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Food and Drug Administration
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Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	NDA20-762/S-038
Drug Name:	Nasonex (mometasone furoate) Nasal Spray 50mcg
Indication(s):	Efficacy supplement for relief of nasal congestion associated with seasonal allergic rhinitis (SAR) in adults and pediatric patients 2 years of age and older
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Table of Contents

1. EXECUTIVE SUMMARY 4

1.1 CONCLUSIONS AND RECOMMENDATIONS 4

1.2 STATISTICAL ISSUES AND FINDINGS 4

2. INTRODUCTION 5

2.1 OVERVIEW 5

2.2 DATA SOURCES 5

3. STATISTICAL EVALUATION 6

3.1 EVALUATION OF EFFICACY 6

3.1.1 Studies P05528, P05529, P05583 6

3.1.2 Subgroup Analyses 15

3.1.2 Studies P04500 P05067, P05106 18

3.1.3 Pediatric Studies 19

3.3 EVALUATION OF SAFETY 19

3.4 LABELING 19

TABLES

Table 1: Efficacy Results of Nasonex 200mcg QD 4
Table 2: Clinical Trials 5
Table 3: Patients' Accountability N (%) 8
Table 4: Patients' Demographic and Baseline Characteristics N (%), (ITT) 9
Table 5: Analysis Results of Nasal Congestion Symptom Score of Three Studies 10
Table 6: Analysis Results of Total Nasal Symptom Score of Three Studies 11
Table 7. Analysis Results of Individual Nasal Symptom Score of Three Studies 13
Table 8: Efficacy Results of Three Supportive Studies 18
Table 9: Efficacy Results of Two Pediatric Studies 19

FIGURES

Figure 1: Study Design Diagram 6
Figure 2: LS Mean Change from Baseline of NCSS over 2-weeks 10
Figure 3: LS Mean Change from Baseline of TNSS over 2-weeks 11
Figure 4: Response Profile (Pooled Three Studies) 12
Figure 5. Response Profile (Pooled Three Studies) 12
Figure 6: LS Mean Change from Baseline of NCSS by Days 14
Figure 7: LS Mean Change from Baseline of Nasal Congestion Score by Center 16
Figure 8: LS Mean Change from Baseline of Nasal Congestion Score by Sex 16
Figure 9: LS Mean Change from Baseline of Nasal Congestion Score by Age Group 17
Figure 10: LS Mean Change from Baseline of Nasal Congestion Score by Race 17

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Nasonex® 50mcg [mometasone furoate nasal spray] (MFNS) is currently marketed for the prophylaxis and treatment of seasonal allergic rhinitis (SAR) in patients 2 years of age and older (NDA 20-762, approved on October 1, 1997) and treatment of nasal polyps (NDA 20-762/S023, approved on December 26, 2004). The Applicant, Schering-Plough, submitted this efficacy supplement to provide clinical support for extending the current approved indication for MFNS to support the specific claim of efficacy in treating nasal congestion associated with SAR in the same age group. The information for the proposed use of Nasonex for this indication consists of the efficacy and safety data collected from three new studies (Studies P05528, P05529, and P05583), in which the nasal congestion symptom score was the primary efficacy endpoint. The Applicant also provided the efficacy and safety data collected from other studies which evaluated the efficacy on nasal congestion as the secondary endpoint and some historical data.

These three new studies were identical in design which was a phase 3, double-blind, placebo controlled, and multi-center trial with 15 days of treatment to 1) assess the efficacy in relieving nasal congestion symptom score (NCSS) with MFNS 200 mcg given once daily compared to placebo in patients with symptomatic SAR; 2) assess the efficacy of MFNS in improving Total Nasal Symptom Score (TNSS). Eligible patients were male or female, ≥ 12 year old of any race with at least 2 years history of SAR and positive skin prick test for SAR. Patients were clinically symptomatic at the screening and baseline visits, with a minimal level of nasal congestion score (≥2) and TNSS (≥6).

Two out of three studies demonstrated that treatment with Nasonex significantly reduced nasal congestion symptom score (NCSS) compared to placebo in patients 12 years of age and older with SAR. Two out of three studies showed that this effect lasts for the whole dosing interval. In addition, three studies confirmed the superior efficacy of MFNS over placebo in improving the Total Nasal Symptom Score (TNSS).

The evidence taken collectively from studies reviewed indicated statistical support in favor of Nasonex in treating nasal congestion associated with SAR in patients 12 years of age and older. I recommend including all three studies in label.

1.2 Statistical Issues and Findings

There is no statistical issue during the review. The main efficacy results are presented in Table 1.

Table 1: Efficacy Results of Nasonex 200mcg QD

Efficacy Endpoints	*Study P05528 (N=324)*	*Study P05529 (n=351)*	*Study P05583 (N=333)*
LS Mean Change from Baseline over 2-weeks (MFNS – Placebo)			
AM/PM Prior NCSS	-0.11, (p=0.102)	-0.15 (p=0.006)	-0.31 (p<.001)
AM/PM Prior TNSS	-0.55 (p=0.019)	-0.82 (p<.001)	-1.27 (p<.001)

LS Mean and p- value were produced from a two-way ANOVA model with treatment, baseline value, and center effects.

2. INTRODUCTION

2.1 Overview

Nasonex® [mometasone furoate nasal spray] (MFNS) is currently marketed for the prophylaxis and treatment of seasonal allergic rhinitis (SAR) in patients 2 years of age and older (NDA 20-762, approved on October 1, 1997) and treatment of nasal polyps (NDA 20-762/S023, approved on December 26, 2004). The usual Nasonex dosages recommended for adult and adolescent patients (200 mcg QD) and pediatric patients (100 mcg QD) were previously established for the marketed indication based on efficacy in reducing total nasal symptom score (TNSS; defined as the sum of scores for rhinorrhea, nasal congestion/stuffiness, nasal itching, and sneezing). The Applicant, Schering-Plough, submitted this efficacy supplement to provide clinical support for extending the current approved indication for MFNS to support the specific claim of efficacy in treating nasal congestion associated with SAR in the same age group.

The submission included six new studies of MFNS that examined efficacy in treating congestion associated with SAR. Three randomized, placebo-controlled, parallel-group, double-blind studies enrolling patients 12 years of age or older with moderate to severe symptomatic SAR for which the effect of MFNS 200 mcg QD on congestion scores was chosen as a primary endpoint (P05528, P05529, P05583); The Applicant submitted the study reports (no data were submitted) for three studies in adolescents and adults in which the effects of MFNS on congestion scores were explored as secondary endpoints (P04500, P05067, P05106). The design of the six studies is described in Table 2. The Applicant claimed that Study P05528 was invalid and only used Study P05529 and P05583 to support the nasal congestion associated with SAR benefit of Nasonex in the label.

Table 2: Clinical Trials

Study	Study Design	Key Inclusion Criteria	Patient entered / completed	Primary Endpoint
P05528 **P05529** **P05583**	Randomized Multi-center Double-blind Parallel-group 15 days trt duration	Age for ≥12 years, SAR for ≥2 years, with exacerbation; positive skin prick test for seasonal allergen and symptomatic (PRIOR score) at screen and baseline	MFNS 200mcg qd: 162/160 Placebo qd: 162/159 MFNS 200mcg qd: 176/174 Placebo qd: 175/174 MFNS 200mcg qd: 168/166 Placebo qd: 165/163	Mean change from baseline over 2-week in NCSS
P04500	Randomized Multi-center Double-blind Parallel-group 15 days trt duration	Age for ≥12 years, SAR for ≥2 years, with exacerbation; positive skin prick test for seasonal allergen and symptomatic (NOW score) at screen and baseline	MFNS 200mcg + OXY qd (1 spray OXY combination): 146 MFNS 200mcg + OXY qd (3 spray OXY combination): 139 MFNS 200mcg qd: 139 OXY bid: 141 Placebo: 142	Mean change from baseline over 2-week in NCSS as a secondary endpoint
P05067 **P05106**	Randomized Multi-center Double-blind Parallel-group 15 days trt duration	Age for ≥12 years, SAR for ≥2 years, with exacerbation; positive skin prick test for seasonal allergen and symptomatic (PRIOR score) at screen and baseline	MFNS 200mcg qd: 211 Placebo: 215 MFNS 200mcg qd: 220 Placebo: 209	Mean change from baseline over 2-week in NCSS as a secondary endpoint

2.2 Data Sources

Documents reviewed were accessed from the CDER document room at:
\\CDSESUB1\EVSPROD\NDA020762\0001\m5\datasets

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

In this efficacy evaluation, a comprehensive review of three studies (P05528, P05529, and P05583) is conducted and the efficacy results from other studies are briefly presented.

