5. laboratory tests:

Laboratory tests were obtained at baseline and at visit 7. Median, minimum and maximum values at baseline and endpoint in regard to changes from baseline by treatment for routine laboratory tests were evaluated. Changes noted after administration of Nasonex at the two dosage levels was evaluated first and then compared with the change seen after administration of placebo if there was a significant change seen in the Nasonex groups. No significant changes in the groups that received Nasonex were seen in hematology or blood chemistry values when all patients were included in the analysis (v8, pgs286-315). The only two laboratory tests considered to be clinically significant occurred in the placebo group (v8, p284). Laboratory results were evaluated in terms of gender (v9, pgs318-376), age (18-64 compared with 65 years and older) (v9, pgs378-437) and race (v9, pgs 439-558) and no clinically significant changes in laboratory any laboratory test was noted after administration of Nasonex . See table below for number (%) of patients with a shift from a normal baseline value to a value outside the normal reference range that could be clinically significant and was greater in one or both of the Nasonex groups than in the placebo group.

Laboratory test	N	Baseline normal Outside normal reference range after treatment
WBC		Low
Nasonex 200 mcg qd	78	None
Nasonex 200 mcg bid	81	2 (2%)
Placebo	80	None
Neutrophils		Low
Nasonex 200 mcg qd	77	None
Nasonex 200 mcg bid	75	4 (5%)
placebo	80	2 (2%)
Glucose		High
Nasonex 200 mcg qd	68	7 (8%)
Nasonex 200 mcg bid	72	4 (5%)
Placebo	65	4 (5%)
SGOT		High
Nasonex 200 mcg qd	83	2 (2%)

Nasonex 200 mcg bid	73	7 (7%)
Placebo	73	3 (4%)
BUN		High
Nasonex 200 mcg qd	85	4 (4%)
Nasonex 200 mcg bid	88	2 (2%)
Placebo	84	1 (1%)

COMMENT: *At a dosage of 200 mcg bid of Nasonex, there were a slightly higher percentage of patients who had a normal SGOT at baseline that became elevated after treatment than was seen after administration of the lower daily dose of Nasonex or placebo. There were a slightly higher percentage of patients who had an elevation of BUN and serum glucose above the upper limit of the normal reference range after administration of Nasonex than after administration of placebo but the percentage was greater in patients who received the lower daily dose of Nasonex, i.e. there was no dose effect. There was a decrease in WBC and neutophils in a small number of patients after administration of Nasonex 200 mcg bid that was not seen after administration of the lower daily dose. The difference in regard to these laboratory parameters between the groups that received Nasonex and placebo is not great enough to conclude that they represent any reason for concern about the safety of administration of Nasonex.*

10.1.2.5. Vital signs (v9, pgs 569-591):

Vital signs were obtained at each visit and included blood pressure, pulse rate and respiratory rate. No clinically significant changes in median, minimum or maximum values were seen in any of the treatment groups for systolic blood pressure, diastolic blood pressure, pulse rate or respiratory rate. There were no clinically significant median changes in vital signs based on gender (v9, pgs572-575), age (patients 18-64 compared to patients 65 years of age and older) (v9, pgs577-580) or race (v9, pgs582-591). There were 3 patients (2%) in the 200 mcg bid group who had an increase in systolic blood pressure of greater than 30%, whereas there were no patients in the other two treatment groups who had such an increase (see table below; v9, p593). There was no clinically significant difference in terms of change in diastolic blood pressure or pulse rate between the three treatment groups. There was no clinically significant difference in terms of any vital sign and gender (v9, pgs595-596), age (v9, pgs 598-599) or race (v9, pgs601-605).

Systolic blood pressure	> 30% ↓	11- 30 % ↓	10-30% ↑	> 30% ↑
Nasonex 200 mcg qd	0	18 (18%)	12 (12%)	0
Nasonex 200 mcg bid	0	10 (8%)	11 (11%)	3 (3%)
Placebo	0	15 (14%)	11 (11%)	0
Diastolic blood pressure				
Nasonex 200 mcg qd	1 (1%)	22 (22%)	11 (11%)	1 (1%)
Nasonex 200 mcg bid	0	18 (18%)	13 (13%)	2 (2%)
Placebo	1 (1%)	19 (18%)	18 (17%)	3 (3%)
Pulse rate				
Nasonex 200 mcg qd	0	12 (12%)	20 (20%)	1(1%)
Nasonex 200 mcg bid	0	22 (22%)	11 (11%)	1(1%)
Placebo	1 (1%)	17 (16%)	14 (13%)	4 (4%)

COMMENT: The safety data from study 1926 does not raise any specific concern about the safe administration of Nasonex Nasal Spray.

CONCLUSION: *Both doses of Nasonex, 200 mcg once a day and 200 mcg bid were effective in relieving nasal congestion/obstruction. A greater mean change from baseline in bilateral polyp grade was seen after administration of Nasonex 200 mcg bid compared with 200 mcg once a day. However, neither dosage of Nasonex produced a statistically significantly greater mean decrease in polyp grade than did placebo, although there was a mean reduction in polyp grade seen in patients who received placebo as well as patients who received Nasonex. Although there is a strong trend favoring the Nasonex 200 mcg bid dosage over placebo, there was not a statistically significant difference between either dosage of Nasonex and placebo in terms of mean polyp grade unless the analysis included baseline as a co-variate. When this re-analysis was done, there was a statistically significant difference between Nasonex 200 mcg bid and placebo (p = 0.05). Given the importance of baseline balance in terms of polyp size as demonstrated in study Q99-925-01 (see discussion below), this re-analysis can be accepted as demonstrating the effectiveness of Nasonex at at dosage of 200 mcg bid in reducing polyp size and supports the findings in study 1925.*

10.1.3. Study Q99-925-01

10.1.3.1. Study Characteristics

Study Q99-925-01 (v12-13) was a randomized, placebo-controlled, double-blind, parallel group, multicenter (12) study performed in Denmark (2 centers), Finland (2 centers), Norway (2 centers) and Sweden (6 centers) with the objective of evaluating the efficacy and safety of Nasonex Nasal Spray 200 mcg per day in the treatment of nasal polyposis. There were 298 patients between the ages of 20-86 years in the study. Of these, 153 received Nasonex Nasal Spray and 145 received placebo. There were 296 patients who received treatment since two patients randomized to receive placebo did not receive study treatment (one patient withdrew to

have surgery to remove nasal polyps and one patient did not fulfill the protocol-specified inclusion criteria. The patient population studied was patients with bilateral nasal polyps with a polyp size of 2 or less (patients with a polyp size of grade 3 were allowed to enroll if nasal blockage did not prevent successful administration of the nasal spray) and who were symptomatic with a nasal congestion score of 2 or greater for at least 4 days a week during the last month prior to screening, at screening and at baseline. Patients received 2 sprays of Nasonex per nostril (50 mcg per spray) in the morning upon awakening (200 mcg per day). There was a run-in period of 2-4 weeks without treatment followed by a treatment period of 16 weeks. Visit 1 was the screening visit, visit 2 was the baseline visit, visit 3 was after 28 days of treatment, visit 4 was after 56 days of treatment, visit 5 was after 84 days of treatment, and visit 6 was after 112 days of treatment. Exclusion criteria included polyp surgery within the previous 6 months, polyp size 3 or greater (with the exception noted above), ongoing concurrent nasal infection, glaucoma with narrow anterior chamber angle, hereditary mucociliary dysfunction, rhinitis medicamentosa, significant nasal structural abnormalities and patients who did not have bilateral nasal polyps.

Evaluation was done by investigators at baseline and on days 28, 56, 84, and 112. *The primary outcome variable was the proportion of patients with improvement during the treatment period (visits 3-6) in nasal congestion as evaluated by the investigator with improvement being defined as a reduction in nasal congestion of at least one point.* Nasal congestion was graded in the following manner: 0 = none, 1 = mild symptom clearly present but minimal awareness and easily tolerated; 2 = definite awareness of moderate symptom which was bothersome but tolerable; 3 = severe symptom hard to tolerate, may have caused interference with activities of daily living or sleeping at night. Symptoms were also evaluated twice daily by patients on a reflective basis in the morning upon arising before medication and approximately 12 hours later in the evening (along with assessment of rhinorrhea as noted below) on a scale of 0-3 where 0 = no symptoms, 1 = mild tolerable symptoms, 2 = moderate symptoms, and 3 = severe symptoms that interfered with daily activity and quality of sleep.

Polyp size was graded as 0 = no polyps; 1 = polyps in the middle meatus, not reaching below the inferior border of the middle concha; 2 = polyps reaching below the inferior border of the middle concha but not the inferior border of the inferior concha; and 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha. *The investigators were instructed that they should grade the size of polyps in both nostrils at the screening visit, choose the grade from the most severe side and enter that score. Investigators were also instructed to follow the largest polyp seen at Visit 1 and how it changed at all subsequent visits. No recored was entered into the CRF as to which polyp was followed or in which nostril the largest polyp was seen. Therefore, it is not known whether investigators consistently followed the polyp assessed at baseline or recorded the grade of the largest polyp found at each visit.*

Secondary efficacy variables were improvement in rhinorrhea, sense of smell, polyp size measured by endoscopy, PNIF, olfactory threshold, patient-assessed symptoms scores, treatment response score and QOL-related variables. PNIF was measured at each visitSeverity of *loss of smell* was graded by patients twice daily on a reflective basis in the morning upon arising before taking medication and approximately 12 hours later in the evening as: 0 = normal, 1 = slightly impaired; 2 = moderately impaired; 3 = absent loss of smell. *Response to treatment* was evaluated by the patient and the investigator at visits 3, 4, 5 and 6 relative to the patient's

baseline visit using the following scale: 0 = complete relief with virtually no symptoms present; 1 = marked relief with greatly improved and scarcely troublesome; 2 = moderate relief with symptoms present but noticeably improved; and 3 = treatment failure with no relief and symptoms unchanged or worse compared to baseline (v12, pgs29-30). The *olfactory threshold test* was performed using butanol at screening, baseline and on visits 5 and 6 to assess the ability of the patient to identify the odor (v12, p28). *Quality of life assessment* included the following investigator questions and possible patient responses: "How is the distribution between mouth and nose breathing?" 1 = mostly mouth breathing; 2 = equal; 3 = mostly nose breathing; "How do you experience smell and taste?" 1 = almost not at all; 2 = fairly; 3= very well; "How do you experience interference with daily activities due to nasal symptoms?" 0 = no; 1 = mild; 2 = moderate; 3 = severe; and "How do you experience sleeping disturbances due to nasal symptoms?" 0 = no; 1 = mild; 2 = moderate; 3 = severe. *Safety variables* included vital signs recorded on visits 1 and 6, nasal examination at all visits and adverse events (v12, p2).

Patients could use oxymetazoline as *rescue medication*. Sites 4 (n=1) and 6 (n=11) were combined for all analyses. *Prohibited medications* during treatment included corticosteroids except for the study drug and inhaled corticosteroids at a stable dosage for asthma (1000 mcg or less of beclomethasone or the equivalent). Also prohibited during treatment were antihistamines and decongestants (24 hours prior to screening for short-acting and 72 hours prior to screening for long-acting), hydroxyzine for 5 days, intranasal ipratropium for 1 week, nasal saline for 24 hours and high potency topical corticosteroids unless the patient was on a stable dosage for a chronic condition.

Data sets analyzed included: 1) an ITT population (n=291) which included all randomized patients who took at least one dose of study drug and had baseline and post-baseline data were included in the ITT analysis, utilizing endpoint analysis where last observation was carried forward. For the primary efficacy variable, an additional supplementary analysis was performed scoring these patients as treatment failures, i.e. non-improvement; endpoint was defined as the last visit during the treatment period for which the patient had non-missing data; 2) a per protocol population (n=179): inclusion in this analysis was based on the criteria defined in the study protocol and included: a baseline visit 14-28 days after the screening visit; a last visit between days 104-126; no more than 10 daily doses missed during the period from baseline to visit 5, no more than 4 daily doses missed during the period from visit 5 to visit 6 and no doses missed during the last 7 days of the treatment period; no prohibited medication taken; and rescue medication taken once daily for a maximum of 7 consecutive days and a maximum of 10 days and none taken during the 48 hours before the last visit; and 3) a population for safety analysis (n=296): all randomized patients who received at least one dose of study medication were included in this analysis. Two patients randomized to receive placebo who did not receive study medication were excluded from the safety analysis.

The study was powered to reject the null hypothesis of equal proportions of patients with improvement in the Nasonex and placebo groups assuming a percentage of patients with improvement in nasal congestion of 40% in the placebo group and 60% in the Nasonex group.

Number (%) of randomized patients who completed double-blind treatment and number (%) who discontinued and reason for discontinuation study Q99-925-01(v12, p46. t4)

Category	Nasonex 200 mcg QD (n=153)	Placebo (n=145)
Number (%) completed DB period	134 (87.6%)	101 (69.7%)
Total discontinued	19 (12.4%)	44 (30.3%)
Reason for discontinuation		
Adverse event	1 (0.7%)	4 (2.8%)
Treatment failure	8 (5.2%)	27 (18.6%)
Treatment failure/noncompliance	0	1 (0.7%)
Significant inter-current illness	0	2 (1.4%)
Did not wish to continue	2 (1.3%)	0
Noncompliance with protocol	4 (2.6%)	6 (4.1%)
Other	4 (2.6%)	4 (2.8%)

Number of patients in subsets analyzed in study Q99-925-01 (v12, p48, t5)

Category	Nasonex 200 mcg QD	Placdbo
All randomized patients	153	145
ITT subset	152	139
Patients without appropriate baseline	1	6
Per protocol subset	107	73

Reasons for exclusion from the per protocol analysis subset in study Q99-925-01 (v12, p49, t6)

Category	Nasonex 200 mcg QD (n=153)	Placebo (n=145)
Patients included in the PP subset	107 (70%)	72 (50%)
Patients excluded from PP subset	46 (30%)	73 (50%)
Discontinuation	19 (12%)	44 (30%)
Visit dates outside accepted range	22 (14%)	16 (11%)
Rescue medication overuse/misuse	4 (3%)	10 (7%)
Prohibited concomitant medication	0	2 (1%)
Other	1 (1%)	1 (1%)

Demographics and baseline symptom severity (v12, p50-51, t7-8, p79) *

Category	Nasonex 200 mcg QD (n=153)	Placebo (n=145)
Mean age	53 years	53 years
Age range	24-84 years	20-86 years
Males	114 (75%)	104 (72%)
Females	39 (25%)	41 (28%)
Mild nasal congestion	2 (1.3%)	1 (0.7%)
Moderate nasal congestion	120 (78.4%)	117 (80.7%)
Severe nasal congestion	32 (20.3%)	27 (18.6%)
Polyp size 1	38 (24.8%)	34 (23.4%)
Polyp size 2	100 (65.4%)	85 (58.6%)
Polyp size 3	15 (9.8%)	28 (17.9%)
Normal sense of smell	17 (11.1%)	10 (6.9%)
Slightly impaired sense of smell	30 (19.6%)	31 (21.4%)
Moderately impaired sense of smell	43 (28.1%)	52 (35.9%)
Absent sense of smell	63 (41.2%)	52 (35.9%)

* no information regarding race was collected in this study

10.1.3.2. Compliance:

Non-compliance was defined as: 1) missed doses of study medication over more than 7 consecutive days, and/or a maximum of 10 days; 2) overuse of rescue medication, i.e. greater than 10 days during treatment; and/or 3) use of prohibited concomitant medications. There were 15 patients (6 in the Nasonex group and 9 in the placebo group) who were excluded from the per-protocol subset due to noncompliance that resulted in discontinuation. In addition, there were 17 patients who completed the study who were excluded because of non-compliance, 4 Nasonex group patients (all because of overuse of rescue medication) and 13 placebo patients (10 because of overuse of rescue medication, 2 because of prohibited concomitant medication and one because of missed doses of study medication).

10.1.3.3. Efficacy:

Improvement in the primary efficacy variable, investigator-assessed nasal congestion, was defined as a reduction of at least one point from baseline to the last visit (see table below) (v12, p52, t9, p81). There was a statistically significant difference between the Nasonex and placebo group based on analysis of both the ITT and the per protocol population. There were 69% of male patients receiving Nasonex who had an improvement in nasal congestion compared to 47.5% of males receiving placebo. There were 89.7% of females receiving Nasonex who had an improvement in nasal congestion compared to 44.7% of females receiving placebo (v12, p212). There were 75.2% of patients < 65 years of age who had an improvement in nasal congestion compared to 47.7% of patients receiving placebo. There were 69.6% of patients 65 years of age and older who had improvement in nasal congestion compared to 42.9% of patients receiving placebo (v12, p213).

