Common Drug Review
Clinical Review Report

May 2016

Drug	Azelastine hydrochloride and fluticasone propionate nasal spray (AZE/FP)
Indication	The symptomatic treatment of moderate-to-severe seasonal allergic rhinitis and associated ocular symptoms in adults and adolescents aged 12 and older for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient.
Listing request	As per indication
Manufacturer	Meda Pharmaceuticals Ltd.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in allergy and immunology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

AZE/FP	azelastine hydrochloride and fluticasone propionate fixed-dose combination
AE	adverse event
a.m.	morning
CDR	CADTH Common Drug Review
CI	confidence interval
FDA	US Food and Drug Administration
iTNSS	instantaneous total nasal symptom score
ITT	intention-to-treat population
LOCF	last observation carried forward
LS	least squares
MCID	minimal clinically important difference
p.m.	evening
rTNSS	reflective total nasal symptom score
rTOSS	reflective total ocular symptom score
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
SAE	serious adverse event
SAR	seasonal allergic rhinitis
SD	standard deviation
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

The prevalence of seasonal allergic rhinitis (SAR) is estimated to be between 20% and 25% in Canada.[1] Up to 40% of patients who visit physicians are diagnosed with SAR, and approximately 70% of SAR patients have moderate-to-severe symptoms.[1] SAR patients present with nasal (congestion, runniness, sneezing, and itchiness) and non-nasal (watery eyes, itchy eyes, and eye redness) symptoms. There is no risk of mortality associated with SAR, but the moderate-to-severe symptoms affect patients' quality of life. Allergy symptoms can have an impact on sleep, daily activities, and workplace productivity.

First-line treatment for SAR is oral antihistamines.[2] Nasal corticosteroids are recommended as second-line options for patients with mild allergic rhinitis and first-line options for patients with moderate-to-severe symptoms.[2] In Canada, a combination of oral antihistamines, corticosteroid nasal sprays, and prescription eye drops is commonly used in patients with allergic rhinitis.[2] Other treatment options include leukotriene receptor antagonists, such as montelukast, and allergen immunotherapy.

AZE/FP is a fixed-dose combination nasal spray of 0.1% azelastine hydrochloride (AZE), an antihistamine, and 0.037% fluticasone propionate (FP), a corticosteroid. It is indicated for symptomatic treatment of moderate-to-severe SAR and associated ocular symptoms in adults and adolescents aged 12 years and older for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient. The recommended dosage regimen is one spray per nostril twice daily (morning and evening). The total daily dose of azelastine and fluticasone in AZE/FP is 548 mcg and 200 mcg, respectively. AZE/FP was first authorized for use in Canada in 2014. Azelastine hydrochloride is a new active substance in Canada that is not available as monotherapy, while fluticasone propionate nasal spray has been approved for use in Canada since 1993, as Flonase.

The objective of this review was to evaluate the beneficial and harmful effects of AZE/FP for the treatment of adults and adolescents with SAR.

Results and Interpretation

Included Studies

Four studies — namely, MP4002 (N = 832), MP4004 (N = 779), MP4006 (N = 1,801), and MP4001 (N = 610) — were included in this review. They were all similar in general design: phase 3, randomized, double-blind, placebo-controlled, parallel-group, 14-day-long studies of patients with moderate-to-severe SAR. After a seven-day, single-blind, placebo lead-in period, patients were randomized in a 1:1:1:1 ratio to receive one spray per nostril twice daily (morning and evening) of AZE/FP, azelastine hydrochloride, fluticasone propionate, or placebo nasal spray. A total daily dose of 548 mcg azelastine and 200 mcg fluticasone was employed in all studies. In studies MP4002, MP4004, and MP4006, azelastine and fluticasone monotherapy was carried in the same vehicle as AZE/FP. In study MP4001, AZE/FP was compared with marketed azelastine (Astelin) and commercially available generic fluticasone propionate; these two monotherapies had different formulations than AZE/FP.