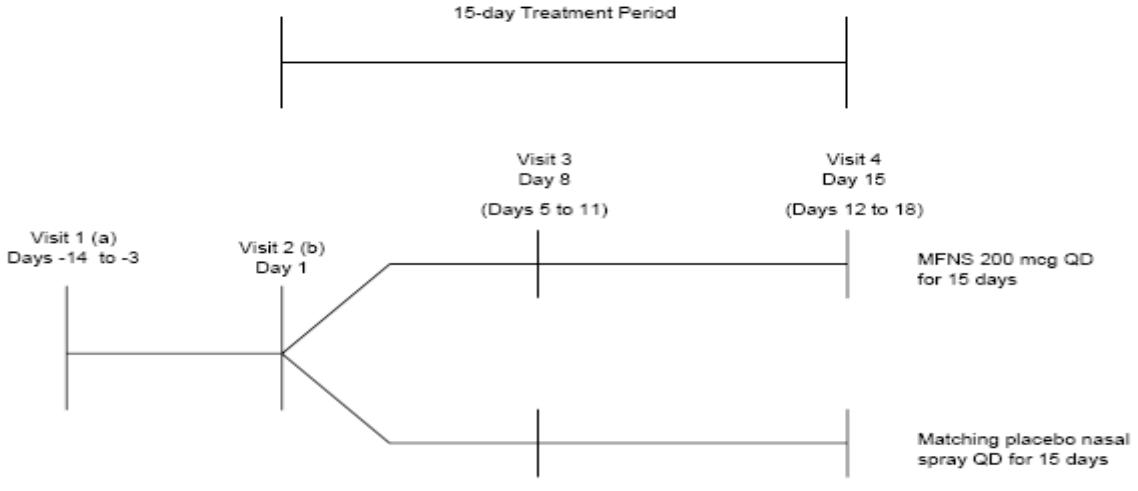
3.1.1 Studies P05528, P05529, P05583

3.1.1.1 Study Design, Efficacy Endpoints, and Statistical Methodologies

The Applicant conducted Studies P05528, P05529, and P05583 in 72 centers in the United States in 2008. The primary objectives of these studies were to 1) assess the efficacy in relieving nasal congestion symptom score (NCSS) with MFNS 200 mcg given once daily compared to placebo in patients with symptomatic SAR; 2) assess the efficacy of MFNS in improving Total Nasal Symptom Score (TNSS).

These studies were identical in design which was a phase 3, double-blind, placebo controlled, and multi-center trial with 15 days of treatment. Eligible patients were male or female, ≥ 12 year old of any race with at least 2 years history of SAR with a positive skin prick test and a minimal level of nasal congestion score (≥2) and TNSS (≥6) at screening (Visit 1). After a non-treatment screening period of 3 to 14 days, eligible patient's the total of the seven run-in diary reflective (PRIOR) scores for the 3 days prior to baseline and the AM of the baseline visit (Visit 2) must have been: nasal congestion score ≥14 and TNSS ≥42. At visit 2, eligible patients were randomized in to Nasonex 200 mcg QD and placebo (1:1) at Visit 2 (Figure 1).

Figure 1: Study Design Diagram



a: Screening period of at least 3 days

b: Randomization

The primary efficacy endpoint was the change from baseline in AM/PM PRIOR nasal congestion symptom score (NCSS) averaged over days 1 to 15. The range of NCSS can be 0 to 3.

The key secondary efficacy endpoint was the change from baseline in AM/PM PRIOR Total Nasal Symptoms Score (TNSS- sum of nasal congestion, rhiniorrhea, nasal itching, sneezing using a 0 to 3 scale) averaged over days 1 to 15. The range of TNSS can be 0 to 12.

Severity of symptoms of allergic rhinitis (Rhinorrhea [nasal discharge/runny nose or postnasal drip], Nasal congestion/stuffiness, Nasal itching, Sneezing) were individually scored twice daily by the patient during the Screening and Treatment Periods and was to be based on the subject's status over the previous 12 hours (reflective or PRIOR) and on the subject's status as the diary was being completed (instantaneous or NOW). These symptoms were to be evaluated upon awakening and approximately 12 hours later in the evening. Severity of symptoms will be graded as follows:

0 = None: No symptom evident;
1 = Mild: Symptom was clearly present but minimal awareness; easily tolerated;
2 = Moderate: Definite awareness of symptom, which was bothersome but tolerable;
3 = Severe: Symptom was hard to tolerate; cause interference with activities of daily living and/or sleeping.

The assessment of severity was to be recorded on the subject's symptoms diary card. The AM/PM score is the average of AM score and PM score.

Additional Secondary Endpoints

- Change from Baseline in average AM/PM PRIOR nasal congestion score and TNSS for each of Days 1, 2, 3, 4, 1 to 8, and 9 to 15.
- Change from Baseline in average AM/PM PRIOR nasal itching, sneezing, and nasal discharge scores for each of Days 1, 2, 3, 4, 1 to 8, 9 to 15, and 1 to 15.
- Change from Baseline in average AM/PM NOW, AM NOW, PM NOW, AM PRIOR, PM PRIOR for nasal congestion score, TNSS, and nasal itching, sneezing, nasal discharge scores for each of Days 1, 2, 3, 4, 1 to 8, 9 to 15, and 1 to 15.
- Change from Baseline in the evaluation of overall condition of SAR by the subject and investigator, separately, at Days 8, 15, and Endpoint.

The primary analyses were performed using the analysis of covariance (ANCOVA) model with treatment and study site, and the baseline nasal congestion score as a covariate. Treatment comparison was based on the least squares means from this model using the pooled standard deviation. Baseline for the primary endpoint was the average of AM/PM PRIOR nasal congestion scores form 3 days prior to the first dose date. AM/PM PRIOR scores are defined as the daily averages of AM and PM PRIOR scores. The primary analysis and all efficacy analyses were conducted on the intent-to-treat (ITT) population that includes all randomized patients.

A sequential step-down procedure was employed for inferential testing of the endpoints. If the primary endpoint reached statistical significance, the sequential procedure would lead to testing the hypothesis on the key secondary endpoint (TNSS) and then to the other four secondary endpoints.

Based on the Applicant's sample size calculation, 160 patients per group were expected to provide 90% power to detect a treatment difference of 0.20 point in change from baseline of NCSS over 2-week study period, assuming a pooled standard deviation of 0.55 point at a significance level of 0.01. For the TNSS, the sample size of 160 for each arm was sufficient to detect a difference of 0.8 point over placebo at 92% power. Joint power for both NCSS and TNSS was 83%. The original protocol was finalized on May 08, 2008 and there were no amendments to the original protocol.

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 1008 patients (506 MFNS and 502 placebo patients) were randomized in three studies. All patients received at lease one dose of study drug. The majority (98%) of patients completed the 15-days of treatment period (Table 3). Overall, 12 patients (6 from the MFNS group and 6 from the placebo group) discontinued form the treatment period. A total of 26 patients (15 in MFNS treatment group and 11 in the placebo group) were considered to have non-evaluable efficacy data (i.e., not representative of the appropriate treatment regimen) due to insufficient efficacy data or non-compliance with the study treatment. These patients were excluded from the efficacy-evaluable data set. These patients were included in the primary efficacy analyses.

Table 3: Patients' Accountability N (%)

Study		***MFNS 200 mcg QD (n=506)***	***Placebo (n=502)***	***Total (n=1008)***
P05528	Randomized patients (ITT)	162 (100)	162 (100)	324 (100)
24 center	Completed treatment period	160 (99)	159 (98)	319 (98)
	Discontinued	2 (1)	3 (2)	5 (2)
P05529	Randomized patients (ITT)	176 (100)	175 (100)	351 (100)
24 center	Completed treatment period	174 (99)	174 (99)	348 (99)
	Discontinued	2 (1)	1 (1)	3 (1)
P05583	Randomized patients (ITT)	168 (100)	165 (100)	333 (100)
24 center	Completed treatment period	166 (99)	163 (99)	329 (99)
	Discontinued	2 (1)	2 (1)	4 (1)
Reason of early discontinuation (combined three studies)				
	Treatment Failure	1	3	4
	Adverse event	2	2	4
	Non-compliance	2	0	2
	Did not wish to continue	1	1	2
Excluded from evaluate data set		7+4+4	3+4+4	26
Evaluable data set		155+172+164	159+171+161	982

The demographic and baseline disease characteristics were generally well balanced between the treatment groups in all three studies (Table 4). Overall, the ages of patients ranged from 12 to 78 with a mean age of 39. In all three studies, approximately two-thirds of patients were male and the majority of patients were Caucasian. Total of the seven run-in diary reflective (PRIOR) scores for the 3 days prior to baseline and the AM of the baseline visit (Visit 2) was ≥14 in nasal congestion and was ≥42 in TNSS, Except for six patients (2 in MFNS and 4 in Placebo), all other patients met the inclusion criteria.