Improvement nasal congestion, baseline to the last visit in study Q99-925-01 based on ITT population (v12, p52, t9)

category	Nasonex 200 mcg QD (n=152)	Placebo (n=139)	P value
Nasal congestion			
Improvement	113 (74.3%)	65 (46.8%)	< 0.001
No improvement	39 (25.7%)	74 (53.2%)	

Improvement in secondary efficacy variables; number (%) of patients with improvement at endpoint in study Q99-925-01 based on ITT population (v12, p54, t10)

Category	Nasonex 200 mcg QD (n=152)	Placebo (n=139)	P value
Polyp size			
Improvement	63 (41.4%)	37 (26.6%)	0.003
No improvement	89 (58.6%)	102 (73.4%)	
Sense of smell			
Improvement	56 (36.8%)	31 (22.3%)	0.007
No improvement	96 (63.2%)	108 (77.7%)	
Rhinorrhea			
Improvement	79 (52%)	49 (35.3%)	0.004
no improvement	73 (48%)	90 (64.7%)	

Therapeutic response			
Complete relief	15 (9.9%)	3 (2.2%)	< 0.001
Marked relief	50 (32.9%)	26 (18.7%)	
Moderate relief	48 (31.6%)	35 (25.2%)	
Treatment failure	39 (25.7%)	75 (54%)	

Mean change in polyp grade at time-points during study Q99-925-01 (v12, p223)

Time-point	N	Nasonex 200 mcg qd	n	Placebo	P value
Baseline	152	1.85	139	1.94	
Month 1	149	-0.22	132	-0.05	0.007
Month 2	146	-0.18	115	-0.12	0.39
Month 3	140	-0.32	105	-0.18	0.07
Month 4	138	-0.36	104	-0.22	0.08
Endpoint	152	-0.35	139	-0.12	0.001

Other secondary efficacy outcome variables: The mean increase in *PNIF* from baseline was 22 L/min in the Nasonex group and 10 L/min in the placebo group (p = 0.025) at endpoint. The mean increase in *olfactory threshold* was 0.90 in the Nasonex group and 0.83 in the placebo group (p = 0.66). In regard to daily symptoms of nasal congestion, rhinitis and sense of smell from baseline to endpoint, see table below (v12, p117). *Quality of life assessment* in the ITT population showed that the % of patients with improvement from baseline to endpoint for nose breathing was 47.4% in the Nasonex group and 26.6% in the placebo group (p < 0.001) (v12, p131), or smell and taste was 42% in the Nasonex group and 39% in the placebo group (p =0.58) (v121, p134), for interference with daily activities was 61.8% in the Nasonex group and 45.3% in the placebo group (p 0.003) (v12, p138), for sleeping disturbances was 57.2% in the Nasonex group and 37.4% in the placebo group (p = 0.001) (v12, p141) and for improvement in smell and taste was 42.1% in the Nasonex group and 38,8% in the placebo group (p =0.58). Usage of rescue medication at least once during the study was 34.2% in the Nasonex group and 50.7% in the placebo group (p = 0.006). There were 34.2% of the Nasonex group who required *rescue medication* compared to 50.7% of the placebo group (v121, p216).

Mean change from baseline in study Q99-925-01 in daily symptoms

Parameter	Nasonex 200 mcg qd	Placebo	P value
Nasal congestion AM	- 0.59	- 0.23	< 0.001
Nasal congestion PM	- 0.59	- 0.24	< 0.001
Rhinorrhea AM	- 0.43	- 0.08	< 0.001
Rhinorrhea PM	- 0.38	- 0.12	< 0.001
Sense of smell AM	- 0.24	- 0.07	0.004
Sense of smell PM	- 0.24	- 0.08	0.005

10.1.3.4. Safety:

Duration of exposure to study drug in study Q99-925-01 for ITT population (v12, p61, t11)

Length of exposure	Nasonex 200 mcg QD (n=153)	Pladebo (n=145)
Any treatment	153	143 (99%)
1 day or more	153	142(98%)
7 days of more	153	141 (97%)

56 days or more	144 (94%)	113 (78%)
84 days or more	141 (92%)	105 (72%)
112 days or more	114 (75%)	76 (52%)
150 days or more	2 (1%)	0
Randomized; did not receive Rx	0	2 (1%)
Missing	0	1 (1%)

Adverse events: Adverse events were reported by 94 (61.4%) of the patients who received Nasonex and 67 (46.9%) of the patients who received placebo. The most frequent adverse events were headache (10.5% of the Nasonex group and 3.5% of the placebo group), epistaxis (15.7% of the Nasonex group and 4.9% of the placebo group) and URI (29.4% of the Nasonex group and 21.7% of the placebo group). Severe treatment-emergent adverse events were reported in 3 patients who received Nasonex and 4 patients who received placebo. Severe treatment-emergent adverse events included cholelithiasis, headache and cardiac failure in the Nasonex group and nasal congestion (2), nasal irritation and dyspnea in the placebo group (v12, p67, t14). Adverse events considered possibly, probably or definitely related to the study drug occurred in 19% of the patients who received Nasonex and 13.3% of the patients who received placebo. Epistaxis that was considered related to the study drug occurred in 20 (13.1%) patients in the Nasonex group and 7 (4.9%) patients in the placebo group. There were 3 adverse events that occurred in more than one patient who received Nasonex and more than occurred in the placebo group. These were: 1) headache that occurred in 2 (1.3%) patients who received Nasonex and none of the patients who received placebo; 2) hemorrhage that occurred in 3 (2%) of patients who received Nasonex and 1 (0.7%) of the patients who received placebo; and 3) epistaxis that occurred in 17 (11.1%) of the patients who received Nasonex and 6 (4.2%) of the patients who received placebo (v12, p66, t13). Epistaxis considered to be possibly, probably or definitely related to treatment occurred in 20 (13.1%) of the patients treated with Nasonex and 7 (4.9%) of the patients treated with placebo. Serious adverse events were reported in 5 patients in the Nasonex group and 4 patients in the placebo treatment group. None were considered related to the study drug. The serious adverse events in the Nasonex group were: 1) severe, unrelated cholelithiasis requiring hospitalization; 2) moderate unrelated anemia due to vitamin B12 deficiency requiring hospitalization; 3) moderate unrelated pneumonia requiring hospitalization; 4) mild unrelated toothache and possibly related sinusitis requiring additional therapy; and 5) severe unrelated cardiac failure requiring hospitalization. The patient with cardiac failure was an 83 year old male who had a previous history of heart disease. Two and one half weeks after starting therapy the patient developed a myocardial infarction. The patient recovered and study medication was continued. The serious adverse events in the placebo group were: 1) moderate unrelated hemorrhagic stroke requiring additional therapy and hospitalization; 2) moderate unrelated asthma requiring hospitalization; 3) mild unrelated rotator cuff syndrome requiring additional therapy and hospitalization; and 4) moderate unrelated asthma requiring hospitalization (v12, p70, t15). Discontinuation of study drug because of an adverse event occurred in 3 patients who received Nasonex and 7 patients who received placebo. The Nasonex patients were discontinued because of: 1) treatment failure after 46 days of treatment; 2) moderate unrelated nasal congestion after 111 days of treatment; and 3) mild related thyroiditis after 28 days of treatment. The placebo patients were: 1) moderate possibly related vertigo; 2) moderate possibly related sore throat; 3) moderate unrelated rheumatoid arthritis; 4) severe probably related nasal irritation; 5) moderate related nasal irritation; 6) moderate unrelated hemorrhagic stroke; and 7) severe unrelated dyspnea (v12, p71, t16). Randomized treatment was

interrupted in 2 patients who received Nasonex and 3 patients who received placebo. In the Nasonex group, interruption was due to mild epistaxis probably related to study treatment in both patients. In the placebo group, interruption was due to moderate possibly related sore throat + nasal congestion, moderate probably related nasal irritation and moderate unrelated rheumatoid arthritis (v12, p71).

Adverse events (considered related and unrelated to administration of the study drug) occurring in at least 3% of patients in any treatment group or 2% in the active treatment group and none in the placebo group in study Q99-925-01 (v12, p64, t12)

Adverse events	Nasonex 200 mcg QD N=153	Placebo N=143
Influenza-like symptoms	5 (3.3%)	1 (0.7%)
Headache	16 (11%)	5 (3.5%)
Sinusitis	5 (3.3%)	3 (2.1%)
Back pain	3 (2%)	0
Pharyngitis	4 (2.6%)	8 (5.6%)
URI	45 (29.4%)	31 (21.7%)
Coughing	7 (4.6%)	6 (4.2%)
Epistaxis *	21 (13.7%)	6 (4.2%)
Accidental injury	3 (2%)	0

* There were 3 patients who received Nasonex and one patient who received placebo who reported nasal hemorrhage rather than epistaxis. In addition, one patient in the Nasonex group reported an accidental injury resulting in epistaxis.

Vital signs: see table below (v12, p277, 279)

Mean blood pressure and pulse rate at screening and visit 6 and mean % change from baseline in study Q99-925-01

Parameter	n	Nasonex 200 mcg qd	n	Placebo
Systolic BP (mmHg)			143	
Screening mean	152	139.3	121	138.7
Visit 6 mean	144	134.8	121	135.2
Mean % change from baseline	143	- 3.00		- 2.66
Diastolic BP (mmHg)				
Screening mean	152	86.6	143	86.9
Visit 6 mean	144	83.3	121	84.5
Mean % change from baseline	143	- 3.23	121	- 2.35
Pulse rate (bpm)				
Screening mean	152	74.0	143	73.3
Visit 6 mean	144	73.5	120	73.9
Mean % change from baseline	143	0.68	120	2.16

COMMENT: The primary outcome variable in study Q99-925-01 was improvement in nasal congestion from baseline to endpoint as assessed by the investigator. Nasonex has already been

shown to be effective for allergic rhinitis, which included demonstration of effectiveness for nasal congestion. Patients with allergic rhinitis were not excluded from the study (and in fact, a study of nasal polyps would be difficult to perform if such patients were excluded). Therefore, improvement in nasal congestion alone can not be used to support the effectiveness of Nasonex in the treatment of nasal polyps, even though nasal congestion is a significant finding in patients with this condition. Nasonex was shown in this study to decrease nasal polyp size to a statistically significantly greater amount than placebo and was statistically significantly more effective in terms of increasing sense of smell and improving other secondary outcome variables. However, the study was not powered to show significant differences in these parameters. The primary efficacy variable chosen by the sponsor was inappropriate for demonstration of efficacy of Nasonex in patients with nasal polyposis beyond that which could represent an improvement in allergic rhinitis. Nevertheless, this study can be used to support the effectiveness of Nasonex at a dose of 200 mcg once a day in the management of nasal polyps that was demonstrated in study 1925. There were no safety concerns raised by the data from this study.

10.1.4. Study 2573:

Study 2573 was a 4 month follow-up study to assess the rate of recurrence of nasal polyps in patients whose condition improved with up to 4 months of treatment with Nasonex Nasal Spray in study 1925. This was a double-blind, multicenter (27 centers in 10 countries), followup study to study 1925 in which patients received Nasonex either once a day or bid at a dose of 200 mcg or placebo. Patients were entered into study 2573 if they had improved with treatment in study 1925 and met the inclusion/exclusion criteria and were then followed for up to 4 months without additional treatment to assess the rate of recurrence of nasal polyps after cessation of treatment.

Improvement with treatment in study 1925 was defined as: 1) the bilateral polyp grade, i.e. the sum of the grade of the polyps from the left and from the right nasal fossa with a maximum possible bilateral polyp grade of 6 points, as assessed by the investigator by endoscopy, decreased from baseline to the end of treatment by at least one point; and 2) the average of the last eight non-missing congestion/obstruction scores (maximum score was 3) recorded by the patient during treatment in study 1925 decreased from the baseline score by at least 0.5 points. Nasal polyps were graded on a 0-3 categorical scale where 0 = no polyps, 1 = polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate; and 3= large polyps reaching to or below the lower border of the inferior turbinate or polyps medial to the middle turbinate (v14, p32).

Patients were evaluated for polyp size which was graded via nasal endoscopy at the beginning of treatment and monthly throughout the study and patients assessed weekly nasal congestion/obstruction, rhinorrhea, postnasal drainage, loss of smell, and PNIF throughout the study. Symptoms and signs were graded by patients on a categorical scale from 0-3 i.e. none, mild, moderate or severe (v14, pgs33, 34). PNIF was measured by patients weekly (v14, p34). Recurrence was considered to have occurred if the bilateral polyp grade as assessed by endoscopy had increased from the study 2573 baseline by at least one point at the termination of

the study AND the last two congestion/obstruction scores increased from the baseline score by at least 0.5 points on each of the last two scores. Other endpoints included change from baseline in other nasal symptoms/signs and change from baseline in PNIF averaged over each month as well as for the entire 4 month observation period.

There were 135 patients in the study (82 males and 53 females) between the ages of 18-78 years. Of these, 46 received 200 mcg once a day of Nasonex in study 1925, 58 received 200 mcg bid of Nasonex in study 1925 and 31 received placebo. These patients were not randomly selected and therefore no inferential analyses among the treatment groups were done. Placebo patients were entered into study 2573 to maintain the blind for study 1925 which was ongoing.

There were 135 patients from 27 centers in 10 countries enrolled in this study. Site 21 was terminated because of significant departure from GCP including fabrication of source document information for non-existent visits and data from this site was excluded from all efficacy and pooled safety analyses (v15, p593). More than 90% of the patients entered into the study remained in the study for at least 1 month. More than 57% remained for at least 3 months. There were 68 patients (50%) who discontinued treatment before 4 months of treatment (see below; v14, p49, t7). A patient was considered to have completed the study is his/her last visit occurred after day 100. As a result, the numbers below taken from table 7 in volume 14 below as patients who completed the study in each treatment group will be different than the number of patients taken from table 16 in volume 14 below who completed 120 days or more.

Patient disposition in studies 1925 and 2573 (v14, p49, t7)

Study 1925	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo
Patients randomized	115	122	117
Patients completing study	101 (88%)	109 (89%)	95 (81%)
Patients improved	48 (43%)	68 (57%)	38 (34%)
Study 2573			
Patients enrolled	46	58	31
Patients completing study	22 (48%)	27 (47%)	18 (58%)
Patients discontinued	24 (52%)	31 (47%)	13 (42%)
Adverse event	2 (4%)	0	0
Relapse/recurrence	14 (30%)	26 (45%)	9 (29%)
Lost to follow-up	1 (2%)	2 (3%)	0
Did not wish to continue	4 (9%)	2 (3%)	2 (6%)
Non-compliance	1 (2%)	1 (2%)	1 (3%)
Did not meet entry criteria	2 (4%)	0	1 (3%)

There were 15 patients (11%), 6 (13%) in the Nasonex 200 mcg qd group, 6 (10%) patients in the Nasonex 200 mcg bid group and 3 (10%) patients in the placebo group who had one or more protocol violations that included not meeting study entry criteria, non-compliance and unacceptable concomitant medications, that excluded them from the evaluation of efficacy (v14, p51, t8).

Number (%) of patients in study 2573 who remained in the study over time (v14, p69, t16)

Duration	Nasonex 200 mcg qd (n=46)	Nasonex 200 mcg bid (N=58)	Placebo (n=31)
8 or more days	46 (100%)	56 (97%)	31 (100%)
30 or more days	42 (91%	52 (90%)	29 (94%)
60 or more days	32 (70%)	38 (66%)	24 (77%)
90 or more days	25 (54%)	30 (52%)	22 (71%)
120 or more days	8 (17%)	15 (26%)	9 (29%)
Mean	85.6	83.2	94.9
Median	102	91	114
Range	26-127	1-140	20-140

The subset of patients that enrolled in study 2573 did not appear to represent a different subset of patients than the original group in study 1925, indicating that there was no prognostic demographic characteristic that might have suggested that a given patient in study 1925 would improve in study 2573 (see table below; v14, p53, t9).

Category	Nasonex 200 mcg qd (n=46)	Nasonex 200 mcg bid (n=58)	Placebo (n=31)
Mean age	47.7 years	46.6 years	47.7 years
Age range	18-78 years	19-74 years	22-78 years
18-64 years	40 (87%)	54 (93%)	28 (90%)
65 years and older	6 (13%	4 (7%)	3 (10%)
Female/male percentage	37%/63%	41%/59%	39%/61%
Caucasian/Black/Asian/Hispanic	52%/2%/2%/43%	47%/2%/3%/48%	48%/6%/0/45%
Asthma history	5 (11%)	12 (21%)	7 (23%)
PAR history	3 (7%)	8 (14%)	8 (26%)

The percentage of patients who had recurrence of polyps was lower and the time to recurrence was longer in patients who had not received Nasonex in study 1925 than in patients who had received either dosage of Nasonex in study 1925 (see table below; v14, p55-56, t10-11). Among patients who had received Nasonex in study 1925, there was less recurrence and a longer time to recurrence in patients who had received the lower dosage of Nasonex.