The objective of all included studies was to test the superiority of the combination of azelastine and fluticasone over each individual drug alone, for the improvement of symptoms of SAR. The primary end point was the change from baseline in combined (morning and evening) 12-hour reflective total nasal symptom scores (rTNSS) for the entire 14-day study period. Secondary end points included change from baseline in combined (morning and evening) 12-hour reflective total ocular symptom scores (rTOSS) for

the entire 14-day study period, and health-related quality of life assessed in patients aged at least 18 years, using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Other efficacy end points were instantaneous TNSS (iTNSS), onset of action, individual symptom scores for rTNSS and rTOSS, and daily scores for rTNSS and rTOSS.

In all studies, patients had a mean age of 40 years, a mean duration of SAR history of 20 years, a mean baseline total daily of rTNSS of approximately 19 (the maximum possible score is 24), and a mean total daily rTOSS of approximately 12 (the maximum possible score is 19). Approximately 10% of the populations were adolescents (12 to < 18 years old), and fewer than 5% were older than 65 years in each of the included studies. The overall score across studies for RQLQ at baseline was approximately 3.9 (the maximum possible score is 6). The minimal clinically important differences (MCIDs) for TNSS and TOSS have not been established. The MCID for the RQLQ is 0.5 points.

In general, the included studies were carried out with methodological rigour. Nevertheless, two limitations are worth noting. First, while statistical analyses were carried out for most efficacy end points in the included studies, adjustment for multiplicity using a gatekeeping strategy was employed for the primary end point (change in rTNSS) only in studies MP4002, MP4004, MP4006, and MP4001, and for the secondary end point (change in rTOSS) in studies MP4004 and MP4006. No adjustment for multiplicity was made for other efficacy, safety, and quality of life end points. Second, it is unclear whether any patients in the included studies had had an insufficient response to prior monotherapy with an antihistamine or an intranasal corticosteroid.

Efficacy

The results of studies MP4002, MP4004, and MP4006 indicated that treatment with AZE/FP for 14 days was associated with a statistically significant improvement in overall rTNSS relative to baseline compared with azelastine ($P < 0.05$) and fluticasone ($P < 0.05$) alone (Table 1). Analysis of relative treatment effects on each individual treatment day indicated that AZE/FP was consistently better than azelastine throughout the 14-day treatment period, whereas the relative benefit of AZE/FP over fluticasone appeared to be driven by greater improvement within the first few days of treatment. The onset of action for AZE/FP was 30 to 45 minutes compared with placebo, which was not statistically significantly faster than azelastine (MP4002, MP4004, and MP4006) or fluticasone (MP4002 and MP4004).

Across the four included studies, the relative benefit of AZE/FP over azelastine for rTNSS ranged from 0.71 to 2.06 points, and over fluticasone ranged from 0.64 to 1.47 points. The validated MCID for rTNSS has not been established definitively, and has been proposed to range from 0.5 to 7.2 points on the 24-point scale. According to the clinical expert consulted by the CADTH Common Drug Review (CDR), an MCID of 1 to 2 points would likely reflect clinically meaningful improvement in practice in Canada. Based on these estimates of the MCID for improvement in rTNSS scores, it is unlikely that the statistically significant improvement in rTNSS attributable to AZE/FP versus the fluticasone component is clinically meaningful, although the benefit over azelastine alone may be.

For overall rTOSS, the effects of AZE/FP were not statistically significantly different from those of azelastine in any study; nor was there a significant difference compared with fluticasone in two studies (MP4002 and MP4006) (Table 1). The mean differences between AZE/FP and fluticasone were 0.88 ($P = 0.009$) in study MP4004 and 1.16 ($P = 0.002$) in study MP4001. In study MP4004, in which AZE/FP was reported to be statistically significantly better than fluticasone for rTOSS, the validity of the claim of statistical significance is uncertain due to apparent violation of the statistical testing hierarchy. Similarly,

there is uncertainty as to the validity of the statistical significance in study MP4001, as no adjustments for multiple comparisons were done for any end points in this study, including rTOSS. In addition, because a validated MCID for rTOSS has not been established, it is unclear whether the differences among treatments observed for this outcome are clinically meaningful, although the clinical expert consulted by CDR reported that an MCID of 1 point on an rTOSS would likely reflect clinically meaningful improvement, suggesting significant improvement of the combination over the fluticasone component in the MP4001 study, but not in the MP4004 study.