Table 4: Patients' Demographic and Baseline Characteristics N (%), (ITT)

Study	P05528		P05589		P055583	
	MFNS 200 mcg QD (N=162)	Placebo (N=162)	MFNS 200 mcg QD (N=176)	Placebo (N=175)	MFNS 200 mcg QD (N=168)	Placebo (N=165)
Age, yrs						
Mean (SD)	40.8 (12.8)	38.2 (12.7)	37.9 (13.3)	38.6 (14.0)	38.6 (14.4)	39.0 (13.9)
Median	41	39	37	40	40	39
Range	13 – 78	15 – 64	12 – 72	12 – 73	13 – 69	12 – 74
11 to <18 yrs	7 (4.3)	8 (4.9)	11 (6.2)	14 (8.0)	14 (8.3)	14 (8.5)
18 to <65 yrs	148 (91.4)	154 (95.1)	162 (92.0)	156 (89.1)	148 (88.1)	146 (88.5)
≥65 yrs	7 (4.3)	0	3 (1.8)	5 (2.9)	6 (3.6)	5 (3.0)
Sex, n (%)						
Female	113 (69.7)	116 (71.6)	107 (60.8)	116 (66.3)	109 (64.9)	103 (62.4)
Male	49 (30.3)	46 (28.4)	69 (39.2)	59 (33.7)	59 (35.1)	62 (37.6)
Race, n (%)						
White	123 (75.9)	124 (76.5)	139 (79.0)	136 (77.7)	138 (82.1)	124 (75.1)
Non-White	39 (24.1)	38 (23.5	37 (21.0)	39 (22.3)	30 (17.9)	41 (24.9)
Sum of AM/PM PRIOR Nasal Congestion scores for the 3 days prior to baseline and the AM of the baseline visit (Visit 2) (Maximum 21)						
Mean (SD)	17.8 (2.5)	17.9 (2.6)	18.3 (2.6)	18.4 (2.5)	18.4 (2.5)	18.3 (2.4)
Median	18	18	19	19	19	19
Range	12 – 21	13 – 21	11 – 21	9 – 21	14 – 21	12 – 21
Sum of AM/PM PRIOR TNSS scores for the 3 days prior to baseline and the AM of the baseline visit (Visit 2)(Maximum 84)						
Mean (SD)	65.2 (10.6)	64.8 (10.5)	66.6 (11.8)	67.5 (10.6)	66.6 (10.7)	67.6 (9.8)
Median	65	65	68.5	67	68.5	69
Range	44 – 84	40 – 84	42 – 84	42 – 84	38 – 84	42 - 84
History of SAR with Duration (yrs)						
N of Patients	162	162	176	175	168	165
Mean (SD)	23 (13.3)	19 (11.6)	21 (13.8)	21 (13.1)	21 (12.3)	21 (12.1)
Range	2 – 60	2 – 55	2 – 68	3 – 52	2 – 54	3 – 50
History of Asthma with Duration (yrs)						
N of Patients	40	22	35	39	26	31
Mean (SD)	20 (13.3)	19 (13.7)	16 (11.5)	17 (14.3)	13 (10.0)	15 (11.6)
Range	2 – 53	2 - 49	1 – 50	1 – 47	1 – 43	1 – 44
History of PAR with Duration (yrs)						
N of Patients	113	111	137	136	131	111
Mean (SD)	24 (14.1)	19 (11.9)	21 (13.9)	21 (12.9)	20 (12.9)	22 (11.3)
Range	1 – 60	2 - 49	3 – 63	3 – 52	1 – 54	3 – 47
Allergy Test (Skin Prick) Results (Diameter mm)– Histamine Positive Control						
N of Patients	162	162	176	175	168	165
Mean (SD)	7.7 (3.2)	7.5 (2.8)	7.6 (2.9)	7.6 (3.0)	7.1 (2.8)	7.1 (2.6)
Range	3 – 17	1 - 17	1 – 17	2 - 21	2 – 17	2 – 21
Allergy Test (Skin Prick) Results (Diameter mm)– Ragweed						
N of Patients	145	146	144	140	142	145
Mean (SD)	8.6 (5.5)	7.6 (4.4)	8.6 (4.4)	8.1 (3.8)	6.8 (3.0)	7.2 (3.6)
Range	0 – 34	0 – 21	0 – 27	0 - 25	0 – 16	0 - 22
Allergy Test (Skin Prick) Results (Diameter mm)– Saline Negative Control						
N of Patients	162	162	176	175	168	165
Mean (SD)	0.43 (1.06)	0.37 (1.08)	0.34 (1.02)	0.44 (1.12)	0.54 (1.35)	0.36
Range	0 – 5	0 – 7	0 – 5	0 - 5	0 – 7	0 - 5

3.1.1.3 Results and Conclusions

In two studies (P05529 and P05583), patients treated with MFNS demonstrated a statistically significant superiority in AM/PM PRIOR nasal congestion symptom score (NCSS) over placebo.

In Study P05528, there is no significant difference in AM/PM PRIOR nasal congestion symptom score (NCSS) between MFNS and placebo.

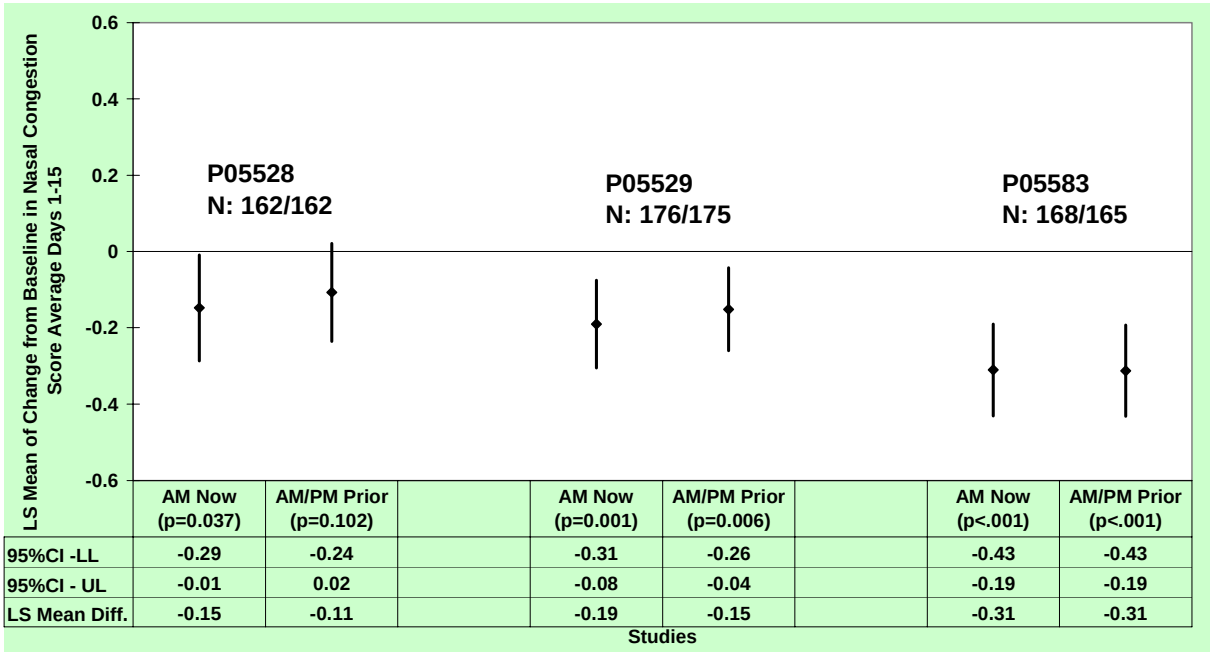
In all three studies, mean difference between MFNS and placebo ranged from 0.11 to 0.31 point in AM/PM prior nasal congestion score. In all three studies, patients treated with MFNS demonstrated statistically significant improvement in the AM now nasal congestion score compared to the placebo group. Mean difference between MFNS and placebo ranged from 0.15 to 0.31 point. (Table 5 and Figure 2)