Number (%) of patients with recurrence of polyps (v14, p55, t10) and time to recurrence (v14, p56, t11) study 2573

Category	Nasonex 200 mcg qd (n=46)	Nasonex 200 mcg bid (n=55) *	Placebo (n=31)
Recurrence **	15 (32.6%)	23 (41.8%)	7 (22.6%)
Non-recurrence, completed	19 (41.3%)	26 (47.3%)	17 (54.8%)
No-recurrence, dropped out	12 (26.1%)	6 (10.9%)	7 (22.6%)
Time to recurrence ***	81 days	61 days	123 days

* 3 of the 58 patients in this group had missing recurrence status and were not included in the analysis

** recurrence was defined as an increase in bilateral polyp grade of 1 point or more relative to baseline AND an increase of 0.5 points or more in the last two consecutive congestion/obstruction scores relative to baseline

*** based on quartile estimates from Kaplan-Meier survival analysis; 25th percentile

The mean change in polyp grade at endpoint in study 2573 was greater in the groups that received Nasonex during study 1925, especially the group that received 200 mcg bid, than the group that received placebo in that study (see table below). In addition, the bilateral polyp grade at baseline of study 2573 can be seen in the following table (v14, p106). There was no significant difference in comparison of the change from baseline between treatment groups based on age (v14, pgs 131-132). There was less of a change in polyp grade in females (n=17, 23, and 12 in the 200 mcg qd, 200 mcg bid and placebo groups, respectively) than in males (n=29, 33, and 19 in the 200 mcg qd, 200 mcg bid and placebo groups, respectively) in all treatment groups (v14, pgs133-134). There was also a greater change in polyp grade in Caucasians (n=24. 26, 15 in the 200 mcg qd, 200 mcg bid and placebo groups, respectively) than in non-Caucasians (n=22, 30, 16 in the 200 mcg qd, 200 mcg bid and placebo groups, respectively) in all treatment groups (v14, pgs 135-136).

Number of patients	Nasonex 200 mcg qd (n=46)	Nasonex 200 mcg bid (n=56)	Placebo (n=31)
Bilateral polyp grade 0-1	14 (30%)	7 (12%)	9 (29%)
Bilateral polyp grade 2	8 (17%)	17 (29%)	7 (23%)
Bilateral polyp grade 3	9 (20%)	13 (22%)	9 (29%)
Bilateral polyp grade 4	7 (15%)	9 (16%)	3 (10%)
Bilateral polyp grade 5	1 (2%)	4 (7%)	1 (3%)
Bilateral polyp grade 6	1 (2%)	0	1 (3%)

Mean change in polyp grade over 4 months from rollover to endpoint in study 2573 (v14, p59, t12)

Visit	n	Nasonex 200 mcg qd	N	Nasonex 200 mcg bid	N	Placebo
Baseline *	46	4.20	56	4.36	31	4.16
Roll-over **	46	-2.28	56	-2.00	31	-2.06
Month 1	344	-2.20	55	-1.51	29	-1.72
Month 2	37	-2.11	42	-1.60	25	-2.00
Month 3	27	-2.11	34	-1.62	23	-1.61
Month 4	23	-1.83	27	-1.56	18	-1.89
Endpoint	46	-1.59 (-0.69 from rollover)	56	-1.02 (-0.98 from rollover)	31	-1.48 (-0.58 from rollover)

* baseline of study 1925
** roll-over= last visit from study 1925

In the Nasonex 200 mcg qd group (n=46), there were 13 patients who had an increased polyp grade of 1 (28%), 7 patients who had an increased polyp grade of 2 (15%), 2 patients who had an increased polyp grade of 3 (4%) and one patient who had an increased polyp grade of 4 (2%). By comparison, in the Nasonex 200 mcg bid group (n=56), there was an increased polyp grade of 1 in 26 patients (46%), 2 in 9 patients (16%), 3 in 1 patient (2%) and 4 in 2 patients (4%). In the placebo group (n=31), there was an increased polyp grade of 1 in 6 patients (19%), 2 in 5

patients (16%), 3 in no patients and 4 in one patient (3%). More severe worsening of polyps (2-4 point change) was not seen with greater frequency in the two Nasonex groups than in the placebo group, but a one point change was seen in 28% and 46% of the Nasonex 200 mcg qd and Nasonex 200 mcg bid groups, respectively, compared to 19% of the placebo group (v14, pgs 85-93).

COMMENT: *In study 1925, a greater improvement in polyp grade was seen in patients receiving Nasonex than in patients receiving placebo. This study demonstrated an increase in polyp grade beyond that which would be expected without any treatment, i.e. as seen in the placebo group, in patients with nasal polyps after discontinuation of treatment with Nasonex. The placebo group followed in this study is, however, atypical of patients with nasal polyposis in general since they did improve significantly in study 1925 while receiving only placebo.*

The mean change in nasal congestion/obstruction at endpoint in study 2573 was greater in the groups that received Nasonex in study 1925 than in the group that received placebo in that study (see table below). There was no significant difference in the mean change seen in any of the treatment groups based on age or gender (v14, pgs 147-150). In Caucasians, there was a greater increase in nasal congestion from roll-over to endpoint in the Nasonex 200 mcg bid group than in the Nasonex 200 mcg qd group while in non-Caucasians, there was a greater increase in nasal congestion from roll-over to endpoint in the Nasonex 200 mcg qd group than in the Nasonex 200 mcg bid group. In the placebo group, there was improvement in nasal congestion in Caucasians and worsening in non-Caucasians (v14, pgs 151-152).

Mean change in nasal congestion/obstruction over 4 months from rollover to endpoint in study 2573 (v14, p61, t13)

Category	n	Nasonex 200 mcg qd	n	Nasonex 200 mcg bid	N	Placebo
Baseline *	46	2.29	56	2.34	31	2.31
Roll-over *	46	-1.43	55	-1.53	31	-1.00
Week 1	45	-1.42	56	-1.44	31	-1.20
Week 2	46	-1.31	56	-1.39	31	-1.05
Week 3	45	-1.18	54	-1.30	31	-1.04
Week 4	42	-1.28	48	-1.29	27	-0.99
Month 1	46	-1.29	56	-1.36	31	-1.08
Month 2	38	-1.21	45	-1.24	26	-1.18
Month 3	29	-1.34	34	-1.44	22	-1.12
Month 4	21	-1.28	528	-1.55	18	-1.25
Endpoint	46	-1.00 (-0.43 from rollover)	56	-1.14 (-0.39 from rollover)	31	-0.97 (-0.03 from rollover)

* baseline of study 1925
* rollover = average of month 4 from study 1925

The mean change in loss of sense of smell at endpoint in study 2573 did not change significantly in any of the three treatment groups compared to the average value at month 4 in study 1925 (see table below)

Mean change in loss of smell over 4 months from rollover to endpoint in study 2573 (v14, p62, t14)

Category	n	Nasonex 200 mcg qd	n	Nasonex 200 mcg bid	n	placebo
Baseline *	46	1.99	56	1.99	31	1.97
Rollover **	46	-0.96	55	-0.73	31	-0.61
Week 1	45	-1.03	56	-0.81	31	-0.89
Week 2	46	-0.92	56	-0.83	31	-0.74
Week 3	45	-0.88	54	-0.77	31	-0.84
Week 4	42	-0.94	48	-0.76	27	-0.68
Month 1	46	-0.95	56	-0.78	31	-0.80
Month 2	38	-0.91	45	-0.74	26	-0.97
Month 3	29	-0.92	34	-0.74	22	-0.73
Month 4	21	-0.99	28	-0.85	18	-0.70
endpoint	46	-0.84	56	-0.66	31	-0.77

There was a decrease in PNIF from the end of treatment in study 1925 until the endpoint in study 2573 in both groups that had received Nasonex in study 1925 while the PNIF increased slightly in the group that had received placebo in study 1925. The decrease in PNIF would be expected in the Nasonex groups because of withdrawal from the active treatment (see table below).

Change in peak nasal flow rate (liters/minute) from rollover to endpoint in study 2573 (v14, p64. t15)

Category	n	Nasonex 200 mcg qd	N	Nasonex 200 mcg bid	N	placebo
Baseline *	46	87.9	56	83.3	31	81.5
Rollover **	46	43.5	55	50.8	31	29.7
Week 1	45	40.9	56	46.6	31	33.4
Week 2	46	39.5	56	41.0	31	31.6
Week 3	45	36.4	54	37.4	30	31.5
Week 4	42	36.6	48	39.6	27	35.8
Month 1	46	38.0	56	41.1	31	32.1
Month 2	38	35.2	45	35.5	25	29.3
Month 3	29	33.7	34	31.9	22	28.9
Month 4	20	41.8	28	32.1	18	26.0
endpoint	46	28.9	56	29.9	31	33.1

Adverse events: Although no treatment was given during this study, adverse events were recorded and reflected at most a possible carryover effect from treatment in study 1925. Adverse events occurred in 35%, 24% and 35% of the groups that had previously in study 1925 received Nasonex 200 mcg qd, Nasonex 200 mcg bid and placebo, respectively. None of these adverse events were considered related to the study medication given in study 1925. The only adverse events that occurred in more than one patient were: 1) viral infection (2 patients in the Nasonex 200 mcg qd group); 2) pharyngitis (2 patients in the Nasonex 200 mcg bid group and one patient in the Nasonex 200 mcg qd group); 3) URI (5 patients in the Nasonex 200 mcg qd and placebo groups and 6 patients in the Nasonex 200 mcg bid group); and 4) rhinitis (2 patients in each of the Nasonex groups). There were 3 severe or life-threatening adverse events reported in the Nasonex 200 mcg qd group (metastatic disease, prostate cancer, and cellulites) and one in the placebo group (sneezing).

COMMENT: Although statistical comparison of the treatment groups, as noted by the sponsor, would not be appropriate, it is hard to ignore the fact that not only was the recurrence rate

higher in patients who had received Nasonex, most notably at the 200 mcg bid dosage, than it was in patients who had received placebo, but the time from discontinuation of treatment to recurrence was shorter in the groups who had received Nasonex, especially in the 200 mcg bid group, than in the group that had received placebo. While the recurrence rate of 33-42% in the groups that received Nasonex is somewhat less than recurrence rates after other therapy for nasal polyps, the even lower rate of recurrence in the placebo group makes it difficult to conclude from this study that Nasonex significantly reduced the rate of recurrence of nasal polyps after treatment. It is interesting to note that the mean change in polyp grade from the end of study 1925 to the end of study 2573 was greater in the group that received Nasonex 200 mcg bid than in the groups that received the lower dosage of Nasonex and placebo, suggesting that the greater the dose of Nasonex, the greater and more rapid is the recurrence of nasal polyps. Hypothetically, it could be argued that there is a rebound effect from the use of Nasonex and the higher the dose, the more rapid is this rebound effect, resulting in more rapid recurrence of nasal polyps. Further study is needed to determine if administration of Nasonex over a longer period of time than the 4 month period in study 1925 and/or with a longer follow-up of patients than the four months in study 2573 would support such a hypothesis.

Vital signs: There was no significant change in systolic or diastolic blood pressure or pulse rate from baseline to endpoint in study 2573 or significant difference in any of the treatment groups based on evaluation of data from all enrolled patients or based on age, gender or race (v14, pgs 242-264). There were no patients in any of the three treatment groups who had more than a 10% change from baseline in systolic or diastolic blood pressure or pulse rate.

10.2. Line-by-Line Labeling Review

Listed and discussed below, as they appear in the proposed labeling starting with the beginning of the labeling, are the applicant's proposed changes in the labeling for the already marketed product and this reviewer's comments.

10.2.1 Clinical Pharmacology section; Pharmacodynamics subsection:

10.2.1.1. In the first sentence of the first paragraph, the applicant has changed (b) (4) to "*Four*" before "clinical pharmacology studies have been conducted. This change simply updates the number of studies of this type that have been done and is acceptable.

10.2.1.2. An additional paragraph has been added after the third paragraph which describes a fourth clinical pharmacology study. The sponsor states that "*In a fourth study, adrenal function was assessed in 213 patients with nasal* (b) (4) *before and after 4 months of treatment with either Nasonex Nasal Spray, 50 mcg (200 mcg once or twice daily) or placebo by measuring 24 hour urinary free cortisol levels. NASONEX Nasal Spray, 50 mcg, at both doses (200 and 400 mcg/day) was not associated with statistically significant decreases in the 24 hour urinary free cortisol levels compared to placebo*." This is an accurate description of the study results and is acceptable.

10.2.2 Clinical Pharmacology section: Clinical Studies subsection:

An additional three paragraphs have been added describing the studies done to evaluate Nasonex in the treatment of nasal polyposis as follows:

There were no clinically relevant differences in the effectiveness of NASONEX Nasal Spary, 50 mcg, in the studies evaluating treatment of nasal polyposis across subgroups of patients defined by gender, age or race."

COMMENT: The applicant should divide the Clinical Studies section into two sections, a section on allergic rhinitis and a section on nasal polyps to clarify if the data refers to studies in allergic rhinitis or studies in patients with nasal polyps. This should be done by inserting subheadings on line 130 under the heading "Clinical Studies" that reads "Allergic Rhinitis" and on line 171 prior to the discussion of the data from studies in patients with nasal polyposis that reads "Nasal Polyps". The applicant should also delete the entire first two new paragraphs in the Clinical Studies section on studies in patients with nasal polyps on lines 171-198 and replace those paragraphs with the following: "Two studies were performed to evaluate the efficacy and safety of Nasonex Nasal Spray in the treatment of nasal polyps. These studies involved 664 patients with nasal polyps, 441 of whom received Nasonex Nasal Spray. These studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in patients 18-86 years of age with bilateral nasal polyps. Patients were randomized to receive Nasonex Nasal Spray 200 mcg once daily, 200 mcg twice daily or placebo for a period of 4 months. The co-primary

efficacy endpoints were 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of treatment as assessed by endoscopy. Efficacy was demonstrated in both studies at a dose of 200 mcg twice daily and in one study at a dose of 200 mcg once a day (see table below).

Effect of Nasonex Nasal Spray in two randomized, placebo-controlled trials in patients with nasal polyps

	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value for Nasonex 200 mcg qd vs placebo	P value for Nasonex 200 mcg bid vs placebo
Study 1	N = 112	N = 121	N = 114		
Baseline bilateral polyp grade *	4.21	4.27	4.25		
Mean change from baseline in bilateral polyp grade	- 1.13	- 0.95	- 0.49	< 0.001	0.01
Baseline nasal congestion **	2.29	2.35	2.28		
Mean change from baseline in nasal congestion	- 0.47	- 0.61	- 0.24	0.001	< 0.001
Study 2	N = 101	N = 101	N =100		
Baseline bilateral polyp grade *	4.00	4.10	4.17		
Mean change from baseline in bilateral polyp grade	- 0.76	- 0.98	- 0.67	0.62	0.04
Baseline nasal congestion **	2.23	2.20	2.18		
Mean change from baseline in nasal congestion	- 0.42	- 0.66	- 0.23	0.01	< 0.001

* polyps were graded by the investigator based on endoscopic visualization, using a scale of 0-3 where 0 = no polyps, 1 = polyps in the middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the midlle turninate but not the inferior border of the inferior turbinate; 3 = polyps reaching to or below the lower border of the inferior turbinate, or polyps medial to the middle turbinate.

** nasal congestion/obstruction was scored daily by the patient using a 0-3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms

These changes provide the reader with a more concise description of the results of the two key studies that provide data on the treatment of nasal polyps.

10.2.3 Indications and Usage section:

The applicant has added an additional paragraph that reads, "*NASONEX Nasal Spray, 50 mcg, is indicated for the treatment of nasal polyps* (b) (4) *in adult and adolescent patients 18 years of age and older. Safety and effectiveness*

of NASONEX Nasal Spray, 50 mcg, for the treatment of nasal [redacted] *in pediatric patients less than 18 years of age have not been established."*

COMMENT: In the Indications and Usage section, the applicant should delete [redacted] on line 214 in the second paragraph in this section.

Precautions section:

10.2.4.1. Information for Patients subsection: The applicant has changed [redacted] to [redacted] and deleted [redacted] to allow for the use of the proposed dosage of 200 mcg bid. This is an acceptable change.

10.2.4.2. Precautions section; Carcinogenesis, Mutagenesis, Impairment of Fertility subsection: see Pharmacology review of this section of the labeling.

10.2.4.3. Precautions section; Pregnancy subsection: see Pharmacology review of this section of the labeling.

10.2.4.4. Precautions section; Pediatric subsection: The term "*allergic rhinitis*" has been added in several spots in this section of the labeling to distinguish data previously in the labeling that referred to studies for allergic rhinitis and that does not apply to evaluation of Nasonex for nasal [redacted] The applicant has added a statement that safety and effectiveness has not been established "*in children less than 18 years of age with nasal* [redacted]. This is an acceptable change.

10.2.4.5. Precautions section; Geriatric use subsection: Based on the data from the studies in patients with nasal polyposis, the first sentence has been reworded to state, "A total of *280* patients above 64 years of age *with allergic rhinitis or nasal* [redacted] (age range 64 to *86* years) have been treated with NASONEX Nasal Spray, 50 mcg for up to 3 *or 4* months, respectively." This is an acceptable change.