In each of the included studies, AZE/FP demonstrated a statistically significant improvement in RQLQ total scores compared with azelastine, but not with fluticasone (Table 1). The difference in the overall RQLQ score between AZE/FP and placebo ranged from 0.56 to 0.79 points across studies, while the difference in the overall RQLQ score between AZE/FP and azelastine ranged from 0.17 to 0.43 points across studies. As the MCID for this outcome is 0.5 points, the difference between AZE/FP and azelastine in RQLQ scores was not clinically meaningful.

Collectively, the results of the included studies suggest that AZE/FP is superior to the individual antihistamine component, azelastine, but is not consistently superior to intranasal fluticasone alone.

Harms

There were no deaths in any of the included studies, and serious adverse events were rare (Table 1). Across the four included studies, treatment-related adverse events (TRAEs) were more frequent in the AZE/FP (10% to 14%) and azelastine (8% to 11%) treatment groups than in the fluticasone (6% to 9%) and placebo (4% to 9%) treatment groups. Most adverse events were mild in nature. The most common TRAEs reported for AZE/FP (pooled data from all included studies) were dysgeusia (5%), epistaxis (3%), and headache (2%). The adverse event profile for AZE/FP observed in a one-year safety study (study MP4000; see APPENDIX 8) was similar to that observed in the studies included in this review.

Other Considerations

A review of the literature by CDR revealed mixed evidence to suggest superior efficacy of AZE versus oral antihistamines and insufficient evidence to suggest any differences in efficacy and safety between AZE and other intranasal antihistamines.

The current review of AZE/FP efficacy and safety appears to meet the expectations of patients that treatment should provide specific benefits such as improved nasal breathing and sleep, were patients to use an antihistamine alone. However, while the combination of azelastine and fluticasone would likely provide superior symptom relief compared with antihistamines alone, the clinical evidence does not suggest that AZE/FP would provide better relief than an intranasal fluticasone alone.

Conclusions

The results of four studies (MP4002 [N = 832], MP4004 [N = 779], MP4006 [N = 1,801], and MP4001 [N = 610]) indicate that treatment of SAR patients for 14 days with AZE/FP provides superior relief of nasal (rTNSS) and ocular (rTOSS) symptoms, as well as quality of life (RQLQ), compared with placebo. Compared with azelastine, AZE/FP was associated with superior nasal symptom relief and improved quality of life, but did not provide superior ocular symptom relief in all studies. Compared with fluticasone, AZE/FP was associated with superior nasal symptom relief, but did not provide consistently greater relief from ocular symptoms or a greater improvement in quality of life. It is unclear whether any of the aforementioned differences between AZE/FP and the individual active components were clinically meaningful. The onset of action of AZE/FP (within 30 to 45 minutes of treatment) was faster than placebo, but was not significantly different compared with the onset of action of intranasal azelastine or

fluticasone alone. The safety profile for AZE/FP was similar across each of the four included studies. There were no deaths or serious adverse events in any of the studies, and most treatment-emergent adverse events and TRAEs were mild in nature. Collectively, these results suggest that the combination therapy with AZE/FP provides better nasal symptom relief than monotherapy with an inhaled antihistamine or corticosteroid, but that this difference may not be clinically important compared with fluticasone alone. The evidence with respect to the relative benefit on ocular symptoms and quality of life does not support the conclusion that combination therapy with AZE/FP is better than monotherapy with an inhaled antihistamine or corticosteroid.