Table 5: Analysis Results of Nasal Congestion Symptom Score of Three Studies

Study/Treatment		Baseline	Change from Baseline over 2-weeks		
		Mean (SE)	Mean (SE)	Median (Range)	LS Mean (SE)[a]
AM/PM Prior NCSS Over 2-weeks (Primary)					
P05528	MFNS (162)	2.54 (0.03)	-0.63 (0.05)	-0.54 (-2.17, 0.62)	-0.68 (0.05)
	Placebo (162)	2.56 (0.03)	-0.52 (0.05)	-0.38 (-2.11, 0.66)	-0.57 (0.05)
P05529	MFNS (176)	2.62 (0.03)	-0.63 (0.04)	-0.51 (-2.45, 0.34)	-0.64 (0.04)
	Placebo (175)	2.62 (0.03)	-0.48 (0.04)	-0.42 (-1.96, 0.35)	-0.49 (0.04)
P05583	MFNS (168)	2.63 (0.03)	-0.70 (0.05)	-0.59 (-2.80, 0.42)	-0.71 (0.05)
	Placebo (165)	2.61 (0.03)	-0.37 (0.04)	-0.29 (-2.09, 0.90)	-0.41 (0.05)
AM Now NCSS Over 2-weeks					
P05528	MFNS (162)	2.58 (0.03)	-0.62 (0.05)	-0.55 (-2.32, 1.46)	-0.65 (0.05)
	Placebo (162)	2.52 (0.03)	-0.45 (0.05)	-0.30 (-2.21, 0.96)	-0.50 (0.05)
P05529	MFNS (176)	2.62 (0.03)	-0.61 (0.04)	-0.52 (-2.86, 0.57)	-0.61 (0.05)
	Placebo (175)	2.60 (0.03)	-0.41 (0.04)	-0.36 (-1.96, 0.64)	-0.42 (0.05)
P05583	MFNS (168)	2.60 (0.03)	-0.62 (0.05)	-0.50 (-2.42, 0.61)	-0.60 (0.05)
	Placebo (165)	2.58 (0.03)	-0.31 (0.04)	-0.21 (-2.07, 0.94)	-0.29 (0.05)

[a]: LS Mean and SE were from a two-way ANOVA model with treatment, baseline value, and center effects.

Figure 2: LS Mean Change from Baseline of NCSS over 2-weeks [a]



[a]: LS Mean, 95%CI, and p- value were from a two-way ANOVA model with treatment, baseline value, and center effects.

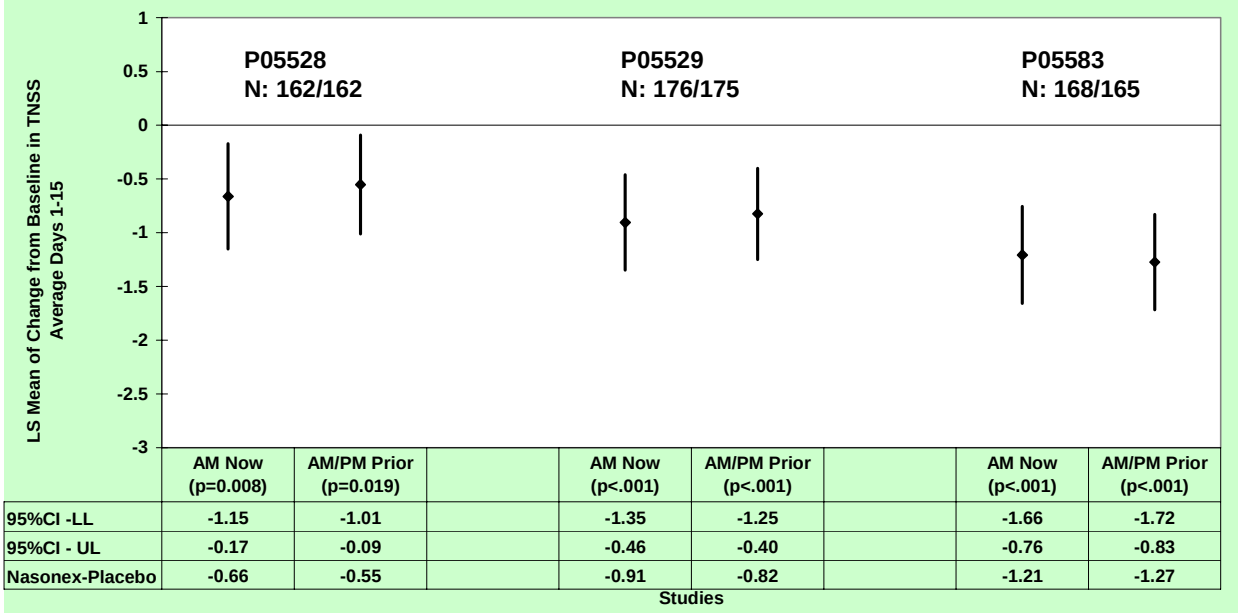
For the key secondary efficacy endpoint, change from Baseline in AM/PM PRIOR TNSS averaged over Days 1 to 15, MFNS demonstrated a statistically significant superiority over placebo in all three studies. Mean difference between MFNS and placebo ranged from 0.55 to 1.27. (Table 6 and Figure 3)

Table 6: Analysis Results of Total Nasal Symptom Score of Three Studies

Study/Treatment		Baseline	Change from Baseline over 2-weeks		
		Mean (SE)	Mean (SE)	Median (Range)	LS Mean (SE)[a]
AM/PM Prior TNSS Over 2-weeks					
P05528	MFNS (162)	9.37 (0.12)	-2.43 (0.18)	-2.38 (-8.44, 2.29)	-2.61 (0.18)
	Placebo (162)	9.31 (0.12)	-1.86 (0.16)	-1.46 (-8.86, 2.36)	-2.06 (0.18)
P05529	MFNS (176)	9.60 (0.12)	-2.63 (0.16)	-2.46 (-10.9, 1.50)	-2.68 (0.17)
	Placebo (175)	9.66 (0.11)	-1.82 (0.15)	-1.63 (-9.74, 1.72)	-1.85 (0.17)
P05583	MFNS (168)	9.55 (0.12)	-2.84 (0.18)	-2.44 (-10.4, 2.72)	-3.00 (0.19)
	Placebo (165)	9.69 (0.11)	-1.62 (0.15)	-1.17 (-8.76, 2.44)	-1.72 (0.20)
AM Now TNSS Over 2-weeks					
P05528	MFNS (162)	9.34 (0.14)	-2.42 (0.19)	-1.96 (-8.48, 2.98)	-2.54 (0.19)
	Placebo (162)	9.16 (0.13)	-1.70 (0.18)	-1.14 (-9.29, 2.61)	-1.88 (0.19)
P05529	MFNS (176)	9.49 (0.13)	-2.58 (0.17)	-2.21 (-11.5, 1.89)	-2.53 (0.18)
	Placebo (175)	9.43 (0.13)	-1.65 (0.15)	-1.29 (-9.57, 3.11)	-1.62 (0.18)
P05583	MFNS (168)	9.25 (0.13)	-2.58 (0.19)	-2.30 (-10.3, 5.14)	-2.67 (0.19)
	Placebo (165)	9.55 (0.11)	-1.51 (0.16)	-1.05 (-8.32, 3.35)	-1.46 (0.20)

[a]: LS Mean and SE were from a two-way ANOVA model with treatment, baseline value, and center effects

Figure 3: LS Mean Change from Baseline of TNSS over 2-weeks [a]



	AM Now (p=0.008)	AM/PM Prior (p=0.019)		AM Now (p<.001)	AM/PM Prior (p<.001)		AM Now (p<.001)	AM/PM Prior (p<.001)
95%CI -LL	-1.15	-1.01		-1.35	-1.25		-1.66	-1.72
95%CI - UL	-0.17	-0.09		-0.46	-0.40		-0.76	-0.83
Nasonex-Placebo	-0.66	-0.55		-0.91	-0.82		-1.21	-1.27