10.2.5. Adverse Reactions section: The applicant has added "*with allergic rhinitis*" in two places to indicate that the data is based on studies of patients with allergic rhinitis. The applicant has also added an additional paragraph that states,

[redacted]

COMMENT: The applicant should divide the Adverse Reactions section into two sections, a section on allergic rhinitis and a section on nasal polyps to clarify if the data refers to studies in allergic rhinitis or studies in patients with nasal polyps. This should be done by inserting subheadings on line 429 under the heading "Adverse Reactions" that reads "Allergic Rhinitis"

and on line 492 prior to the discussion of the data from studies in patients with nasal polyps that reads "Nasal Polyps". In the new paragraph on lines 492-497 under the Adverse Reactions section, dealing with adverse events in patients with nasal polyposis, insert an additional sentence at the end of the paragraph that reads, "The incidence of epistaxis was greater in patients who received Nasonex Nasal Spray compared to placebo". *The higher dose-related incidence of epistaxis seen in patients who received Nasonex Nasal Spray needs to be mentioned in the labeling since it is recognized that intranasal corticosteroid sprays can produce this adverse event. The applicant should combine the data from studies 1925, 1926 and Q99-925-01 in regard to the incidence of epistaxis in patients who received each dose of Nasonex and patients who received placebo and provide those data in parentheses after the above sentence.*

10.2.6. Dosage and Administration section: The applicant has added "*Allergic Rhinitis*" before the approved labeling for allergic rhinitis and has deleted (b) (4) from before "recommended dose" in two places. In addition, the applicant has added the following paragraph:

(b) (4)

COMMENT: *The applicant has not performed step down studies to demonstrate that it is safe and effective to reduce the dose of Nasonex once symptoms are controlled. Therefore, suggesting this approach for the management of patients with nasal polyposis is not evidence-based and is inappropriate. The new 5th paragraph on lines 541-547 under the Dosage and Administration section should be deleted and replaced with the following: "The recommended dose for nasal polyps is two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg). A dose of two sprays (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 mcg) is also effective in some patients*."

10.2.7. Patient instructions for use:

10.2.7.1. The applicant has changed the wording of the last sentence under instruction 3 to read, "DO NOT spray directly onto nasal septum, *the wall between the two nostrils."* This is an acceptable addition.

10.2.7.2. Under Caution, the applicant has made appropriate changes to incorporate the proposed new indication for nasal (b) (4)

10.2.8. In addition, the applicant should change (b) (4) (b) (4) to "nasal polyps" throughout the labeling for consistency. Under Patients Instructions for Use, under the Caution section on lines 639-653, in the last sentence of the first paragraph on line 645 the applicant should add "helps to" after "50 mcg" and before "control".

10.3. Submission of 12 November 2004:

This submission was a response by the applicant to a FAX from the Division requesting clarification about data submitted by the applicant. Specifically, the Division asked the applicant to provide documentation about specific instructions given to investigators in study Q099-925-01 in reagard to polyp grade assessment, explain why some dropouts had missing data in study Q99-925-01, respond about any additional studies assessing Nasonex for the treatment of nasal polyps, indicate whether there was identification of patients at baseline who had allergic rhinitis, submit an analysis of the primary outcome variables in the three key studies for patients with and without allergic rhinitis if they had been identified at baseline, and comment on the large number of dropouts in the placebo group in study Q99-925-01 and what effect this had on the study results.

10.3.1. Documentation of specific instructions given to investigators regarding polyp grade assessment in study Q999-925-01:

The applicant responded that no specific instructions were given to investigators regarding how polyp grade assessment was to be made at each clinic visit. Investigators were instructed at the study center initiation visit that they should grade the size of polyps and choose the grade from the most severe side and enter that score in the CRF. Investigators were then instructed to follow the largest polyp seen at visit 1 and how it changed in size at all subsequent visits. No record was entered into the CRF as to which polyp was followed or in which nostril the largest polyp was seen. It is not known if investigators followed consistently the original largest polyp or recorded the grade of the largest polyp found at each visit. *This inconsistency in grading of nasal polyps does not sufficiently damage the credibility of the data to alter the conclusions regarding the efficacy of Nasonex Nasal Spray.*

10.3.2. Dropouts in study Q99-925-01

The applicant responded that in the event of a patient's early discontinuation from the study, the investigators were instructed to perform all procedures and evaluations scheduled for the final visit but some investigators recorded these data in one place and others recorded these data in another place. *This is an acceptable response by the applicant*.

10.3.3. Additional studies with Nasonex in the treatment of nasal polyps

The applicant responded that there are no additional completed or ongoing studies assessing Nasonex in the treatment of nasal polyps except for an ongoing study examining the effiacacy and safety of Nasonex following post-surgical removal of nasal polyps. *This is an acceptable response by the applicant.*

10.3.4. Identification of patients with allergic rhinitis

The applicant responded that in studies 1925 and 1926 were identified by history as having PAR. Patients with SAR were excluded from those studies. In study Q99-925-01 which did not exclude patients with allergic rhinitis, a history of allergic rhinitis was captured for 12 patients

entered into the study. No analyses were performed for this study with respect to allergic rhinitis. Approximately 20% of the patients in studies 1925 and 1926 had PAR. Inferential analyses to assess the consistency of treatment with respect to PAR are provided by the applicant in regard to the two co-primary endpoints. Analysis was performed only on pooled data from these two studies. The results of that analysis can be seen in the table below.

	Bilateral polyp grade	Congestion/obstruction	Loss of smell
Without PAR			
200 mcg qd vs placebo	N=354, Δ-0.49, p<.001	N=355, Δ-0.21,p<.001	N=355, Δ-0.15, p=0.005
200 mcg bid vs placebo	N=350, Δ -0.46, p<.001	N=351, Δ-0.35, p<.001	N=351, Δ-0.09,p=0.09
With PAR			
200 mcg qd vs placebo	N=73, Δ 0.37, p=0.3	N=77, Δ-0.19, p0.16	N=77, Δ-0.10, p=0.39
200 mcg bid vs placebo	N=86, Δ 0.04, p=0.8	N=89, Δ-0.57, p<.001	N=89, Δ-0.29, p=0.01

COMMENT: Nasonex Nasal Spray has been approved for allergic rhinitis. If there were a large number of patients in the key studies who had associated allergic rhinitis, the data could have been driven by the already established efficacy of Nasonex Nasal Spray for symptoms of allergic rhinitis. The data submitted in this submission by the applicant demonstrate the efficacy of Nasonex in patients with nasal polyps without allergic rhinitis, supporting the indication for nasal polyps independent of any effect on allergic rhinitis. The number of patients who had co-existing allergic rhinitis is too small to reach any conclusion about lack of efficacy that was seen in patients who have co-existing allergic rhinitis and nasal polyps. More importantly, the diagnosis of allergic rhinitis was based only on patient history. No skin testing was done. As a result, the actual number of patients who had allergic rhinitis was not established in these studies. Therefore, no conclusion about this data in terms of efficacy in patients with concomitant allergic rhinitis and nasal polyps can be made.

10.3.5. Dropouts in study Q99-925-01

A total of 298 patients were randomized in this study. There were 7 patients excluded from the ITT population, one in the Nasonex group and 6 in the placebo group. Two patients were randomized to placebo but never received treatment. The other five patients had no baseline or post-baseline data. Removing these 7 patients leaves an ITT population of 291. The applicant performed sensitivity analyses on polyp grade and improvement in nasal congestion at endpoint. These analyses indicated that only if a very high percentage of placebo patients showed improvement among the placebo patients with no month 4 data would it change the statistical significance observed at this time point. *This is an acceptable response by the applicant (see Statistical Review).*

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/s/

Richard Nicklas
12/10/04 11:05:47 AM
MEDICAL OFFICER

Eugene Sullivan
12/10/04 11:27:58 AM
MEDICAL OFFICER
Agree with recommendation. See my memorandum.

Medical Officer Review
Division of Pulmonary and Allergy Drug Products (HFD-570)

Application number: NDA 20,762
Application type: supplemental NDA
Sponsor: Schering Corporation
Product name: Nasonex
Established name: mometasone furoate
Category of Drug: corticosteroid
Route of Administration: aqueous nasal spray

Medical Reviewer: Richard Nicklas MD
Date of Review: 2 April 2004
Review for filing meeting to be held on 29 March 2004

Document Date: 26 February 2004
CDER Stamp Date: 27 February 2004
Submission type: efficacy supplement for nasal polyposis
PUDFA date: 26 December 2004
Division goal date: 12 December 2004

Overview of Supplemental Submission:

Background: The sponsor has submitted a supplemental NDA for the use of Nasonex Nasal Spray at a dose of 200 mcg once a day and 200 mcg bid for the treatment of nasal polyps (b) (4) in patients 18 years of age and older. The clinical program needed to support an indication for the treatment of nasal polyps was initially discussed with the Agency on the conference call of 21 February 2001. The Division indicated that two studies, and in addition, evaluation of polyp recurrence rate over at least 4 months, would be needed. Recommended endpoints were: 1) change from baseline in polyp grade based on rhinoscopy; and 2) nasal symptoms scores. On 14 October 2003, a preNDA meeting was held with the Division. At this time, the sponsor presented their proposed clinical program for Nasonex Nasal Spray in the treatment of nasal polyps, which the Division considered adequate for filing of this supplemental NDA.

Nasonex was approved for the treatment of SAR and PAR in October 1997 for patients 12 years of age and older at a dose of 200 mcg once a day and in July 2002 for patients 2-11 years of age at a dose of 100 mcg once a day. In addition, Nasonex is approved for the prophylaxis of nasal symptoms of SAR in patients 12 years of age and older. Nasonex is a synthetic corticosteroid delivered as an aqueous nasal solution.

Nasal polyps occur in 0.2-4% of the general population. Patients present with nasal obstruction, as well as other symptoms of rhinitis, and often loss of smell. Nasal polyps

occur much more frequently in adults than in children. They lead to a decreased quality of life and are often associated with asthma, ASA intolerance and cystic fibrosis.

> This submission contains efficacy and safety data from three clinical studies and one observational follow-up study. Two of the controlled studies are considered pivotal by the sponsor and were designed to include recommendations made by the Agency. These two studies (1925 and 1926) are randomized, double-blind, placebo-controlled parallel multicenter studies with administration of Nasonex at a dose of 200 mcg once a day or bid for a period of 4 months. There were 962 patients 18 years of age and older who participated in these studies, 594 of whom received Nasonex 200 mcg once daily or bid. In addition, the sponsor has submitted the results from study 2573, a 4 month follow-up study to assess the rate of recurrence of nasal polyp disease in patients whose condition improved with up to 4 months treatment in study 1925. These three studies reflect the recommendations made by the Division to the sponsor on 21 February 2001 and 14 October 2003. The Division concluded that this database was adequate for filing this supplemental NDA, but noted that safety and efficacy determinations, assessment of the appropriate dose and analysis of the data would be review issues and asked the sponsor to perform a responder analysis based on polyp size alone. The sponsor has performed this analysis. William LaMear MD was an investigator in study 1925 (site 8). Dr LaMear has been previously cited for falsifying information in a previous study. The sponsor was asked at the pre-NDA meeting to analyze the data with and without inclusion of Dr LaMear's study site. The sponsor has done this.

Based on the data from these studies the clinical Pharmacology, Indications and Usage, Precautions, Adverse Reactions, and Dosage and Administration sections of the labeling have been modified. In the Pharmacodynamics section, there is a new paragraph describing a study assessing adrenal function in 213 patients with nasal polyposis before and after 4 months of treatment based on 24 hour urinary free cortisol levels. In the Clinical Studies section there is a description of the studies performed to support a claim for treatment of nasal polyps. Under the Indications and Usage section, an additional paragraph has been added that states, (b) (4) [redacted] In the Adverse Reactions section there is a new paragraph reflecting the safety data form the studies on nasal polyposis. Under the Dosage and Administration section, there is a new paragraph indicating the dosage that should be used for the treatment of nasal polyps. Other changes in the labeling are relatively minor and generally are changed based on the data from the studies on nasal polyposis.

Filing Contents: Included are a cover letter, application form, user fee information, electronic filing requirements, environmental assessment, investigator debarment certification, financial disclosure, proposed labeling changes, statistical dataset, case report tabulations, case report forms, statement of good clinical practice, statement that all clinical studies were conducted in accordance with IRB and informed consent procedures, an integrated summary of efficacy, safety and benefits/risks, reports of post-marketing experience, and patent information. There are no deficiencies in clinical data required for filing.

Filing Issues:

The sponsor is requesting a waiver for the assessment of the safety and efficacy of Nasonex in the treatment of nasal polyposis in patients less than 18 years of age. The sponsor's rationale for requesting this waiver is based on the low occurrence of nasal polyposis in children and adolescents and the contention that Nasonex in this age group does not represent a meaningful therapeutic benefit over existing treatment, i.e. endoscopic surgery.

The data supplied by the sponsor indicates that nasal polyposis occurs, although infrequently, in patients 6-17 years of age. The percentage of patients 6-17 years of age who have nasal polyps associated with cystic fibrosis or secondary to allergic rhinitis is not clear from the data that is provided. The labeling for beclomethasone nasal spray states that it is indicated for the prevention or recurrence of nasal polyps following surgical removal and is approved for patients 6 years of age and older. Therefore, it is reasonable that the sponsor study Nasonex for the treatment of nasal polyps in patients 6-17 years of age. In doing so, the sponsor will have the opportunity to determine the appropriate dose for the treatment of nasal polyposis in this patient population. Therefore, the sponsor's request for a waiver for the study of Nasonex in the treatment of nasal polyposis in patients less than 18 years of age is not granted.

There are no other clinical filing issues. The NDA does not need to be discussed at an advisory committee meeting. DSI does not need to audit any of the studies submitted, based on the fact that the number of patients at the study sites in the key studies, especially study 1925, were similar (i.e. no single large center was driving the study results), no significantly different findings at any center were noted and there was no basis for suspecting any irregularities in the pivotal studies. The review of this supplemental NDA will be completed by 1 July 2004. The clinical data submitted in electronic form is acceptable.

Outstanding Issues: The Project Manager will inform that the request for a waiver on the study of Nasonex for nasal polyps in patients under the age of 18 years is denied.

Recommended Regulatory Action: The clinical recommendation is to file the application.

Medical Reviewer Signature and Date:

Medical Team Leader Signature and Date:

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/s/

Richard Nicklas
4/2/04 08:28:18 AM
MEDICAL OFFICER

Eugene Sullivan
4/2/04 12:43:22 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-762/S023

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #2

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPDP	20-762

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

4. AF NUMBER

5. SUPPLEMENT(S)
NUMBER(S) DATES(S)
SE1-023 2/26/04(assigned 2/27/04)

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Nasonex® Nasal Spray	mometasone furoate nasal spray

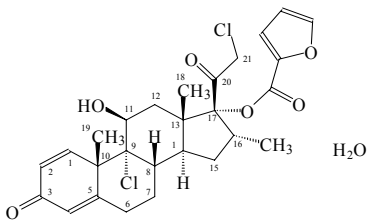
8. SUPPLEMENT PROVIDES FOR: The use of Nasonex Nasal Spray for the treatment of nasal polyps (b) (4) in adults.

9. AMENDMENT(S), REPORT(S), ETC.
SE1-023 BL 19-NOV-2004*
*Subject of current review.

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
anti-inflammatory corticosteroid	RX X OTC __	

13. DOSAGE FORM(S)	14. POTENCY
aqueous nasal spray	100 or 200 µg/day

15. CHEMICAL NAME AND STRUCTURE
9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methylpregna-1,4-diene-3,20-dione Monohydrate



Mometasone Furoate Monohydrate

16. RECORDS AND REPORTS
CURRENT YES__NO___
REVIEWED YES__NO___

17. COMMENTS: The labeling amendment submitted on 19-NOV-2004 includes labels and labeling that are consistent with those that were recently approved with the reformulation supplement (removal of phenylethyl alcohol, SCF-007), with the exception of the removal of the phrase "New Scent-Free Mist" from the trade and professional sample cartons, and the change in the color on the trade and sample bottle labels from teal to blue. The phrase "New Scent-Free Mist" was to be removed after 6 months of marketing as agreed earlier.

cc:
Orig. NDA 20-762
HFD-570/div. File
HFD-570/CBertha/11/19/04
HFD-570/RLostritto
HFD-570/LGarcia
R/D Init. by:_____
F/T by: CBertha/11/19/04
doc # 04-02-26 rev.doc

18. CONCLUSIONS AND RECOMMENDATIONS: From a CMC perspective, the supplement, as amended, is recommended for approval (AP).