TABLE 1: SUMMARY OF RESULTS

Study	Clinical Outcomes	AZE/FP	Azelastine	Fluticasone	Placebo
Change in rTNSS (ITT population)					
MP4002	N	207	208	207	209
	Δ (95% CI)[a]; *P* value	---	**–1.38 (–2.22 to –0.54); 0.001**	**–0.9 (–1.74 to –0.07); 0.034**	**–2.69 (–3.48 to –1.91); < 0.001**
MP4004	N	193	193	188	199
	Δ (95% CI)[a]; *P* value	---	**–1.00 (–1.90 to –0.09); 0.032**	**–0.99 (–1.91 to –0.05); 0.038**	**–2.51 (–3.33 to –1.67); < 0.001**
MP4006	N	448	445	450	448
	Δ (95% CI)[a]; *P* value	---	**–0.71 (–1.30 to –0.13); 0.016**	**–0.64 (–1.22 to –0.07); 0.029**	**–2.13 (–2.70 to –1.57); < 0.001**
MP4001	N	153	152	151	150
	Δ (95% CI)[a]; *P* value	---	**–2.06 (–2.98 to –1.14); < 0.001**	**–1.47 (–2.44 to –0.50); 0.003**	**–3.11 (–4.03 to –2.19); < 0.001**
Change in rTOSS (ITT population)					
MP4002	N	207	208	207	209
	Δ (95% CI)[a]; *P* value	---	–0.25 (–0.90 to 0.41); 0.457	–0.52 (–1.14 to 0.10); 0.097	**–1.17 (–1.77 to –0.57); < 0.001**
MP4004	N	193	192	188	199
	Δ (95% CI)[a]; *P* value	---	–0.60 (–1.25 to 0.05); 0.069	**–0.88 (–1.54 to –0.23); 0.009**	**–1.54 (–2.16 to –0.92); < 0.001**
MP4006	N	448	443	450	448
	Δ (95% CI)[a]; *P* value	---	–0.03 (–0.47 to 0.42); 0.912	–0.26 (–0.69 to 0.18); 0.247	**–1.07 (–1.50 to –0.64); < 0.001**
MP4001	N	153	152	151	150
	Δ (95% CI)[a]; *P* value	---	–0.71 (–1.49 to 0.06); 0.071	**–1.16 (–1.91 to –0.42); 0.002**	**–2.01 (–2.70 to –1.33); < 0.001**
Change in RQLQ (ITT population)					
MP4002	Δ LS mean; *P value*	---	**–0.28; 0.029**	–0.01; 0.907	**–0.79; < 0.001**
MP4004		---	**–0.28; 0.031**	–0.20; 0.123	**–0.71; < 0.001**
MP4006		---	**–0.17; 0.043**	–0.04; 0.629	**–0.56; < 0.001**
MP4001		---	**–0.43; 0.005**	–0.17; 0.286	**–0.59; < 0.001**

Study	Safety Outcomes	AZE/FP	Azelastine	Fluticasone	Placebo
Pooled data for studies MP4002, MP4004, and MP4006[b]					
	N	853	851	846	862
	Withdrawals				
	n (%)	38 (4.5)	38 (4.5)	35 (4.1)	36 (4.2)
	WDAEs				
	n (%)	10 (1.2)	6 (0.7)	4 (0.5)	9 (1.0)
	SAEs				
	n (%)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
	Notable harms				
	Dysgeusia, n (%)	30 (3.5)	44 (5.2)	4 (0.5)	2 (0.2)
	Epistaxis, n (%)	15 (1.8)	12 (1.4)	13 (1.5)	15 (1.7)
	Headache, n (%)	12 (1.4)	14 (1.6)	15 (1.8)	6 (0.7)
MP4001	N	153	153	153	151
	Withdrawals				
	n (%)	8 (5.2)	9 (5.9)	9 (5.9)	7 (4.6)
	WDAEs				
	n (%)	1 (0.7)	3 (2.0)	1 (0.7)	1 (0.7)
	SAEs				
	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Notable harms				
	Dysgeusia, n (%)	11 (7.2)	3 (2.0)	0 (0.0)	0 (0.0)
	Epistaxis, n (%)	6 (3.9)	3 (2.0)	6 (3.9)	5 (3.3)
	Headache, n (%)	3 (2.0)	1 (0.7)	5 (3.3)	1 (0.7)