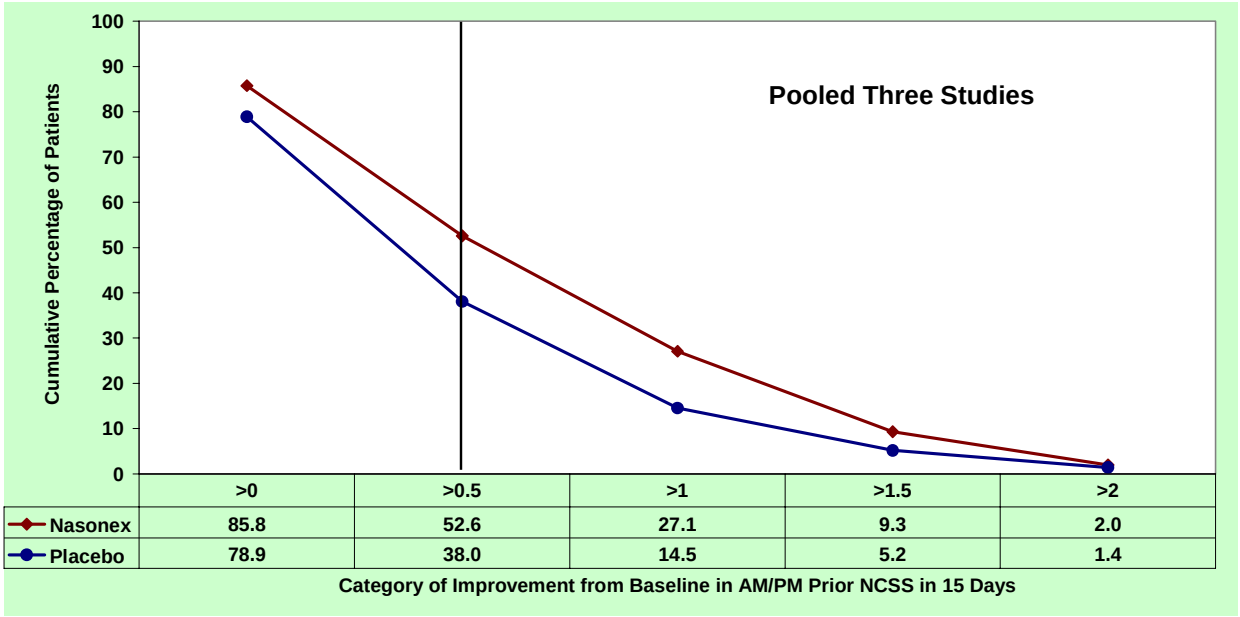
Studies

[a]: LS Mean, 95%CI, and p- value were from a two-way ANOVA model with treatment, baseline value, and center effects.

I also performed a responder analysis combining data from three studies. Note that these figures were created to provide a visual display of the relative benefit of MFNS across the entire range of response of over 2-weeks study period. The x-axis shows the category of improvement from

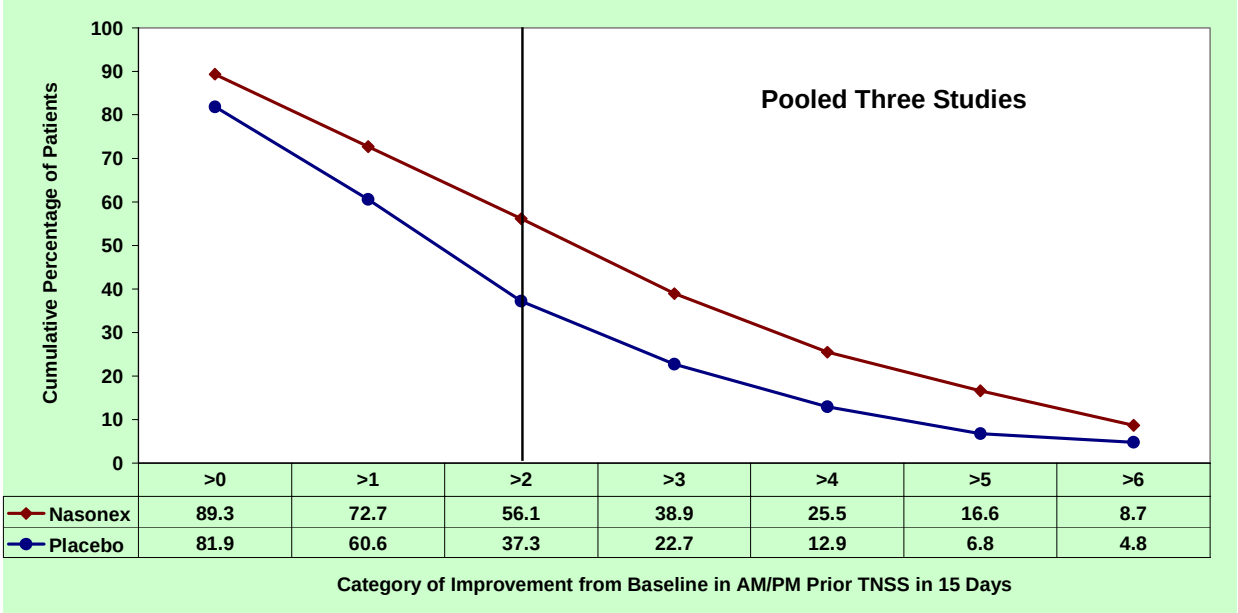
baseline in AM/PM prior NCSS throughout the 2-week study period, and the y-axis shows the corresponding percentage of patients achieving that level of AM/PM prior NCSS or greater. The positive treatment effect of MFNS was demonstrated by consistent separation of the curve. Fifty-three percent of MFNS-treated patients have at least 0.5 point improvement from baseline in AM/PM prior NCSS compared to 38% in placebo (Figure 4). This evidence is also seen in the secondary endpoint (TNSS). Fifty-six percent of MFNS-treated patients have at least 2 points improvement from baseline in AM/PM prior TNSS compared to 38% in placebo. (Figure 5)

Figure 4: Response Profile (Pooled Three Studies)



	>0	>0.5	>1	>1.5	>2
Nasonex	85.8	52.6	27.1	9.3	2.0
Placebo	78.9	38.0	14.5	5.2	1.4

Figure 5. Response Profile (Pooled Three Studies)



Individual Nasal Symptoms Score - Two out of three studies demonstrated that MFNS statistically significantly improved nasal discharge and nasal congestion symptoms. Three studies showed that MFNS statistically significantly improved nasal itching and sneezing symptom over placebo. Overall, the individual nasal symptoms scores numerically were similar to the results with TNSS and were not statistically significant in all studies (Table 7).

Table 7. Analysis Results of Individual Nasal Symptom Score of Three Studies

Study / Treatment		*Baseline*	*Change from Baseline over 2-weeks*		
		Ls Mean (SE)	*LS Mean (SE)*	*LS Mean Diff (MFNS-PLB)*	*95% CI*
AM / PM Prior Nasal Discharge Over 2-weeks					
P05528	MFNS (162)	2.47 (0.04)	-0.58 (0.05)	-0.11 (0.06)	(-0.23, 0.02)
	Placebo (162)	2.39 (0.04)	-0.48 (0.05)	--	--
P05529	MFNS (176)	2.50 (0.04)	-0.61 (0.05)	-0.17 (0.06)	(-0.29, -0.06)
	Placebo (175)	2.49 (0.04)	-0.44 (0.04)	--	--
P05583	MFNS (168)	2.47 (0.04)	-0.70 (0.05)	-0.29 (0.06)	(-0.40, -0.17)
	Placebo (165)	2.43 (0.04)	-0.41 (0.05)	--	--
AM / PM Prior Nasal Congestion Over 2-weeks					
P05528	MFNS (162)	2.55 (0.03)	-0.68 (0.05)	-0.11 (0.06)	(-0.23, 0.02)
	Placebo (162)	2.57 (0.03)	-0.57 (0.05)	--	--
P05529	MFNS (176)	2.63 (0.03)	-0.64 (0.04)	-0.15 (0.05)	(-0.26, -0.04)
	Placebo (175)	2.62 (0.03)	-0.49 (0.04)	--	--
P05583	MFNS (168)	2.61 (0.03)	-0.71 (0.05)	-0.31 (0.06)	(-0.43, -0.19)
	Placebo (165)	2.59 (0.03)	-0.40 (0.06)		
AM / PM Prior Nasal Itching Over 2-weeks					
P05528	MFNS (162)	2.32 (0.05)	-0.68 (0.05)	-0.14 (0.07)	(-0.27, -0.01)
	Placebo (162)	2.34 (0.05)	-0.54 (0.05)	--	--
P05529	MFNS (176)	2.39 (0.05)	-0.71 (0.05)	-0.24 (0.06)	(-0.36, -0.12)
	Placebo (175)	2.36 (0.05)	-0.47 (0.05)	--	--
P05583	MFNS (168)	2.33 (0.05)	-0.81 (0.05)	-0.31 (0.06)	(-0.44, -0.19)
	Placebo (165)	2.38 (0.05)	-0.49 (0.06)		
AM / PM Prior Sneezing Over 2-weeks					
P05528	MFNS (162)	2.01 (0.05)	-0.67 (0.05)	-0.20 (0.07)	(-0.34, -0.07)