19. REVIEWER NAME:	SIGNATURE	DATE COMPLETED
Craig M. Bertha, Ph.D.		19-NOV-2004

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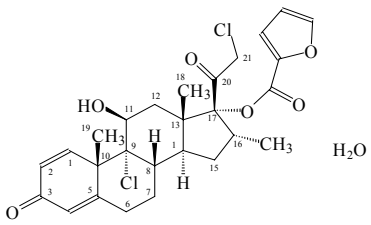
/s/

Craig Bertha
11/29/04 08:16:38 AM
CHEMIST

Richard Lostritto
12/1/04 02:19:48 PM
CHEMIST

CHEMIST'S REVIEW #1

	1. ORGANIZATION HFD-570 DPDP	2. NDA NUMBER 20-762
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033		4. AF NUMBER
		5. SUPPLEMENT(S) NUMBER(S) DATES(S) SE1-023 2/26/04(assigned 2/27/04)
6. NAME OF DRUG Nasonex® Nasal Spray	7. NONPROPRIETARY NAME mometasone furoate nasal spray	
8. SUPPLEMENT PROVIDES FOR: The use of Nasonex Nasal Spray for the treatment of nasal polyps (b) (4) in adults.		9. AMENDMENT(S), REPORT(S), ETC.
10. PHARMACOLOGICAL CATEGORY anti-inflammatory corticosteroid	11. HOW DISPENSED RX X OTC __	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) aqueous nasal spray	14. POTENCY 100 or 200 µg/day	
15. CHEMICAL NAME AND STRUCTURE 9,21-Dichloro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methylpregna-1,4-diene-3,20-dione Monohydrate  Mometasone Furoate Monohydrate		16. RECORDS AND REPORTS CURRENT YES__NO___ REVIEWED YES__NO___

17. COMMENTS: See review notes attached.

cc:
Orig. NDA 20-762
HFD-570/div. File
HFD-570/CBertha/3/2/04
HFD-570/RLostritto
HFD-570/LGarcia
R/D Init. by:_____
F/T by: CBertha/3/2/04
doc # 04-02-26 rev.doc

18. CONCLUSIONS AND RECOMMENDATIONS: From a CMC perspective, the supplement is recommended for approval (AP).

19. REVIEWER NAME:	SIGNATURE	DATE COMPLETED
Craig M. Bertha, Ph.D.		3/2/04

Chemist's Review Notes

The efficacy supplement provides data to support the use of the product for treatment and (b) (4) nasal polyps in adults. There is no CMC information other than in a section related to an environmental assessment. The addition of a new indication increases the use of the active moiety. The firm has filed an exclusion from submission of a full environmental assessment under 21 CFR 25.31 (b). They state that the estimated concentration of the substance at the point of entry into the aquatic environment will still be below 1 ppb and that no extraordinary circumstances (as listed in 21 CFR 25.21) apply. In appendix I to module 1.12.14 Environmental Analysis the calculated estimation yields an expected introduction concentration (EIC) of 1.7×10^{-2} ppb.

Evaluation: Satisfactory. The exclusion from the requirements to prepare and submit an environmental assessment are consistent with that stated in 21 CFR 25.31 (b).

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/s/

Craig Bertha
3/2/04 07:06:32 AM
CHEMIST

Richard Lostritto
3/4/04 12:36:47 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-762/S023

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 20-762/S-023

Drug Name: Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray, 50mcg

Indication(s): Treatment of Nasal Polyposis

Applicant: Schering Corporation

Date(s): Volumes dated February 26, 2004, April 06, 2004, and April 26, 2004 and November 12, 2004. Data files dated February 26, 2004, April 6, 2004, April 26, 2004

Review Priority: Regular

Biometrics Division: Biometrics II (HFD-715)

Statistical Reviewer: James R. Gebert, Ph.D.

Concurring Reviewers: Sue Jane Wang, Ph.D.

Stephen Wilson, Dr. P.H.

Medical Division: Division of Pulmonary and Allergy Drug Products (HFD-570)

Clinical Team: Richard Nicklas, M.D.

Project Manager: Ms Lori Garcia

Keywords: Clinical Studies, NDA Review

TABLE OF CONTENTS

1 Executive Summary

1.1 Conclusions and Recommendations

The sponsor has provided data from three Phase 3 efficacy studies of Nasonex in patients with nasal polyposis. Study P01925 showed that Nasonex at doses of 200 mcg QD AM and 200 mcg BID was more effective than placebo in changes from baseline in Nasal Congestion/Obstruction averaged over the first month and changes from baseline in Bilateral Polyp Grade at Endpoint, the protocol defined primary assessment times. Study P01926 showed that both doses were more effective than placebo in changes from baseline in Nasal Congestion/Obstruction averaged over the first month. Neither dose showed efficacy in reducing Bilateral Polyp Grade at Endpoint compared to placebo in that study although the results were approaching significance for the 200 mcg BID dose (P=0.078). In a post-hoc analysis, the sponsor found the 200 mcg BID dose significant for polyp grade if baseline polyp grade is added as a covariate. Including baseline seems justified as baseline is consistently a large explainer of variability in these studies.

The sponsor provided the results of Nordic Study Q99-925 as a supportive study. Although this study had a different way to assess these efficacy variables than in Studies P01925 and P01926, when analyzed similarly, Nasonex 200 mcg QD AM, the only Nasonex dose in that study, was significantly different from placebo in changes from baseline in Nasal Congestion/Obstruction averaged over the first month and changes from baseline in Polyp Grade at Endpoint. The grading of polyp size was slightly different than in the other studies. It might have not been consistently measured by the investigators.

The overall conclusion is that Nasonex at a dose of 200 mcg BID is effective in the treatment of nasal polyps. The BID dose showed more efficacy for changes from baseline in Nasal Congestion/ Obstruction Score than the QD AM dose.

1.2 Brief Overview of Clinical Studies

After discussion with the Agency about obtaining a claim for the treatment of nasal polyps, the sponsor was told that Nasonex would have to show an effect in both nasal congestion/obstruction and reduction of polyp size. The sponsor was also told that they should investigate whether the efficacy persists after treatment is stopped. The sponsor presented data from 2 studies (Studies P01925 and P01926) with a four month treatment period in patients with Nasal Polyposis at a pre-NDA meeting with the Agency. Both studies showed an effect on Nasal Congestion/Obstruction for both Nasonex 200 mcg QD AM and 200 mcg BID. Only Study P01925 showed an effect on Bilateral Polyp Grade, where both doses were significantly more effective than placebo.

The sponsor decided to include in the submission the results of a Nordic Study, Q99-925, which compared Nasonex 200 mcg QD and placebo over a 4 month treatment period. This study had similar efficacy variables. Although the protocol primary efficacy analyses were different than in Studies P01925 and P01926, the sponsor provided similar analyses in their Clinical Overview Section of volume 1.

Study P02573 was an observational, follow-up study on subjects who improved in Study P01925 to see if there was recurrence of polyposis.

1.3 Statistical Issues and Findings

This reviewer was able to duplicate the sponsor's results for the primary efficacy variables in Studies P01925, P01926 and Q99-925.

The results of Study P02573 are more problematic since it isn't a randomized study. Although this study showed a higher recurrence rate in Nasonex patients than in the placebo patients, the placebo patients are a very selective group of patients.

2. Introduction

2.1 Overview

Nasonex (Mometasone Furoate Nasal Spray), denoted by MFNS in the remainder of this review, is approved for the treatment of Seasonal and Perennial Allergic Rhinitis at a dose of 200 mcg QD AM. The sponsor provided this submission for the treatment of nasal polyps. The sponsor chose the doses of 200 mcg QD AM and 200 mcg BID because they stated that other corticosteroids have been approved for nasal polyps in other countries at the SAR dose but it was felt that a higher dose might be needed. No corticosteroid has a label claim for the treatment of nasal polyps in the US.

The sponsor had numerous interactions with the agency with regard to this submission. The sponsor originally wanted to use only changes from baseline in Nasal Congestion/Obstruction Score as the primary efficacy variable. The agency insisted that changes from baseline in Nasal Polyp Grade must be made a co-primary efficacy variable. The sponsor was asked to include a study of whether MFNS affected the recurrence of nasal polyps. The sponsor provided the protocol for Study P02573 which was reviewed by the agency. At a pre-NDA meeting the sponsor provided the results of Studies P01925, P01926, and P02573. The agency noted that Study P01926 failed to demonstrate efficacy for changes from baseline in Bilateral Polyp Grade and stated that the sponsor should provide any additional evidence of efficacy they possessed and that approval would be a review issue. The sponsor held up their submission after learning about Study Q99-925, done by an affiliate, until the results of that study could be included in the submission. The sponsor stated that they or their affiliates have conducted no other nasal polyp studies.

This review will mainly focus on Studies P01925, P01926 and Q99-925. Study P02573 is an observational follow-up study that followed most of the patients that improved in Study P01925 to see if the improvement was maintained. Although improved placebo patients were included to maintain the blind, comparison between treatments is difficult since the improved patients are no longer the random sample that entered Study P01925.

This reviewer originally had difficulty duplicating the results of Study Q99-925. This reviewer made an information request to the sponsor on March 29, 2004 to help understand the difficulties. The sponsor in their April 6, 2004 and April 26, 2004 responses provided information about their analyses. The sponsor's contract statistician had used a worst case value of Polyp Grade (3) for subject 406 at endpoint. When this reviewer used that value he got results identical to that of the sponsor. [The results of changes from baseline in Polyp Grade is also significant if that subject was deleted from the analysis.] The sponsor has adequately addressed all concerns of the March 29, 2004 fax.

2.1.1 Study P01925

Study P01925 was a multicenter, randomized, double-blind, parallel group, three arm study evaluating two doses of MFNS compared with placebo in subjects with nasal polyps. This study had a single-blind placebo Run-in Period of 14 days followed by 4 months of double-blind treatment. The two MFNS doses were 200 mcg QD and 200 mcg BID. Randomization was stratified by asthma status. Subjects with asthma could continue their inhaled corticosteroid if the dose was held stable.

There were two co-primary efficacy endpoints: (1) change from baseline in Congestion/Obstruction Score averaged over the first month of the treatment period, and (2) change from baseline to the last assessment in the Bilateral Polyp Grade during the entire four months of the treatment period.

Nasal congestion/obstruction is the most frequent symptom occurring in subjects with nasal polyposis. Congestion/obstruction was scored every morning before dosing by the subjects (0 to 3 scale; 0=none; 1=mild; 2=moderate; 3=severe) and recorded in a daily diary.

To enter the study, patients had to have clinically significant nasal congestion/obstruction with a score ≥2 on each day of the last seven days (including the day of randomization) of the 14-day Run-in Period. They also had to have bilateral nasal polyps at both Screening and Baseline (Day 1).

The primary parameter, effect on congestion/obstruction, was evaluated as the change from baseline (average of the last seven days of the placebo run-in plus the Baseline visit) averaged over the first month of the Treatment Period.

The change in polyp size was a co-primary endpoint. The polyp size in each nasal fossa was graded directly through the investigator's visual assessment by endoscopic nasal examination at all monthly visits. In the sponsor's MFNS clinical program, polyp size was evaluated as the change from baseline to Endpoint (final evaluation) in the sum of the polyp scores (0 to 3 scale; maximum score of 6) from the left and from the right nasal fossa, and referred to as Bilateral Polyp Grade. Nasal polyps were graded endoscopically 0-3 using the following range of grades:
0 no polyps
1 polyps in the middle meatus, not reaching below the inferior border of the middle turbinate
2 polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate
3 large polyps reaching to or below the lower border of the inferior turbinate or polyps medial to the middle turbinate.

For the analysis of both endpoints, an ANOVA was performed with treatment, center, and asthma status (stratification variable) effects. Although asthma status was not mentioned in the protocol as being included in the model, it was included in the model at the recommendation of the FDA since randomization was stratified by asthma status. Comparisons between treatment groups were to be based on the differences in least squares mean estimates from the models. The sponsor used a step-down procedure to handle the multiple comparison issue.

In order to assess the rate of recurrence of nasal polyposis disease in subjects improving with treatment, improvement to treatment had been prospectively defined in the protocols and data analysis plans. A subject with improvement was any subject who demonstrated a reduction in Bilateral Polyp Grade score ≥1 point from baseline to Endpoint and a reduction in Congestion/Obstruction Score ≥0.5 points from baseline to the average of the last 8 days of treatment. These changes in the combined scores of the two primary efficacy endpoints were considered clinically relevant. The primary evaluation time point for congestion/obstruction was the average of the scores recorded during the first month of treatment because MFNS was expected to exert its effect on the nasal mucosa within the first month of treatment. However, in the determination of a subject with improvement to treatment, the end of the treatment period was felt to be of utmost importance in this assessment. Therefore, in the definition of improvement, only the last 8 days of recorded signs/symptoms were considered.

2.1.2 Study P01926

This study was similar to Study P01925 and was analyzed similarly.

In addition, to further explore the impact of baseline imbalance in the results of Study P01926, baseline polyp grade was added as a covariate to the model for the analysis (ANCOVA) of the changes from baseline in polyp grade.

2.1.3 Study Q99-925

This was a Nordic, multicenter, randomized, double-blind, placebo-controlled study of MFNS 200 mcg QD AM in the treatment of nasal polyposis. There was a no treatment run-in period followed by a 16-week treatment period.

The grading scale of nasal polyps was similar to Study P01925 with slightly different but similar wording.

The case report form indicated that the investigator was to assess both nostrils and give an overall grade. The study report stated that at baseline the investigator was told to assess both nostrils and score the most severe nostril. The study report further states that they should follow the largest polyp. [Since there was no place for the sponsor to indicate which nostril he was following, this measurement might not have been consistently captured.]

To enroll, subjects had to have an investigator assessed Nasal Congestion Score ≥ 2 (moderate), for at least 4 days per week, during the last month prior to screening, and at screening and baseline visit. Subjects were to have bilateral nasal polyps with polyp size ≤ 2. Subjects with polyp size of grade 3 where nasal blockage did not obstruct successful application of nasal spray were mistakenly allowed to enter because of wording on the CRF at screening.

The original randomization (1:1) was done in blocks of eight. Due to slow enrolment block size was lowered to 4 to insure better balance.

Use of oxymetazoline was permitted during the study for a maximum of 7 consecutive days, and no more than 10 days total duration during the treatment period. The grading scale for nasal polyps, assessed by endoscopy, was the same as in Study P01925. However, the score assigned to the subject at a visit was the grade of the most severe side.
Subjects assessed nasal congestion twice daily based on their status over the previous 12 hours.

The primary efficacy variable was the proportion of subjects with improvement during the treatment period with respect to investigator's overall evaluation of nasal congestion, improvement defined as a reduction of at least one point. Clinic visits were at screening, baseline, and days 28, 56, 84, and 112 of treatment.
The primary efficacy endpoint was analyzed by the Cochrane-Mantel-Haenszel chi-square test stratified by center.

The sponsor also analyzed this study using analyses similar to those of Studies P01925 and P01926.

2.1.4 Study P02573

Any subject that improved in Study P01925 had the opportunity to participate in this study if his center participated. Subjects who enrolled were assessed an additional 4 months. There was no further treatment of these patients. It is an observational, follow-up study to see how many subjects would have a recurrence of their polyps.

In this follow-up study, subjects were evaluated for polyp size, graded via nasal endoscopy, at the beginning and monthly throughout the study, and on self-assessed, weekly Nasal Congestion/Obstruction Scores. The same scales were used as in Study P01925. Subjects were to be considered to have experienced a recurrence if the Bilateral Polyp Grade increased from the Study P02573 baseline by at least 1 point at the termination of Study P02573 and the last two Congestion/Obstruction Scores (maximum score of 3) increased from the baseline score of P02573 by at least 0.5 each.

There was no hypothesis testing in this study because the patients are not a random sample. The protocol only mentions that data summaries would be provided.

2.2 Data Sources

Data for this submission was contained in \\Cdsesub1\n20762\S_023\2004-02-26 , \\Cdsesub1\n20762\S_023\2004-04-06 , and \\Cdsesub1\n20762\S_023\2004-04-26 .

3 Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study P01925

The data from Centers 08 (6 subjects, 2 terminated) and 31 (30 subjects, 14 terminated) were excluded from all analyses because of significant departures from good clinical practice.

With the exclusion of centers 08 and 31, there were 354 subjects randomized at 44 centers in 10 countries to the following treatments: MFNS 200 mcg QD AM, 115 subjects; MFNS 200 mcg BID, 122 subjects; and placebo, 117 subjects. Five patients did not contribute data to the analysis of nasal congestion/obstruction and 7 patients did not contribute data to the analysis of nasal polyp grade. Three hundred and five subjects [101 on MFNS 200 mcg QD AM (88%), 109 on MFNS 200 mcg BID (89%), and 95 on placebo (81%)] completed the study. There were 29 subjects who were randomized out of sequence. The study was to be stratified based on the presence or absence of asthma. Any subject who presented with concurrent asthma was to be assigned a randomization number in ascending sequential order using the lowest number available at the site, and any subject without asthma was to be assigned a randomization number in descending sequential order. Subjects randomized out of sequence continued with their assigned numbers.