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; Δ = treatment difference; ITT = intention-to-treat; LS = least-squares; NS = not statistically significant; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; rTNSS = reflective total nasal symptom score; rTOSS = reflective total ocular symptom score; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] CI for treatment differences is specified as AZE/FP treatment LS mean change (or % LS mean change) minus the indicated comparator LS mean change (or % LS mean change).

[b] Pooled data of MP4002, MP 4004, and MP4006: done by CADTH clinical reviewer.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

The prevalence of seasonal allergic rhinitis (SAR) is estimated to be between 20% and 25% in Canada. The seasonal allergic period is approximately two weeks, but patients may require pharmacologic intervention up to four weeks. Up to 40% of patients who visit physicians are diagnosed with SAR, and approximately 70% of SAR patients have moderate-to-severe symptoms.

Patients will present with both nasal (congestion, runniness, sneezing, and itchiness) and non-nasal (watery eyes, itchy eyes, and eye redness) symptoms. Depending on the particular geographic area in Canada, there is a great variation of seasonal allergens. Generally, tree pollens are produced during spring, grass pollens during early summer, and ragweed pollens during late summer and fall.

There is no risk of mortality associated with SAR, but the moderate-to-severe symptoms have a significant impact on patients' day-to-day quality of life. Patients experience a substantial impact from allergy symptoms on sleep, daily activities, and workplace productivity.

1.2 Standards of Therapy

First-line treatment for SAR is oral antihistamines. In Canada, the first-generation oral antihistamines include diphenhydramine, chlorpheniramine, and clemastine, and the second-generation antihistamines include desloratadine, loratadine, cetirizine, and fexofenadine. Second-generation antihistamines are preferred because they do not have the same sedative properties as the first-generation antihistamines.

Nasal corticosteroids are recommended as second-line options for patients with mild allergic rhinitis and first-line options for patients with moderate-to-severe symptoms. Corticosteroid nasal sprays available in Canada include fluticasone furoate, fluticasone propionate, beclomethasone, mometasone furoate, budesonide, triamcinolone acetonide, ciclesonide, and flunisolide.

A combination of oral antihistamines, corticosteroid nasal sprays, and prescription eye drops is commonly used.

Input from patient groups indicated that half of surveyed patients were satisfied, while the other half were somewhat or very unsatisfied with current treatment. They reported that the available treatment options have slow onset of action and do not address all nasal and ocular symptoms effectively. Side effects include nosebleed, nose congestion, drowsiness, headache, bitter taste, dry nose, throat irritation, asthma attacks, cough, fatigue, and mood changes.

A leukotriene receptor antagonist such as montelukast, which is available in Canada, is also effective in treating allergy rhinitis. However, it is recommended for use only when antihistamines or nasal corticosteroids are not effective or not tolerated.

Allergen immunotherapy is another method of treatment for allergic rhinitis.

1.3 Drug

AZE/FP is a fixed-dose combination nasal spray of 0.1% azelastine hydrochloride (AZE), an H_1 receptor antagonist, and 0.037% fluticasone propionate (FP), a corticosteroid. The recommended dosage regimen

is one spray per nostril twice daily (morning and evening), for a total daily dose of 548 mcg of azelastine hydrochloride and 200 mcg of fluticasone propionate.

AZE/FP is indicated for symptomatic treatment of moderate-to-severe SAR and associated ocular symptoms in adults and adolescents aged 12 years and older, for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient.