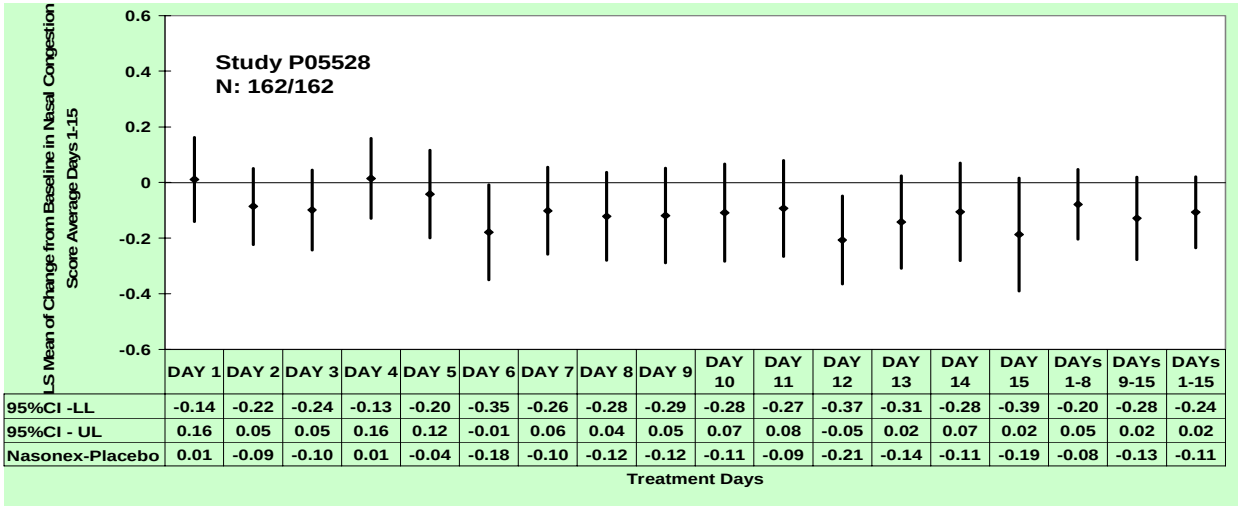
	Placebo (162)	2.03 (0.05)	-0.47 (0.05)	--	--
P05529	MFNS (176)	2.08 (0.05)	-0.71 (0.05)	-0.27 (0.06)	(-0.40, -0.14)
	Placebo (175)	2.19 (0.05)	-0.44 (0.05)	--	--
P05583	MFNS (168)	1.98 (0.06)	-0.78 (0.05)	-0.35 (0.06)	(-0.48, -0.23)
	Placebo (165)	2.10 (0.06)	-0.43 (0.06)		

[a]: LS Mean and 95%CI were from a two-way ANOVA model with treatment, baseline value, and center effects

Assessment of Treatment Effect over Time

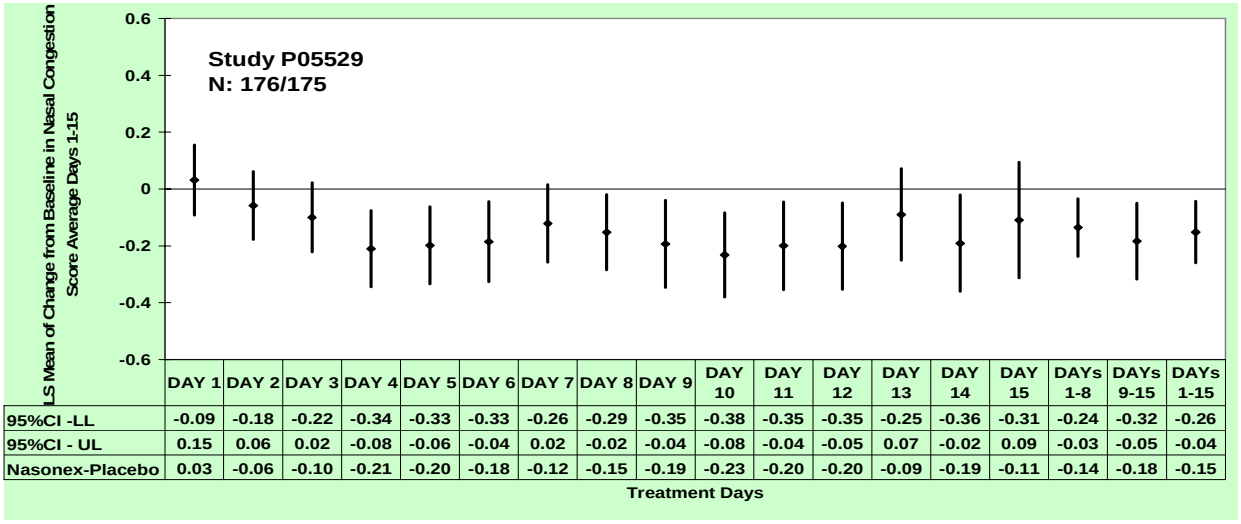
For Studies P05528 and P05529, the treatment effect varied over time. For Study P05583, MFNS demonstrated a numerically superiority over placebo overtime. (Figure 6)

Figure 6: LS Mean Change from Baseline of NCSS by Days [a]



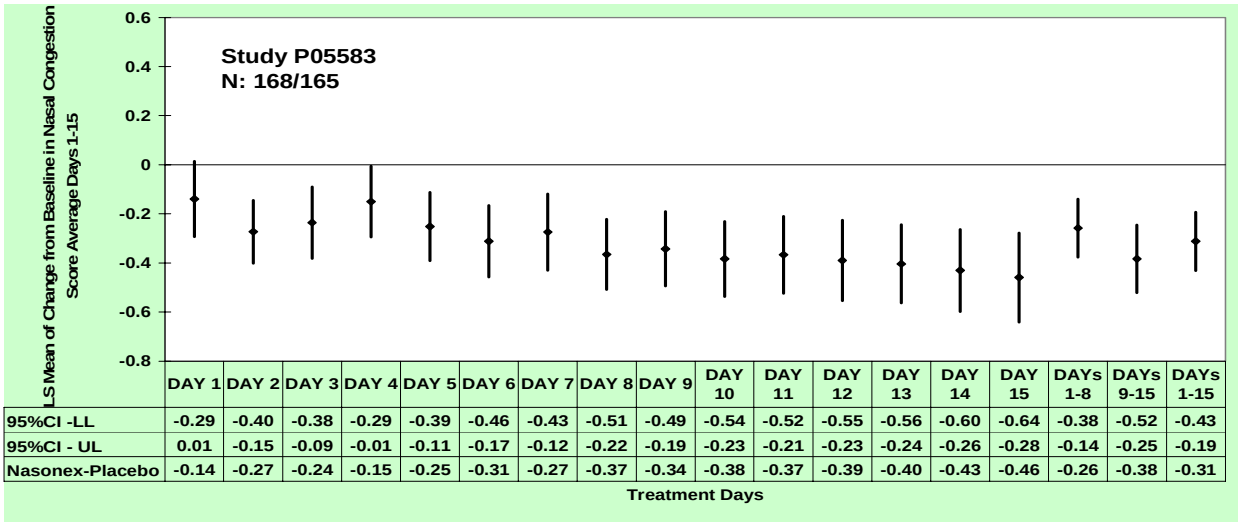
	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAYs 1-8	DAYs 9-15	DAYs 1-15
95%CI -LL	-0.14	-0.22	-0.24	-0.13	-0.20	-0.35	-0.26	-0.28	-0.29	-0.28	-0.27	-0.37	-0.31	-0.28	-0.39	-0.20	-0.28	-0.24
95%CI - UL	0.16	0.05	0.05	0.16	0.12	-0.01	0.06	0.04	0.05	0.07	0.08	-0.05	0.02	0.07	0.02	0.05	0.02	0.02
Nasonex-Placebo	0.01	-0.09	-0.10	0.01	-0.04	-0.18	-0.10	-0.12	-0.12	-0.11	-0.09	-0.21	-0.14	-0.11	-0.19	-0.08	-0.13	-0.11

Treatment Days



	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAYs 1-8	DAYs 9-15	DAYs 1-15
95%CI -LL	-0.09	-0.18	-0.22	-0.34	-0.33	-0.33	-0.26	-0.29	-0.35	-0.38	-0.35	-0.35	-0.25	-0.36	-0.31	-0.24	-0.32	-0.26
95%CI - UL	0.15	0.06	0.02	-0.08	-0.06	-0.04	0.02	-0.02	-0.04	-0.08	-0.04	-0.05	0.07	-0.02	0.09	-0.03	-0.05	-0.04
Nasonex-Placebo	0.03	-0.06	-0.10	-0.21	-0.20	-0.18	-0.12	-0.15	-0.19	-0.23	-0.20	-0.20	-0.09	-0.19	-0.11	-0.14	-0.18	-0.15

Treatment Days



	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAYs 1-8	DAYs 9-15	DAYs 1-15
95%CI -LL	-0.29	-0.40	-0.38	-0.29	-0.39	-0.46	-0.43	-0.51	-0.49	-0.54	-0.52	-0.55	-0.56	-0.60	-0.64	-0.38	-0.52	-0.43
95%CI - UL	0.01	-0.15	-0.09	-0.01	-0.11	-0.17	-0.12	-0.22	-0.19	-0.23	-0.21	-0.23	-0.24	-0.26	-0.28	-0.14	-0.25	-0.19
Nasonex-Placebo	-0.14	-0.27	-0.24	-0.15	-0.25	-0.31	-0.27	-0.37	-0.34	-0.38	-0.37	-0.39	-0.40	-0.43	-0.46	-0.26	-0.38	-0.31

Treatment Days

[a]: LS Mean and 95%CI were from a two-way ANOVA model with treatment, baseline value, and center effects.