The three treatment groups were well matched with regard to baseline demographic and disease characteristics. About 2/3 were males. The mean age across the treatment groups was 46.7 to 48.3 years. A majority of subjects had no history of asthma (79-82%/group) or PAR (75-83%/group). The study population was comprised of Caucasian (43-54%/group), Hispanic (38-45%/group), Asian (0-4%/group), and Black/Other (3-12%/group.)

The table below provides the results for the analysis of change from baseline in Congestion/Obstruction Score. Both treatment groups were significantly different from placebo after week 1 with MFNS 200 mcg BID showing significance at Week 1. Both MFNS treatments were significantly different from placebo at the protocol specified primary time, average over the first month. MFNS 200 mcg BID showed significantly more efficacy than MFNS 200 mcg QD AM at most summarization times.

Congestion/Obstruction Score Summary and Analysis Results (All Randomized Subjects)
Study P01925

	MFNS 200 mcg QD (A)		MFNS 200 mcg BID (B)		Placebo (C)		Pairwise P-values		
Visit	N	LS Mean	N	LS Mean	N	LS Mean	A-B	A-C	B-C
Baseline	113	2.29	122	2.35	114	2.28			
Change From Baseline									
Week 1	113	-0.24	122	-0.37	114	-0.16	0.051	0.203	0.001
Week 2	113	-0.49	121	-0.57	111	-0.20	0.315	<.001	<.001
Week 3	111	-0.55	121	-0.72	110	-0.28	0.047	0.002	<.001
Week 4	110	-0.58	121	-0.76	109	-0.32	0.032	0.002	<.001
Month 1	113	-0.47	122	-0.61	114	-0.24	0.039	0.001	<.001
Month 2	109	-0.68	119	-0.83	107	-0.32	0.093	<.001	<.001
Month 3	104	-0.78	112	-1.01	101	-0.48	0.027	0.004	<.001
Month 4	102	-0.86	109	-1.10	96	-0.50	0.024	0.001	<.001
Months 1-2	113	-0.57	122	-0.72	114	-0.28	0.047	<.001	<.001
Months 3-4	104	-0.83	112	-1.07	101	-0.48	0.018	<.001	<.001

The table below provides the results for the analysis of change from baseline in Bilateral Polyp Grade. Both treatment groups were significantly different from placebo for most clinic assessment times. Both MFNS treatments were significantly different from placebo at the protocol specified primary time, Endpoint. There was little difference seen between the MFNS treatments for Bilateral Polyp Grade at any clinic visit. Numerically MFNS 200 mcg QD AM was more effective than MFNS 200 mcg BID for change from baseline in Bilateral Polyp Grade except at Month 1.

Bilateral Polyp Grade Summary and Analysis Results (All Randomized Subjects)
Study P01925

	MFNS 200 mcg QD (A)		MFNS 200 mcg BID (B)		Placebo (C)		Pairwise P-values		
Visit	N	LS Mean	N	LS Mean	N	LS Mean	A-B	A-C	B-C
Baseline	112	4.21	121	4.27	114	4.25			
Change From Baseline									
Month 1	111	-0.57	119	-0.61	114	-0.33	0.773	0.053	0.024
Month 2	107	-0.87	114	-0.83	104	-0.52	0.800	0.035	0.058
Month 3	102	-1.10	111	-0.93	99	-0.56	0.341	0.003	0.036
Month 4	102	-1.20	108	-1.14	94	-0.63	0.747	0.005	0.011
Endpoint	112	-1.13	121	-0.95	114	-0.49	0.342	<.001	0.011

Because baseline polyp grade was a significant factor in other studies for the analysis of endpoint polyp grade, it was included in the model to verify that its inclusion did not change the significance of the endpoint results in this study. With its inclusion both 200 mg QD and 200 mg BID were significantly different from placebo with p-values of <0.001 and 0.010 respectively.

The table below provides the results of the proportion of patients showing improvement. MFNS 200 mcg BID showed a significantly higher proportion of improved patients than placebo or MFNS 200 mcg QD AM.

Summary of Improvement

Response Status[a,b]	MFNS 200 mcg QD AM (A) N=111	MFNS 200 mcg BID (B) N=119	Placebo (C) N=112
Improved	48 (43.24%)	68 (57.14%)	38 (33.93%)
Not Improved	63 (56.76%)	51 (42.86%)	74 (66.07%)
Pairwise Comparison (P-Values)[c]			
A vs B	A vs C	B vs C	
0.035	0.159	<0.001	

a: Based on subjects for whom improvement classification could be determined.
b: A subject with improvement was defined as a subject who demonstrated a decrease in bilateral polyp grade of ≥1 from Baseline to the last visit and a decrease in congestion/obstruction score of ≥0.5 from Baseline to the average of the last 8 days of the study.
c: Based on Cochran Mantel Haenszel test stratified by asthma status.

3.1.2 Study P01926

There were 310 subjects randomized at 24 centers in 17 countries to the following treatments: MFNS 200 mcg QD AM, 102 subjects; MFNS 200 mcg BID, 102 subjects; and placebo, 106 subjects. Five patients did not contribute data to the analysis of nasal congestion/obstruction and 8 patients did not contribute data to the analysis of nasal polyp grade. Two hundred and seventy four subjects [94 on MFNS 200 mcg QD AM (92%), 93 on MFNS 200 mcg BID (91%), and 87 on placebo (82%)] completed the study. There were 15 subjects who were randomized out of sequence.

The three treatment groups were well matched with regard to baseline demographic and disease characteristics. About 2/3 were males. The mean age across the treatment groups was 47.2 to 50.9 years. A majority of subjects had no history of asthma (81-85%/group) or PAR (79-86%/group). The study population was comprised of Caucasian (63-64%/group), Hispanic (27-28%/group), Asian (7-8%/group), and Black/Other (1-3%/group.)

The table below provides the results for the analysis of change from baseline in Congestion/Obstruction Score. MFNS 200 mcg QD BID was significantly different from placebo at all evaluation summaries while MFNS 200 QD AM was significantly different from placebo at most evaluation summaries. Both MFNS treatments were significantly different from placebo at the protocol specified primary time, average over the first month. MFNS 200 mcg BID showed significantly more efficacy than MFNS 200 mcg QD AM at all summarization times after Week 1.

Congestion/Obstruction Score Summary and Analysis Results (All Randomized Subjects)
Study P01926

	MFNS 200 mcg QD (A)		MFNS 200 mcg BID (B)		Placebo (C)		Pairwise P-values		
Visit	N	LS Mean	N	LS Mean	N	LS Mean	A-B	A-C	B-C
Baseline	101	2.23	100	2.20	104	2.18			
Change From Baseline									
Week 1	101	-0.25	100	-0.38	104	-0.12	0.051	0.074	<.001
Week 2	100	-0.43	99	-0.65	99	-0.22	0.011	0.014	<.001
Week 3	99	-0.48	98	-0.81	96	-0.30	<.001	0.036	<.001
Week 4	99	-0.54	98	-0.83	95	-0.36	0.003	0.054	<.001
Month 1	101	-0.42	100	-0.66	104	-0.23	0.001	0.010	<.001
Month 2	98	-0.66	96	-0.90	95	-0.43	0.011	0.019	<.001
Month 3	97	-0.74	94	-1.04	88	-0.58	0.004	0.137	<.001
Month 4	95	-0.86	92	-1.09	87	-0.61	0.034	0.020	<.001
Months 1-2	101	-0.53	100	-0.76	104	-0.31	0.004	0.005	<.001
Months 3-4	97	-0.78	94	-1.05	88	-0.59	0.009	0.060	<.001

The table below provides the results for the analysis of change from baseline in Bilateral Polyp Grade. Neither treatment group was significantly different from placebo at all assessment times although MFNS 200 mcg BID was approaching significance (P=0.078) at Endpoint.

Bilateral Polyp Grade Summary and Analysis Results (All Randomized Subjects)
Study P01926

	MFNS 200 mcg QD (A)		MFNS 200 mcg BID (B)		Placebo (C)		Pairwise P-values		
Visit	N	LS Mean	N	LS Mean	N	LS Mean	A-B	A-C	B-C
Baseline	101	4.00	101	4.10	100	4.17			
Change From Baseline									
Month 1	100	-0.36	100	-0.51	97	-0.34	0.276	0.909	0.234
Month 2	96	-0.52	97	-0.88	93	-0.56	0.033	0.810	0.061
Month 3	97	-0.61	96	-0.89	89	-0.56	0.118	0.772	0.070
Month 4	93	-0.81	93	-0.98	88	-0.78	0.336	0.876	0.271
Endpoint	101	-0.76	101	-0.98	100	-0.67	0.212	0.602	0.078

The sponsor stated that due to slight numeric differences at baseline, baseline polyp grade was added as a covariate to the model for the analysis of the change from baseline in polyp grade. [The p-value for treatments at baseline was 0.6079, which suggest the treatment groups were fairly comparable at baseline.] For this analysis MFNS 200 mcg BID achieved statistical superiority to placebo (p=0.039) at Endpoint. Baseline was a highly significant effect (F=47.38, P<0.0001) in this model. The inclusion of baseline did not affect the significance of the MFNS 200 mcg QD dose (P-value=0.331).

The table below provides the results of the proportion of patients showing improvement. MFNS 200 mcg BID showed a significantly higher proportion of improved patients than placebo or MFNS 200 mcg QD AM.

Summary of Improvement

Response Status[a,b]	MFNS 200 mcg QD AM (A) N=101	MFNS 200 mcg BID (B) N=100	Placebo (C) N=98
Improved	34 (33.66%)	49 (49.00%)	24 (24.49%)
Not Improved	67 (66.34%)	51 (51.00%)	74 (75.51%)
Pairwise Comparison (P-Values)[c]			
A vs B	A vs C	B vs C	
0.028	0.158	<0.001	

a: Based on subjects for whom improvement classification could be determined.
b: A subject with improvement was defined as a subject who demonstrated a decrease in bilateral polyp grade of ≥1 from Baseline to the last visit and a decrease in congestion/obstruction score of ≥0.5 from Baseline to the average of the last 8 days of the study.
c: Based on Cochran Mantel Haenszel test stratified by asthma status.

3.1.3 Study Q99-925

There were 298 subjects (153 MFNS 200 mcg QD, 145 Placebo) who were randomized into the study. Sixty-three patients (19 MFNS and 44 Placebo) discontinued before completion. The main reason for discontinuing was treatment failure (8 MFNS and 27 placebo). Seven patients (1 MFNS and 6 placebo) had no appropriate baseline/postbaseline efficacy data and were excluded from the ITT subset that included 291 patients (152 MFNS and 139 placebo).

The treatment groups were comparable in demographic variables and baseline symptomatology.

Primary Variable: Nasal Congestion- baseline visit to Last Visit (ITT Population)

	MFNS 200 mcg QD (N=152)	Placebo (N=139)	P-value[a]
Nasal Congestion			
Improvement	113 (74.3%)	65 (46.8%)	<0.001
No Improvement	39 (25.7%)	74 (53.2%)	

a: Improvement in nasal congestion was analyzed by Cochran-Mantel -Haenszel test stratified by center.

The table provides the results of the proportion of patients improving in polyp size from baseline to last visit.

	MFNS 200 mcg QD (N=152)	Placebo (N=139)	P-value[a]
Polyp Size			
Improvement	63 (41.4%)	37 (26.6%)	0.003
No Improvement	89 (58.6%)	102 (73.4%)	

The table below provides the results of the analysis during month 1 for changes from baseline in AM and PM nasal congestion. MFNS 200 mcg QD AM was significantly different from placebo for both AM and PM assessment.

	MFNS 200 mcg QD AM			Placebo			
Nasal Congestion, AM							
	N	LS Mean	Mean % Change	N	LS Mean	Mean % Change	P-value
Baseline	152	2.00		138	1.98		
Change from Baseline							
Month 1	152	-0.40	(-19.4%)	138	-0.09	(-4.3%)	<0.001
Nasal Congestion, PM							
	N	LS Mean	Mean % Change	N	LS Mean	Mean % Change	P-value
Baseline	152	1.84		138	1.85		
Change from Baseline							
Month 1	152	-0.39	(-18.8%)	138	-0.12	(-4.4%)	<0.001

The table below provides the results of the analyses of changes from baseline in polyp grade at the monthly assessments. MFNS 200 mcg QD AM was significantly different from placebo at Endpoint.

	MFNS 200 mcg QD AM			Placebo			
	N	LS Mean	Mean % Change	N	LS Mean	Mean % Change	P-value
Baseline	152	1.85		139	1.94		
Change from Baseline							
Month 1	149	-0.22	(-8.2%)	132	-0.05	(+ 0.4%)	0.007
Month 2	146	-0.18	(-7.4%)	115	-0.12	(- 3.9%)	0.393
Month 3	140	-0.32	(-17.6%)	105	-0.18	(- 8.9%)	0.068
Month 4	138	-0.36	(-21.5%)	104	-0.22	(-11.9%)	0.080
Endpoint	152	-0.35	(-20.0%)	139	-0.12	(- 5.3%)	0.001

If baseline polyp grade is put in model as a covariate then most month data are significant for polyp grade.

	MFNS 200 mcg QD AM			Placebo			
	N	LS Mean	Mean % Change	N	LS Mean	Mean % Change	P-value
Baseline	152	1.85		139	1.94		
Change from Baseline							
Month 1	149	-0.24	(-8.2%)	132	-0.04	(+ 0.4%)	0.001
Month 2	146	-0.20	(-7.4%)	115	-0.11	(- 3.9%)	0 20
Month 3	140	-0.33	(-17.6%)	105	-0.17	(- 8.9%)	0.03
Month 4	138	-0.38	(-21.5%)	104	-0.21	(-11.9%)	0.03
Endpoint	152	-0.38	(-20.0%)	139	-0.11	(- 5.3%)	<0.001

The following table contains the F-value and P-value if baseline is added to the model. This indicates that baseline polyp grade is a major source of variability in this study.

Analysis	F-Value of Baseline	P-value of Baseline
Month 1	37.02	<0.0001
Month 2	108.23	<0.0001
Month 3	28,22	<0.0001
Month 4	19.14	<0.0001
Endpoint	118.98	<0.0001

The P-value of treatment at baseline for polyp-size is 0.1769.

The following table contains the F-value and P-value of baseline if added to the model for the U.S. studies.

Study	F-Value of Baseline	P-value of Baseline
P01925	7.33	0.0072
P01926	47.38	<0.0001

These analyses give support to the sponsor's post hoc analysis of Study 01926. The near significance of the completer analysis of polyp grade without baseline covariate and the significance with baseline covariate support the LOCF analysis. The LOCF analysis is further supported by the fact that over half the dropouts were for lack of efficacy with over 3 times as many drop-outs on placebo.

3.1.4 Study P02573

The data from Site 21 was excluded from this study because of significant departures from Good Clinical Practice (i.e., fabrication of source documents information for non-existent visits). With the exclusion of Site 21, a total of 135 subjects (46 MFNS 200 mcg QD AM, 58 MFNS 200 mcg BID, and 31 Placebo) were enrolled into this study. Sixty seven subjects (22 MFNS 200 mcg QD AM, 27 MFNS 200 mcg BID, and 18 Placebo) completed the study. The main reason given on the CRF for discontinuation was relapse/ recurrence (14 MFNS 200mcg QD AM, 26 MFNS 200 mcg BID, and 9 Placebo). The demographic variables and baseline disease characteristics were comparable across the three groups and were comparable to the complete population from Study P01925

The table below provides the recurrence information in this study. The MFNS subjects showed a 30 to 40% recurrence of their polyps. Less recurrence was seen in the Placebo patients.

Response Status	MFNS 200 mcg QD AM (A) N=46	MFNS 200 mcg BID (B) N=55[a]	Placebo (C) N=31
Recurrence	15 (32.6%)	23 (41.8%)	7 (22.6%)
No recurrence	31 (67.4%)	32 (58.2%)	24 (77.4%)
-Completed	19 (41.3%)	26(47.3%)	17(54.85%)
-Dropped Out	12(26.1%)	6(10.9%)	7(22.6%)

a: Three of the 58 subjects in this group were missing recurrence status and were not included in this table.

The tables below provide summaries of the Nasal Congestion/Obstruction Scores and Bilateral Polyp Grade scores in this study. Rollover is the average of month 4 from Study 01925. Baseline is the P01925 Baseline.