Azelastine hydrochloride is a new active substance in Canada. It is a potent long-acting, anti-allergic drug with selective H_1 antagonist, mast cell–stabilizing, and anti-inflammatory properties. Azelastine inhibits the synthesis and release of various chemical mediators involved in the early- and late-stage allergic reactions.

Fluticasone propionate nasal spray has been approved for use in Canada since 1993, as Flonase. It is a synthetic corticosteroid that has a high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action. The precise mechanism of the effect of fluticasone in allergic rhinitis symptoms is unknown.

Indication under review
Dymista (azelastine hydrochloride and fluticasone propionate) is indicated for the symptom treatment of moderate-to-severe seasonal allergic rhinitis (SAR) and associated ocular symptoms in adults and adolescents aged 12 years and older for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient.
Listing criteria requested by sponsor
As per indication.

Table 2 presents the key characteristics of AZE/FP and its two components, azelastine and fluticasone. However, azelastine represents a new active component in Canada.

TABLE 2: KEY CHARACTERISTICS OF AZE/FP, FLUTICASONE, AND OTHER COMPARATORS

	AZE/FP[3]	Fluticasone propionate (Flonase, ratio-fluticasone)[4,5]	Fluticasone furoate (Avamys)[6]	Mometasone furoate (APO-mometasone, Nasonex)[7,8]	Beclomethasone dipropionate (Mylan-Beclo AQ)[9]	Triamcinolone acetonide (Nasacort AQ)[10]	Budesonide (Mylan-Budesonide AQ, Rhinocort Aqua)[11,12]	Ciclesonide (Omnaris)[13]	Levocabastine (Livostin)[14]
Mechanism of Action	Antihistamine plus corticosteroid	Corticosteroid						Glucocorticoid	Histamine H_1-antagonist
Indication[a]	Symptomatic treatment of moderate-to-severe SAR and associated ocular symptoms in adults and adolescents aged ≥ 12 years for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient.	Treatment of SAR, including hay fever, and PAR poorly responsive to conventional treatment. In patients with allergic rhinitis, FP aqueous nasal spray is also indicated for the management of associated sinus pain and pressure.	Treatment of the symptoms of SAR and PAR in patients aged ≥ 2 years.	Treatment of the symptoms of SAR and PAR in adults, adolescents, and children (aged ≥ 3 years).	Treatment of PAR and SAR unresponsive to conventional treatment.	Adults and adolescents: Temporary relief of multiple symptoms of PAR and SAR, such as nasal congestion, runny nose, sneezing, and itchy nose. Children (aged 4 to 12 years): treatment of symptoms of PAR and SAR unresponsive to conventional treatment.	Treatment of seasonal allergic and allergic or non-allergic perennial and vasomotor rhinitis unresponsive to conventional therapy. Also indicated for the treatment of nasal polyps and the prevention of nasal polyps after polypectomy.	Treatment of SAR, including hay fever, and PAR in adults and adolescents aged ≥ 12 years.	Symptomatic treatment of allergic rhinitis (sneezing, itchy nose, or runny nose) in patients aged ≥ 12 years.
Route of Administration	Intranasal								
Recommended Dose	One spray in each nostril twice daily (morning and evening). Each spray contains 137 mcg AZE and	For patients aged ≥ 12 years: 2 sprays per nostril once a day (total	Adults and adolescents (aged ≥ 12 years): 2 sprays per nostril once	Adults and adolescents (aged ≥ 12 years): 2 sprays per nostril once a	Patients of all ages: 2 sprays (100 mcg) per nostril twice daily.	Adults and adolescents (aged ≥ 12 years): 2 sprays per nostril once a	Mylan-Budesonide: Adults and children (aged ≥ 6 years): two	Adults and adolescents (aged ≥ 12 years): 2 sprays per nostril once a	Adults and adolescents (aged ≥ 12 years): 2 sprays per nostril twice a