Conclusion

Two of out three studies demonstrated that treatment with Nasonex significantly reduced nasal congestion symptom score (NCSS) compared to placebo in patients 12 years of age and older with SAR. All three studies showed that this effect lasts for the whole dosing interval. In addition, three studies confirmed the efficacy of MFNA over placebo in improving the Total Nasal Symptom Score (TNSS). All key secondary efficacy endpoints and exploratory endpoints support the primary efficacy finding.

3.1.2 Subgroup Analyses

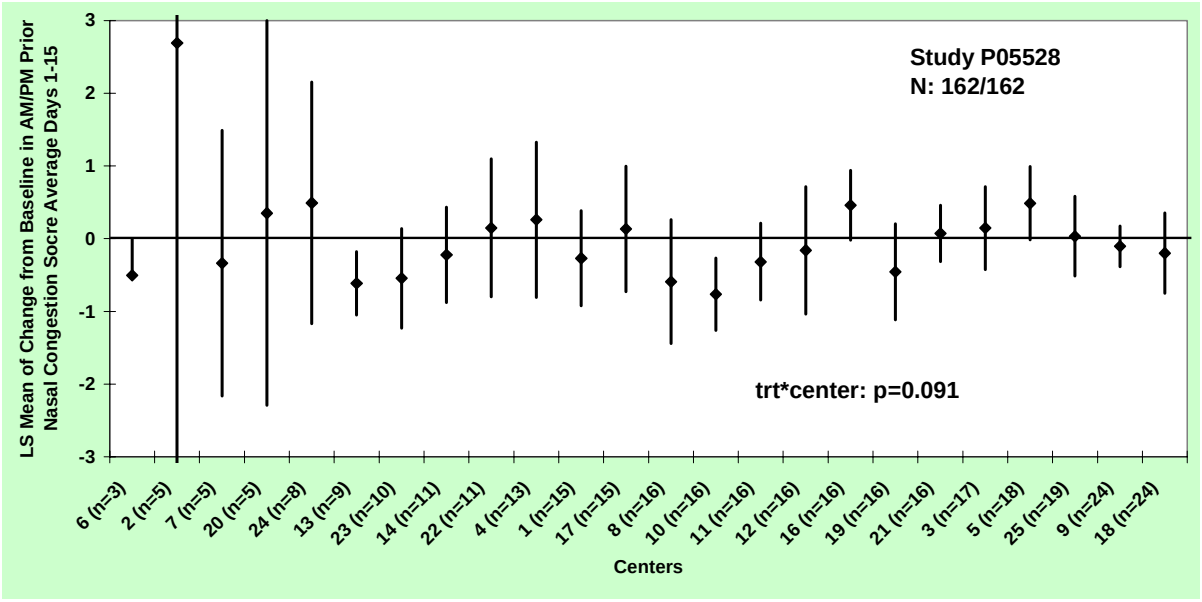
The treatment comparison MFNS with placebo in change from baseline over 2-week treatment period in NCSS for subgroups were displayed in Figure 7, Figure 8, Figure 9, and Figure 10.

The Applicant stated, *"Study P05528 was considered to be invalid on the basis of a treatment-by-site interaction."* I conducted a test of treatment-by-site interaction and there is evidence of a qualitative interaction between treatment and site (Figure 7). There are a few large sites

(centers) in this study where the data favors placebo. However, because of the small numbers of patients in each site, any claims of variation in treatment effects for the subgroup of site are essentially unsupported.

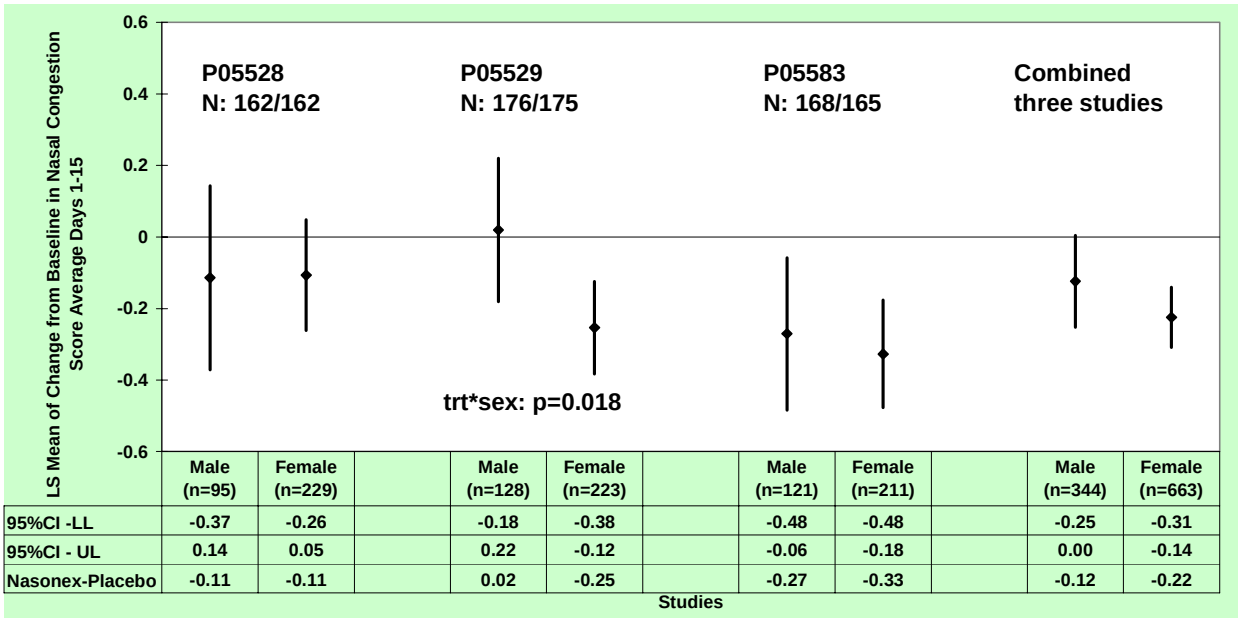
Although Study P05529 showed a significant treatment-by-subgroup interaction for gender and age group, such a differential gender and age effect was not seen in other two studies. The results of overall subgroup analyses using pooled data from three studies show that treatment effect of MFNS was slightly better on female and adult (18+ years old). However, because two-thirds of patients are female, and 93% are over 18 years of age, it is impossible to confidently distinguish the possible treatment effects for the subgroup of gender and age.

Figure 7: LS Mean Change from Baseline of Nasal Congestion Score by Center [a]



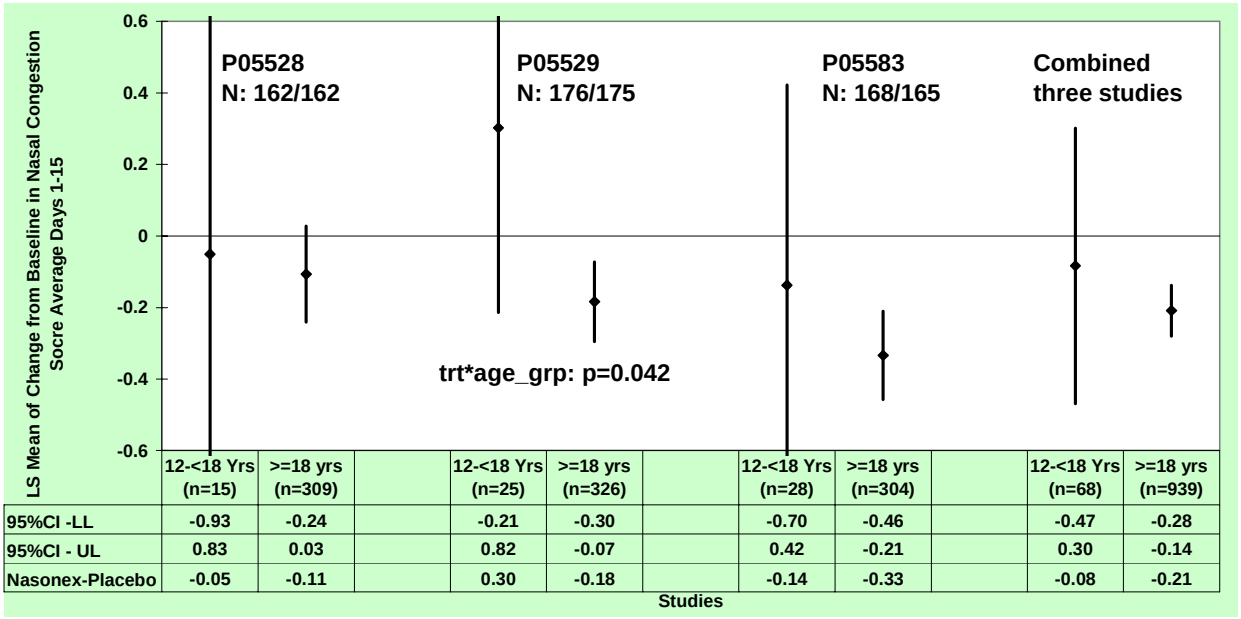
[a]: LS Mean and p- value were from a two-way ANOVA model with treatment and baseline value.