Congestion/Obstruction Score Summary (All Randomized Subjects)
Study P02573

	MFNS 200 mcg QD (A)		MFNS 200 mcg BID (B)		Placebo (C)	
Visit	N	Mean	N	Mean	N	Mean
Baseline	46	2.29	56	2.34	31	2.31
Change from Baseline						
Roll-over	46	-1.43	55	-1.53	31	-1.00
Month 1	46	-1.29	56	-1.36	31	-1.08
Month 2	38	-1.21	45	-1.24	26	-1.18
Month 3	29	-1.34	34	-1.44	22	-1.12
Month 4	21	-1.28	28	-1.55	18	-1.25
Endpoint	46	-1.00	56	-1.14	31	-0.97

Bilateral Polyp Grade Summary (All Randomized Subjects)
Study P02573

	MFNS 200 mcg QD (A)		MFNS 200 mcg BID (B)		Placebo (C)	
Visit	N	Mean	N	Mean	N	Mean
Baseline	46	4.20	56	4.36	31	4.16
Change from Baseline						
Roll-over	46	-2.28	56	-2.00	31	-2.06
Month 1	44	-2.20	55	-1.51	29	-1.72
Month 2	37	-2.11	42	-1.60	25	-2.00
Month 3	27	-2.11	34	-1.62	23	-1.61
Month 4	23	-1.83	27	-1.56	18	-1.89
Endpoint	46	-1.59	56	-1.02	31	-1.48

3.2. Evaluation of safety

Nasonex is approved for Seasonal Allergic Rhinitis and Perennial Allergic Rhininitis. It was studied at doses ranging from 50 to 800 mcg/day. The majority of patients were treated at 200 mcg/day. The safety of nasonex was established in those studies. No new safety concerns have been found in the Post Marketing experience. The only safety signal found by the sponsor in the polyposis trials (Studies 01925 and P01926) was for epistaxis. Epistaxis occurred more frequently in the MFNS 200 mcg BID group than the other treatment groups (MFNS 200 mcg QD 6%, MFNS 200 mcg BID 13%, Placebo 5%). The epistaxis rate for MFNS 200 mcg BID was not dissimilar to the rate seen in the Allergic Rhinitis trials.

4. Findings in Special/ Subgroup Populations

4.1 Gender/age/race

The sponsor provided treatment means for the changes from baseline in bilateral polyp grade and nasal congestion/obstruction score for these subgroup categories for Studies P01925 and P01926. The subgroup categories for age were subjects younger than 65 years, and subjects ≥ 65 years of age. The race categories were Caucasians, and Non-Caucasians. There was no indication that Nasonex was not effective in the various age, race or gender categories.

4.2 Other special/subgroup populations

The sponsor provided treatment means for the changes from baseline in bilateral polyp grade and nasal congestion/obstruction score for asthmatics and non-asthmatics subgroups for Studies P01925 and P01926. There was no indication that Nasonex was not effective in the each of the two categories.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

There were no statistical issues with the sponsor's analyses.

5.2 Conclusions and Recommendations

The sponsor has provided data from three Phase 3 efficacy studies of Nasonex in patients with nasal polyposis. Study P01925 showed that Nasonex at doses of 200 mcg QD AM and 200 mcg BID were more effective than placebo in changes from baseline in Nasal Congestion/Obstruction averaged over the first month and changes from baseline in Bilateral Polyp Grade at Endpoint, the protocol defined primary

assessment times. Study P01926 showed that both doses were more effective than placebo in reducing Nasal Congestion/Obstruction averaged over the first month. Neither dose showed efficacy in reducing Bilateral Polyp Grade at Endpoint compared to placebo although the results were approaching significance for the 200 mcg BID dose (P=0.078). In a post-hoc analysis, the sponsor found the 200 mcg BID significant for polyp grade if baseline polyp grade is added as a covariate. Including baseline seems justified as baseline is consistently a large explainer of variability in these studies.

The sponsor provided the results of Nordic Study Q99-925 as a supportive study. Although this study had a different way to assess these efficacy variables than in Studies P01925 and P01926, when analyzed similarly, Nasonex 200 mcg QD AM, the only Nasonex dose in that study, was significantly different from placebo in changes from baseline in Nasal Congestion/Obstruction averaged over the first month and changes from baseline in Polyp Grade at Endpoint. The grading of polyp size was slightly different than in the other studies. It might have not been consistently measured by the investigators.

The overall conclusion is that Nasonex at a dose of 200 mcg BID is effective in the treatment of nasal polyps. The BID dose showed more efficacy for changes from baseline in Nasal Congestion/ Obstruction Score than the QD AM dose.

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/s/

James Gebert
11/24/04 02:26:53 PM
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Sue Jane Wang
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concur with review

Steve Wilson
11/26/04 09:59:21 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-762/S023

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20,762 **Date of Submission:** February 26, 2004
November 19, 2004

Serial # S-023

Generic Name	Mometasone Furoate Monohydrate
Brand Name:	**NASONEX**
Formulations:	Aqueous Nasal Spray (50 mcg)
Route of Administration:	Nasal
Indication:	Nasal Polypsois
Type of Submission:	New Indication
Sponsor:	Schering Corporation
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.
Date of Submission:	February 26, 2004
Date Received:	March 10, 2004
Review Date:	December 3, 2004
DFS Draft:	December 3, 2004

Backround:

This is a supplement NDA containing supporting clinical information for the treatment of nasal polyps (b) (4) in adult patients. The product is currently approved for the treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis, in adults and pediatric patients 2 years of age and older. In addition, it is indicated for the prophylaxis of the nasal symptoms of seasonal allergic rhinitis in adult and adolescent patients 12 years and older.

In this submission no clinical Pharmacology or PK related information has been submitted. The primary endpoints in this submission are polyp size as assessed by endoscopy and peak nasal inspiratory flow. Therefore, no OCPB comments can be made at this time.

RECOMMENDATION:

From the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) perspective, no comments can be made at this time. In addition, no PK or clinical pharmacology labeling comments are necessary at this time. The sponsor's revised labeling is acceptable to OCPB. Overall, the NDA is acceptable.

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaulation II

Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader----------

cc: HFD-570, HFD-870 (Al Habet, Fadiran, and Malinowski), Drug file (Biopharm File, Central Document Room).

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/s/

Sayed Al-Habet
12/3/04 10:42:22 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
12/6/04 02:52:24 PM
BIOPHARMACEUTICS
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-762/S023

OTHER REVIEW(S)

Project Manager Labeling Review

NDA 20-762/S-023

DRUG: Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray, 50mcg

SPONSOR: Schering Corporation

SUBMISSIONS:	February 26, 2004	RECEIVED: February 26, 2004
DATED	November 19, 2004	November 22, 2004
	November 30, 2004	December 1, 2004
	December 7, 2004	December 8, 2004
	December 9, 2004	December 9, 2004

BACKGROUND: This efficacy supplement provides clinical data for the use of Nasonex Nasal Spray for the treatment of nasal polyps (b) (4) in adults. The original proposed labeling was submitted on February 26, 2004. Revised labeling was submitted on November 19, 2004, to incorporate the changes made to the labeling with the approval of supplement 007 to N20-762. The Division proposed revisions to the November 19, 2004, labeling, which were communicated to Schering via fax on November 23, 2004. Schering submitted revised labeling on November 30, 2004, and a teleconference was held on December 3, 2004, to discuss this proposed labeling. Additionally, minor labeling comments were communicated to Schering via e-mail on December 8 and 9, 2004. Schering submitted revised labeling on December 9, 2004, incorporating the revisions proposed by the Division during the teleconference on December 3, 2004, and the e-mail communications dated December 8 and 9, 2004.

REVIEW: I compared the labeling submitted on November 19, 2004, to supplement 023 with the last approved labeling from N20-762/S-007, dated August 25, 2004. The labeling changes approved in supplement 007 were incorporated. There was one additional change noted:

1. On line 413 in the **ADVERSE REACTIONS, Allergic Rhinitis** section of the approved labeling from supplement 007, the number of Pediatric Patients who received Placebo and reported coughing was 15. On line 449 of the proposed labeling (clean version) submitted December 9, 2004, the number reported was 5. I spoke with Teresa Perney from Schering, who stated that this was an erroneous change. The correct number is 15.

Next, I compared the labeling submitted November 19, 2004, to the labeling submitted December 9, 2004. All the revisions proposed by the Division and agreed to in the December 3, 2004, teleconference, and the e-mail communications dated December 8 and 9, 2004, were made as requested. The labeling submitted December 9, 2004, was forwarded to the review team. The review team concurred that the appropriate revisions had been made.

However, the following minor errors were noted and discussed with Schering. Schering agreed that the following items should be corrected:

1. Line 175 (clean version) in the **CLINICAL PHARMACOLOGY, Clinical Studies: Nasal Polyps** section of the labeling submitted December 9, 2004, reads (b) (4) The wording recommended by the Division in the fax dated November 23, 2004, was "…multi-center studies in patients 18-86 years of age with bilateral *nasal* polyps."

2. In the **PRECAUTIONS, Pregnancy: Teratogenic Effects:** section
   - Line 349 (clean version) requires a "…)." after the word "basis"
   - Line 338 (clean version) requires a "…)" after the word "basis" and before the period.
   - Line 341 (clean version). Delete the extra space after the number "10"

3. Line 629-631 (clean version) of the **Patient's Instructions for Use** should read "…helps to control your condition so it is important that you use it regularly as directed by your physician." The phrase (b) (4) should have been deleted per the revisions proposed by Schering on December 7, 2004.

Schering agreed with the revisions noted above, and also requested that the phrase "…adults and adolescents…" be deleted from Line 211 (clean version) in the **INDICATIONS AND USAGE** section. This was discussed with the clinical reviewer and the clinical team leader who agreed to this change.

All corrections will be made to the labeling submitted December 9, 2004, and the corrected labeling will be enclosed with the action letter.

_____

Lori A. Garcia, R.Ph.
Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products

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/s/

Lori Garcia
12/15/04 01:20:07 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20762 Supplement # 023 **SE1** SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: NASONEX Aqueous Nasal Spray
Generic Name: mometasone furoate
Strengths: 50mcg

Applicant: Schering Corporation

Date of Application: February 26, 2004
Date of Receipt: February 26, 2004
Date clock started after UN:
Date of Filing Meeting: 3/29/04
Filing Date: April 26, 2004
Action Goal Date (optional): User Fee Goal Date: 12/26/04

Indication(s) requested: **Treatment of nasal polyps** (b) (4) **in adults**.

Type of Original NDA: (b)(1) _____ (b)(2) _____
OR
Type of Supplement: (b)(1) ____**X**_____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S _____**X**_____ P _____
Resubmission after withdrawal? _____**No**____Resubmission after refuse to file? _____No_____
Chemical Classification: (1,2,3 etc.) _____3____
Other (orphan, OTC, etc.) _____

User Fee Status: Paid ___X_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: **xxYES** NO
User Fee ID # __**4702**_____
Clinical data? **YES x** NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

xxYES **NO**

If yes, explain:
I-360 Exclusivity Exp 17-Jul-2005
PED Exclusivity Exp 17-Jan-2006

Does another drug have orphan drug exclusivity for the same indication? YES **xx NO**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES **xxNO**
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? **xNA** YES NO

- Does the submission contain an accurate comprehensive index? **xYES** NO
- Was form 356h included with an authorized signature? **xYES** NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? **xx YES** NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? **X N/A** **YES** NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  .

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? **xN/A** YES NO
- Is it an electronic CTD? **xN/A** YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? **xYES** NO
- Exclusivity requested? **YES, 3 years** NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? **xYES** NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? **xYES** NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES **xNO**

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **xYES** NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? **YES**. If not, have the Document Room make the corrections.

- List referenced IND numbers: **IND 35,932**

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) __**14-Oct-2003**_____
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  xYES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? **xN/A** YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? **xN/A** YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  xN/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  xN/A YES NO

- Has DOTCDP been notified of the OTC switch application? **xN/A** YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  xN/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **X YES** NO

If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES **xxNO**

- If a parenteral product, consulted to Microbiology Team (HFD-805)? **xNA** YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications

that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # _____ NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 29, 2004

BACKGROUND: Efficacy Supplement submitted to NDA 20-762. This supplement provides clinical support for the use of Nasonex Nasal Spray for the treatment of nasal polyps (b) (4) in adults. A pediatric waiver was requested for children < 18 years of age.

ATTENDEES:

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Richard Nicklas
Secondary Medical:	
Statistical:	James Gebert
Pharmacology:	Virgil Whitehurst
Statistical Pharmacology:	
Chemistry:	Craig Bertha
Environmental Assessment (if needed):	
Biopharmaceutical:	Sayed Al Habet
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Lori Garcia
Other Consults: Labeling consult to DDMAC	

Per reviewers, are all parts in English or English translation? **xYES** NO
If no, explain:

CLINICAL **FILE X** REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known **X NO**
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

X N/A YES NO

CLINICAL MICROBIOLOGY **N/A X** FILE _____ REFUSE TO FILE _____

STATISTICS **FILE X** REFUSE TO FILE _____

BIOPHARMACEUTICS **FILE X** REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ **FILE X** REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY **FILE X** REFUSE TO FILE _____

- Establishment(s) ready for inspection? **X N/A** YES NO
- Microbiology **X N/A** YES NO

ELECTRONIC SUBMISSION:
Any comments:

Mixed submission: paper and electronic

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

____X___ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___X___ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.

2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. Document filing issues/no filing issues conveyed to applicant by Day 74.

_____
Lori Garcia, Regulatory Project Manager, HFD-570

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/s/

Lori Garcia
12/15/04 11:37:04 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-762/S023

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # _N20-762_ SUPPL #__023_____

Trade Name _Nasonex Nasal Spray_ Generic Name __Mometasone Furoate Monohydrate

Applicant Name _Schering_____ HFD # _____570_____

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_x__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

_____SE1_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /__x_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_x__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_3 years _____

e) Has pediatric exclusivity been granted for this Active Moiety?

Through 1/17/2006 YES /__x_/ NO /___/

<u>If the answer to the above question in YES,</u> is this approval a result of the studies submitted in response to the Pediatric Written Request?

_____

IF YOU HAVE ANSWERED "NO" TO <u>ALL</u> OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. <u>Single active ingredient product</u>.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_x__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# ___19-543_____ Mometasone Furoate 0.1% Ointment

NDA# ___19-796_____ Mometasone Furoate 0.1% Lotion

NDA# ___19-625_____ Mometasone Furoate 0.1% Cream

NDA# ___20-762_____ Mometasone Furoate Monohydrate Aqueous Nasal Spray

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.) IF “YES” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_x__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__x_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__x_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's

conclusion? If not applicable, answer NO.

YES /___/ NO /__x_/

If yes, explain:

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_x__/

If yes, explain:

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

___Study#P01925_____

___Study#P01926_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not re-demonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug

product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /__x_/

Investigation #2 YES /___/ NO /__x_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__x_/

Investigation #2 YES /___/ NO /__x_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_Study P01925_____

_Study P01926_____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50

percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _35,932 YES /_x__/ NO /___/ Explain: _____

Investigation #2

IND # _35,932 YES /__x_/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x__/

If yes, explain: _____

Signature : Lori A. Garcia Date December 10, 2004
Title: Regulatory Project Manager

Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

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/s/

Badrul Chowdhury

12/15/04 01:44:01 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 20-762 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 023

Stamp Date: February26, 2004 **Action Date:** December 26, 2004

HFD 570 **Trade and generic names/dosage form:** Nasonex (mometasone furoate) Aqueous Nasal Spray

Applicant: Schering Corporation **Therapeutic Class:** corticosteroid

Indication(s) previously approved: Allergic Rhinitis

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of nasal polyps (b) (4) in adults.

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **_X_No: Please check all that apply: __X__Partial Waiver __X__Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.** 0	**Tanner Stage**
Max	**kg**	**mo.**	**yr.** <6	**Tanner Stage**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **_X_Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**

- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.** 6 yo **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 17 yo **Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **_X_Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 20-762 S-023
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA ##-###
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Lori Garcia

12/15/04 01:30:46 PM

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: December 9, 2004

APPLICATION NUMBER: N20-762/S-023

BETWEEN:

Name: Teresa Perney
Phone: (908) 740-2095
Representing: Schering

AND

Name: Lori Garcia
DPADP, HFD-570

SUBJECT: The following comments regarding the revised labeling submitted via e-mail by Schering on 07-Dec-2004, were conveyed today via e-mail and followed up with a phone call:

1). On line 524 (proposed2.doc, submitted 12/7/04), delete [redacted] (b) (4) This portion of the sentence should now read "...except for epistaxis, which was ..."

2). On line 525 (proposed2.doc, submitted 12/7/04) change the semicolon following "once daily" to a comma.

Schering agreed to make the requested revisions to the package insert.

_____

Lori Garcia, R.Ph.
Regulatory Project Manager

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/s/

Lori Garcia
12/10/04 12:26:18 PM
CSO

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: December 8, 2004

APPLICATION NUMBER: N20-762/S-023

BETWEEN:

Name: Teresa Perney
Phone: (908) 740-2095
Representing: Schering

AND

Name: Lori Garcia
DPADP, HFD-570

SUBJECT: The following comments regarding the revised labeling submitted via e-mail by Schering on 07-Dec-2004, were conveyed today via e-mail and followed up with a phone call:

1) Delete the word (b) (4) in the Patient Instructions for Use (line 688) for consistency with the PI and leave it as "...can also be used to help prevent seasonal nasal allergy symptoms..."

2) Amend the table following line 188, so that the data for the "Mean change from baseline in bilateral polyps grade" for Study 1 reflect the statistical analysis that included baseline polyp grade as a covariate.

Schering agreed to revise the labeling as requested by FDA.

_____

Lori Garcia, R.Ph.
Regulatory Project Manager

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/s/

Lori Garcia

12/10/04 12:01:17 PM

CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 3, 2004

To: Teresa Perney	**From:** LT Lori Garcia Regulatory Project Manager
Company: Schering Corporation	Division of Pulmonary and Allergy Drug Products
Fax number: 908-740-4131	**Fax number:** 301-827-1271
Phone number: 908-740-2095	**Phone number:** 301-827-5580

Subject: Labeling comment re: N20-762/S-023

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES XX NO

NDA 20-762/S-023
Nasonex Nasal Spray

Dear Dr. Perney:

After reviewing your Statistical Analysis Plan and reflecting on our labeling discussions in the telecon of December 3, 2004, we are still of the opinion that you have not adequately established efficacy (b) (4) you state in your analysis plan that both primary endpoints would have to be significant (alpha=0.05) for the comparison of the 200 mcg BID dose against placebo. The 200 mcg BID dose was not significant for Polyp Grade using the protocol specified analysis. It was only significant if baseline was added to the model. Therefore, we do not think that (b) (4) section of the label.

If you have any questions, please call contact Lori Garcia, Regulatory Project Manager, at (301) 827-5580.

Drafted: LGarcia/December 3, 2004

Initialed: SBarnes/ December 3, 2004
JGebert/ December 3, 2004
SJWang/ December 3, 2004
BChowdhury/ December 3, 2004

Finalized: LGarcia/ December 3, 2004

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/s/

Lori Garcia
12/3/04 04:47:35 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: November 23,2004

To: Teresa Perney	**From:** Ladan Jafari
Company: Schering	Division of Pulmonary and Allergy Drug Products
Fax number: 908-740-2243	**Fax number:** 301-827-1271
Phone number: 908-740-2095	**Phone number:** 301-827-1084
Subject: NDA 20-762/S-023	
Total no. of pages including cover: 6	

Comments: labeling comments

Document to be mailed: " YES ☑ NO

NDA 20-762/S-023

Dear Dr. Perney:

We are reviewing your supplemental new drug application for Nasonex, and we have the following labeling comments.

Submit revised labeling incorporating these comments by November 30, 2004.
Words in Italics are explanatory comments on rationale for the proposed changes. All deletions are marked by strikeouts and insertions are marked by underlines.

1. Change (b) (4) (b) (4) to "nasal polyps" throughout the labeling for consistency.

2. Divide the Clinical Studies subsection of the Clinical Pharmacology section into two sections, a section on allergic rhinitis and a section on nasal polyps to clarify if the data refers to studies in allergic rhinitis or studies in patients with nasal polyps. This should be done by inserting subheadings on line 130 under the heading "Clinical Studies" that reads "Allergic Rhinitis" and on line 171 prior to the discussion of the data from studies in patients with nasal polyposis that reads "Nasal Polyps".

3. Delete the entire first two new paragraphs in the Clinical Studies subsection of the Clinical Pharmacology section on studies in patients with nasal polyps on lines 171-198 and replace those paragraphs with the following: "Two studies were performed to evaluate the efficacy and safety of Nasonex Nasal Spray in the treatment of nasal polyps. These studies involved 664 patients with nasal polyps, 441 of whom received Nasonex Nasal Spray. These studies were randomized, double-blind, placebo-controlled, parallel group, multicenter studies in patients 18-86 years of age with bilateral nasal polyps. Patients were randomized to receive Nasonex Nasal Spray 200 mcg once daily, 200 mcg twice daily or placebo for a period of 4 months. The co-primary efficacy endpoints were 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment; and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of treatment as assessed by endoscopy. Efficacy was demonstrated in both studies at a dose of 200 mcg twice daily and in one study at a dose of 200 mcg once a day (see table below).

Effect of Nasonex Nasal Spray in two randomized, placebo-controlled trials in patients with nasal polyps

	Nasonex 200 mcg qd	Nasonex 200 mcg bid	Placebo	P value for Nasonex 200 mcg qd vs placebo	P value for Nasonex 200 mcg bid vs placebo
Study 1	N = 112	N = 121	N = 114		
Baseline bilateral polyp grade *	4.21	4.27	4.25		
Mean change from baseline in bilateral polyp grade	- 1.13	- 0.95	- 0.49	< 0.001	0.01
Baseline nasal congestion **	2.29	2.35	2.28		
Mean change from baseline in nasal congestion	- 0.47	- 0.61	- 0.24	0.001	< 0.001
Study 2	N = 101	N = 101	N =100		
Baseline bilateral polyp grade *	4.00	4.10	4.17		
Mean change from baseline in bilateral polyp grade	- 0.76	- 0.98	- 0.67	0.62	0.04
Baseline nasal congestion **	2.23	2.20	2.18		
Mean change from baseline in nasal congestion	- 0.42	- 0.66	- 0.23	0.01	< 0.001

* polyps were graded by the investigator based on endoscopic visualization, using a scale of 0-3 where 0 = no polyps, 1 = polyps in the middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the midlle turninate but not the inferior border of the inferior turbinate; 3 = polyps reaching to or below the lower border of the inferior turbinate, or polyps medial to the middle turbinate.

** nasal congestion/obstruction was scored daily by the patient using a 0-3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms

4. In the INDICATIONS AND USAGE section, delete [redacted] (b) (4) on line 214 in the second paragraph in this section.

5. Divide the ADVERSE REACTIONS section into two sections, a section on allergic rhinitis and a section on nasal polyps to clarify if the data refers to studies in allergic rhinitis or studies in patients with nasal polyps. This should be done by inserting subheadings on line 429 under the heading “Adverse Reactions” that reads “Allergic Rhinitis” and on line 492 prior to the discussion of the data from studies in patients with nasal polyps that reads “Nasal Polyps”.

6. In the new paragraph on lines 492-497 of the ADVERSE REACTIONS section, dealing with adverse events in patients with nasal polyposis, insert an additional sentence at the end of the paragraph that reads, "The incidence of epistaxis was greater in patients who received Nasonex Nasal Spray compared to placebo". *The higher dose-related incidence of epistaxis seen in patients who received Nasonex Nasal Spray needs to be mentioned in the labeling since it is recognized that intranasal corticosteroid sprays can produce this adverse event. Combine the data from studies 1925, 1926 and Q99-925-01 in regard to the incidence of epistaxis in patients who received each dose of Nasonex and patients who received placebo and provide those data in parentheses after the above sentence.*

7. The new 5th paragraph on lines 541-547 of the DOSAGE AND ADMINISTRATION section should be deleted and replaced with the following: "The recommended dose for nasal polyps is two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg). A dose of two sprays (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 mcg) is also effective in some patients."

8. In the Patients Instructions for Use subsection of the PRECAUTIONS section on lines 639-653, in the last sentence of the first paragraph on line 645 add "helps to" after "50 mcg" and before "control".

9. At the end of the second paragraph on line 653 in the Patients Instructions for Use Subsection of the PRECAUTIONS section, add the sentence "Side effects were generally mild and included headache, viral infection, sore throat, nosebleeds, and coughing."

10. Revise the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection of the PRECAUTIONS section as follows.

    In a 2-year carcinogenicity study in Sprague Dawley rats, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 67 mcg/kg (approximately 1 (b) (4) and 2 times the maximum recommended daily intranasal dose [MRDID] in adults [400 mcg] and children [100 mcg], respectively, on a mcg/m^2 basis). In a 19-month carcinogenicity study in Swiss CD-1 mice, mometasone furoate demonstrated no statistically significant increase in the incidence of tumors at inhalation doses up to 160 mcg/kg (approximately (b) (4) -2 times the MRDID in adults and children, respectively, on a mcg/m^2 basis).

Mometasone furoate increased chromosomal aberrations in an *in vitro* Chinese hamster ovary-cell assay, but did not increase chromosomal aberrations in an *in vitro* Chinese hamster lung cell assay. Mometasone furoate was not mutagenic in the Ames test or mouse-lymphoma assay, and was not clastogenic in an *in vivo* mouse micronucleus assay and a rat bone marrow chromosomal aberration assay or a mouse male germ-cell chromosomal aberration assay. Mometasone furoate also did not induce unscheduled DNA synthesis *in vivo* in rat hepatocytes.

In reproductive studies in rats, impairment of fertility was not produced by subcutaneous doses up to 15 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis).

11. Revise the **Pregnancy:** ***Teratogenic Effects: Pregnancy Category C*** subsection of the PRECAUTIONS section as follows

When administered to pregnant mice, rats, and rabbits, mometasone furoate increased fetal malformations. The doses that produced malformations also decreased fetal growth, as measured by lower fetal weights and/or delayed ossification. Mometasone furoate also caused dystocia and related complications when administered to rats during the end of pregnancy.

In mice, mometasone furoate caused cleft palate at subcutaneous doses of 60 mcg/kg and above [redacted] (b) (4) less than the MRDID in adults on a mcg/m^2 basis). Fetal survival was reduced at 180 mcg/kg (approximately 2 times the MRDID in adults on a mcg/m^2 basis). No toxicity was observed at 20 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis).

In rats, mometasone furoate produced umbilical hernia at topical dermal doses of 600 mcg/kg and above (approximately [redacted] (b) (4) 10 times the MRDID in adults on a mcg/m^2 basis). A dose of 300 mcg/kg (approximately ~~5~~6 times the MRDID in adults on a mcg/m^2 basis) produced delays in ossification, but no malformations.

In rabbits, mometasone furoate caused multiple malformations (eg, flexed front paws, gallbladder agenesis, umbilical hernia, hydrocephaly) at topical dermal doses of 150 mcg/kg and above (approximately [redacted] (b) (4) 6 times the MRDID in adults on a mcg/m^2 basis). In an oral study, mometasone furoate increased resorptions and caused cleft palate and/or head malformations (hydrocephaly or domed head) at 700 mcg/kg (approximately [redacted] (b) (4) 30 times the MRDID in adults on a mcg/m^2 basis). At 2800 mcg/kg (approximately [redacted] (b) (4) 110 times the MRDID in adults on a mcg/m^2 basis), most litters were aborted or resorbed. No toxicity was observed at 140 mcg/kg (approximately [redacted] (b) (4) 6 times the MRDID in adults on a mcg/m^2 basis).

When rats received subcutaneous doses of mometasone furoate throughout pregnancy or during the later stages of pregnancy, 15 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis) caused prolonged and difficult labor and reduced the number of live births, birth weight, and early pup survival. Similar effects were not observed at 7.5 mcg/kg (less than the MRDID in adults on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. NASONEX Nasal Spray, 50 mcg, like other corticosteroids, should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

12. Revise the **OVERDOSAGE** section as follows.

There are no data available on the effects of acute or chronic overdosage with NASONEX Nasal Spray, 50 mcg. Because of low systemic bioavailability, and an absence of acute drug-related systemic findings in clinical studies, overdose is unlikely to require any therapy other than observation. Intranasal administration of 1600 mcg (b) (4) 4 times the recommended dose of NASONEX Nasal Spray, 50 mcg) daily for 29 days, to healthy human volunteers, was well tolerated with no increased incidence of adverse events. Single intranasal doses up to 4000 mcg have been studied in human volunteers with no adverse effects reported. Single oral doses up to 8000 mcg have been studied in human volunteers with no adverse effects reported. Chronic overdosage with any corticosteroid may result in signs or symptoms of hypercorticism (see **PRECAUTIONS**). Acute overdosage with this dosage form is unlikely since one bottle of NASONEX Nasal Spray, 50 mcg contains approximately 8500 mcg of mometasone furoate.

If you have any questions, please contact Ms. Lori Garcia at 301-827-5580.

Drafted by: LJ/11-23-04

Initialed by: Barnes/11-23-04
Whitehurst/11-23-04
McGovern/11-23-04
Nicklas/11-23-04
Chowdhury/11-23-04

Filename:N20762S23labeling comments.doc

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/s/

Ladan Jafari
11/23/04 03:17:01 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-762/S-023

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Attention: Ronald J. Garutti, M.D.
Group Vice President
Global Regulatory Affairs

Dear Dr. Garutti:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray, 50mcg

NDA Number: 20-762

Supplement number: S-023

Review Priority Classification: Standard (S)

Date of supplement: February 26, 2004

Date of receipt: February 26, 2004

This supplemental application provides clinical support for the treatment of nasal polyps (b) (4) in adults.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 26, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 26, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research

Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lori Garcia
10/8/04 12:31:56 PM
signed for Sandy Barnes

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-762/S-023

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Attention: Ronald J. Garutti, M.D.
Group Vice President
Global Regulatory Affairs

Dear Dr. Garutti:

Please refer to your February 26, 2004, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nasonex (mometasone furoate monohydrate) Aqueous Nasal Spray, 50mcg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 26, 2004, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
5/10/04 04:41:15 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 29, 2004

To: Teresa Perney	**From:** Lori Garcia, Project Manager
Company: Schering	Division of Pulmonary and Allergy Drug Products
Fax number: 908-740-5100	**Fax number:** 301-827-1271
Phone number	**Phone number:** 301-827-5580

Subject: Information Request from statistician for NDA 20-762 S-023

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES xNO

In order to review your efficacy supplement S-023 for NDA 20-762, the Division is requesting the following information:

1. Provide new datafiles NASALEX and SGNSX for Study Q99925 that contain a visit identification variable so that your analyses can be duplicated. There are up to six records per subject. If the first record is for screening visit, then your Table 8 of Volume 32, page 51, (Study Report of Study Q99925) corresponds to screening and not baseline.

2. Provide a derived dataset for diary data from Study Q99925, as was done for Studies P01925 and P01926, so that analyses from your study report can be verified.

3. How were your analyses of Polyp Grade Size in Table 5 for Study Q99925 of the Clinical Overview section (Volume 1, page 17 of section) done? The baseline least squares means did not correspond to either the first or second patient record in datafile NASALEX. The changes from baseline at endpoint also did not agree using the last patient record for each patient as endpoint visit. If your analysis is correct provide SAS printout of analysis results that might help me understand how you got your results.

4. There were problems duplicating your visit results for Bilateral Polyp Grade in Studies P01925 and P01926. The results for baseline and endpoint seemed to be verified. The analyses for the other visits are more problematic. The datafile L01900 contain endpoint assessments, such as _2070= "2/1", but some of the values of _2040, _2050, _2060 were "*" {subject record with NAME="Left/Right &"}. What is the relation between endpoint and the Visit (Month 1, Month 2, Month 3, and Month 4)? To help resolve the issue, give the subjects who are in the endpoint analysis but were excluded from the monthly analyses for each Month. Provide the values of _2040, _2050, _2060, and _2070 from the NAME="Days @" record for each subject with an explanation of why the patient was excluded from that monthly analysis.

If you have any questions, please contact Lori Garcia, Regulatory Project Manager, at 301-827-5580.

Drafted: LAG/March 26, 2004
Initialed: Barnes/ March 26, 2004
Gebert/March 29, 2004
Sabhon/March 29, 2004

Finalized: LAG/March 29, 2004

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/s/

Lori Garcia
3/29/04 09:22:34 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Drug Marketing, Advertising and Communications
HFD-244 PKLN Rm. 17B-17

FROM: **Lori Garcia, Regulatory Project Manager**
Division of Pulmonary and Allergy Drug Products
HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 17, 2004		20762 S-023	Efficacy supplement (SE1)	2/26/04

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nasonex Nasal Spray, 50mcg	S	steroid	October 26, 2004 PDUFA goal: December 26, 2004

NAME OF FIRM: Schering Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: draft labeling review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:
New efficacy supplement received for NDA 20-762 (Nasonex Nasal Spray) and a labeling review is requested. Requested indication: Treatment of nasal polyps (b) (4) in adults.
Note: draft labeling and containers/cartons are available in the EDR (http://edr/)

PDUFA DATE: December 26, 2004
ATTACHMENTS:
CC:
Archival NDA 20-762 S-023
HFD-570/Division File
HFD-570/Garcial
HFD-570/Reviewers and Team Leaders

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL **X ☐ HAND**
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Lori Garcia

3/17/04 02:29:17 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM: **Lori Garcia, Project Manager**
Division of Pulmonary and Allergy Drug Products
HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 17, 2004		20762	Efficacy supplement (SE1)	2/26/04

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nasonex Nasal Spray, 50mcg	S	steroid	October 26, 2004 PDUFA goal: December 26, 2004

NAME OF FIRM: Schering Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
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Note: labeling and containers/cartons are available in the EDR (http://edr/)

PDUFA DATE:
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC:
Archival NDA 20-762 S-023
HFD-570/Division File
HFD-570/Garcial
HFD-570/Reviewers and Team Leaders

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X ☐ HAND
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/s/

Lori Garcia

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