Figure 8: LS Mean Change from Baseline of Nasal Congestion Score by Sex [a]



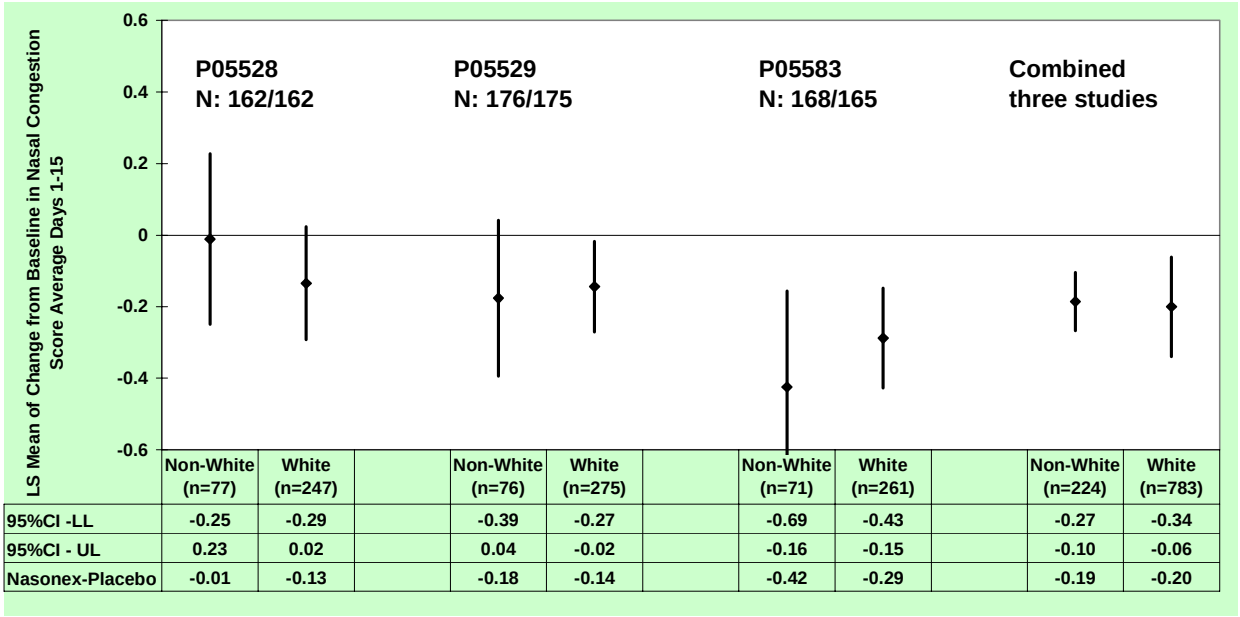
[a] LS Mean and 95%CI were from a two-way ANOVA model with treatment, baseline value, and center effects.

Figure 9: LS Mean Change from Baseline of Nasal Congestion Score by Age Group [a]



[a]: LS Mean and 95%CI were from a two-way ANOVA model with treatment, baseline value, and center effects.

Figure 10: LS Mean Change from Baseline of Nasal Congestion Score by Race [a]



	Non-White (n=77)	White (n=247)		Non-White (n=76)	White (n=275)		Non-White (n=71)	White (n=261)		Non-White (n=224)	White (n=783)
95%CI -LL	-0.25	-0.29		-0.39	-0.27		-0.69	-0.43		-0.27	-0.34
95%CI - UL	0.23	0.02		0.04	-0.02		-0.16	-0.15		-0.10	-0.06
Nasonex-Placebo	-0.01	-0.13		-0.18	-0.14		-0.42	-0.29		-0.19	-0.20

[a]: LS Mean and 95%CI were from a two-way ANOVA model with treatment, baseline value, and center effects.

3.1.2 Studies P04500 P05067, P05106

The Applicant submitted the study reports for all three studies to support the effects of MFNS on nasal congestion score, which were explored as the secondary endpoints. The Applicant did not submit the data for these three studies, the efficacy results, which are presented in Table 8, were copied from the Applicant's study report. The magnitudes of treatment effect were similar to the previous three studies.

Table 8: Efficacy Results of Three Supportive Studies

Study	*Treatment*	*N*	*Baseline*	*Mean Change from Baseline*	*MFNS - Placebo p-value* [a]
AM/PM Prior TNSS Over 2-weeks					
P05106 (SAR)	MFNS 200 mcg	220	9.76	-2.88	-1.06
	Placebo	209	9.77	-1.82	P<0.01
P05067 (SAR)	MFNS 200 mcg	211	10.18	-2.65	-0.59
	Placebo	215	10.15	-2.06	P=0.004
P04500 (SAR)	MFNS 200 mcg	139	9.98	-3.06	-1.13
	Placebo	142	10.18	-1.93	P<.001
AM/PM Prior Nasal Congestion Score Over 2-weeks					
P05106 (SAR)	MFNS 200 mcg	220	2.63	-0.70	0.29
	Placebo	209	2.65	-0.41	P<0.01
P05067 (SAR)	MFNS 200 mcg	211	0.73	-0.67	0.16
	Placebo	215	0.69	-0.51	P=0.003
P04500 (SAR)	MFNS 200 mcg	139	2.69	-0.75	0.30
	Placebo	142	2.71	-0.45	P<.001

Results are copied from the summary of clinical efficacy report.

3.1.3 Pediatric Studies

The efficacy MFNS Nasal Spray 50mcg for the treatment for nasal symptoms of SAR and PAR in pediatric subjects (6 to 11 years of age) has been previously evaluated in two controlled clinical studies [Study C95-161 (SAR) and Study 196-090 (PAR) submitted under NDA 20/762/S-004)]. The efficacy results for both studies, copied from Medical review of 20/762/S-004, are presented in Table 9. Both of these studies demonstrated significant improvements in subject-reported nasal congestion, which was a secondary endpoint. The observed effect size of 0.2 ($p<.01$) in the average AM/PM nasal congestion score over Days 1 to 15 for both studies is similar to that of the effect size observed in the adult population (0.2, 0.4 point). Therefore, the effect of MFNS on nasal congestion is similar in adult and pediatric allergic rhinitis patients (6-11 years of age).

Table 9: Efficacy Results of Two Pediatric Studies

Study	*Treatment*	*N*	*Baseline*	*Mean Change from Baseline*	*p-value MFNS vs. Placebo* [a]
AM/PM Prior TNSS Over 2-weeks					
C95-161 (SAR)	MFNS 200 mcg	133	6.9	-1.8	<0.01
	MFNS 100 mcg	134	6.9	-1.9	<0.01
	Placebo	134	6.8	-1.2	--
196-090 (PAR)	MFNS 100 mcg	187	5.9	-1.7	<0.01
	Placebo	189	6.8	-1.1	--
AM/PM Prior Nasal Congestion Score Over 2-weeks					
C95-161 (SAR)	MFNS 200 mcg	133	2.1	-0.5	<0.01
	MFNS 100 mcg	134	2.2	-0.5	<0.01
	Placebo	134	2.1	-0.3	--
196-090 (PAR)	MFNS 100 mcg	187	2.3	-0.6	<0.01
	Placebo	189	2.3	-0.4	--

Results are copied from the summary of clinical efficacy report.

3.3 Evaluation of Safety

Dr. Xu Wang, the Medical Reviewer, conducted the evaluation of the safety data separately. Reader is referred to Dr. Wang's review for information regarding the safety profile of the drug.

3.4 Labeling

I recommend including all three studies in the label and change the table 3 in section 14.4 as follows:

(b) (4)

1 page of Statistical Review: Draft Labeling has been withheld in full immediately following this page as B4 CCI/TS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20762	SUPPL-38	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	NASONEX NASAL SPRAY (MOMETASONE FUROATE)

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

/s/

FENG ZHOU
03/22/2010

JOAN K BUENCONSEJO
03/22/2010