	AZE/FP[3]	Fluticasone propionate (Flonase, ratio-fluticasone)[4,5]	Fluticasone furoate (Avamys)[6]	Mometasone furoate (APO-mometasone, Nasonex)[7,8]	Beclomethasone dipropionate (Mylan-Beclo AQ)[9]	Triamcinolone acetonide (Nasacort AQ)[10]	Budesonide (Mylan-Budesonide AQ, Rhinocort Aqua)[11,12]	Ciclesonide (Omnaris)[13]	Levocabastine (Livostin)[14]
	50 mcg FP	daily dose: 200 mcg). Patients with severe rhinitis may benefit from 2 sprays in each nostril every 12 hours	a day (total daily dose: 110 mcg) Children (aged 2 to < 12 years old): 1 spray per nostril once a day (total daily dose: 55 mcg)	day (total daily dose: 200 mcg) Children (aged 3 to < 12 years): 1 spray per nostril once a day (total daily dose: 100 mcg)	Adults: max total daily dose: 600 mcg Children: max total daily dose: 400 mcg	day (total daily dose: 220 mcg) Children (aged 4 to < 12 years): 1 spray per nostril once a day (total daily dose: 110 mcg)	sprays per nostril once a day (total daily dose: 400 mcg) Rhinocort: Adults and children (aged ≥ 6 years): initial — 2 sprays per nostril once a day, or 1 spray per nostril twice a day (total daily dose: 256 mcg)	day (total daily dose: 200 mcg)	day (total daily dose: 200 mcg). Dose can be increased to 2 sprays 3 to 4 times daily
Serious Side Effects or Safety Issues	Potential systemic effects include cushingoid features, adrenal suppression, growth retardation in children and adolescents, reduction in bone density, cataract, and glaucoma. Eye symptoms include glaucoma and/or cataracts. May mask signs of infection and new infections may appear.								No major concerns

AZE = azelastine hydrochloride; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; FP = fluticasone propionate; PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis.

[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of the nasal spray (Dymista) containing a mixture of azelastine hydrochloride and fluticasone propionate for the treatment of SAR and associated ocular symptoms in adults and adolescents aged 12 years and older, for whom monotherapy with either antihistamines or intranasal corticosteroids is not considered sufficient.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult and adolescent patients aged 12 years and older with moderate-to-severe SAR[a] **Subgroups of interest:** • Age • Disease severity • Treatment history (naive versus experienced) • Duration of symptoms
Intervention	AZE/FP — Nasal spray suspension containing 0.1% azelastine hydrochloride (w/w) and 0.037% fluticasone propionate (w/w), administered 1 actuation per nostril twice daily
Comparators	• Antihistamines (oral or intranasal) • Intranasal corticosteroids • Others (decongestants, intranasal cromolyn, intranasal anticholinergics, leukotriene receptor antagonists, or combination therapy)
Outcomes	**Key efficacy outcomes:** • Allergy symptom severity/symptom relief (nasal and ocular symptoms) including onset of action of the treatments • Quality of life (e.g., RQLQ)[b] **Harms outcomes:** • AEs, SAEs, WDAEs, deaths • Notable harms or harms of special interest: dysgeusia, headache, somnolence, dry mouth, epistaxis, other nasal symptoms, eye symptoms.
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; RCT = randomized controlled trial; rTNSS = reflective total nasal symptom score; RCT = randomized controlled trial; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SAE = serious adverse event; SAR = seasonal allergic rhinitis; WDAE = withdrawal due to adverse events.

[a] 12-hour reflective rTNSS (a.m. or p.m.) of at least 8/12 with a congestion score of 2 or 3.

[b] The RQLQ is a 28-item in 7 domains, disease-specific quality of life instrument that measures activities, emotions, sleep, non-nasal symptoms, practical problems, and nasal symptoms. Domains were measured on a 7-point Likert scale, where 0 = no impairment and 6 = maximum impairment.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH

(Medical Subject Headings), and keywords. The main search concepts were AZE/FP and azelastine hydrochloride and fluticasone propionate.

Methodological filters were not applied to limit the retrieval to study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on January 29, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on May 20, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of 57 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

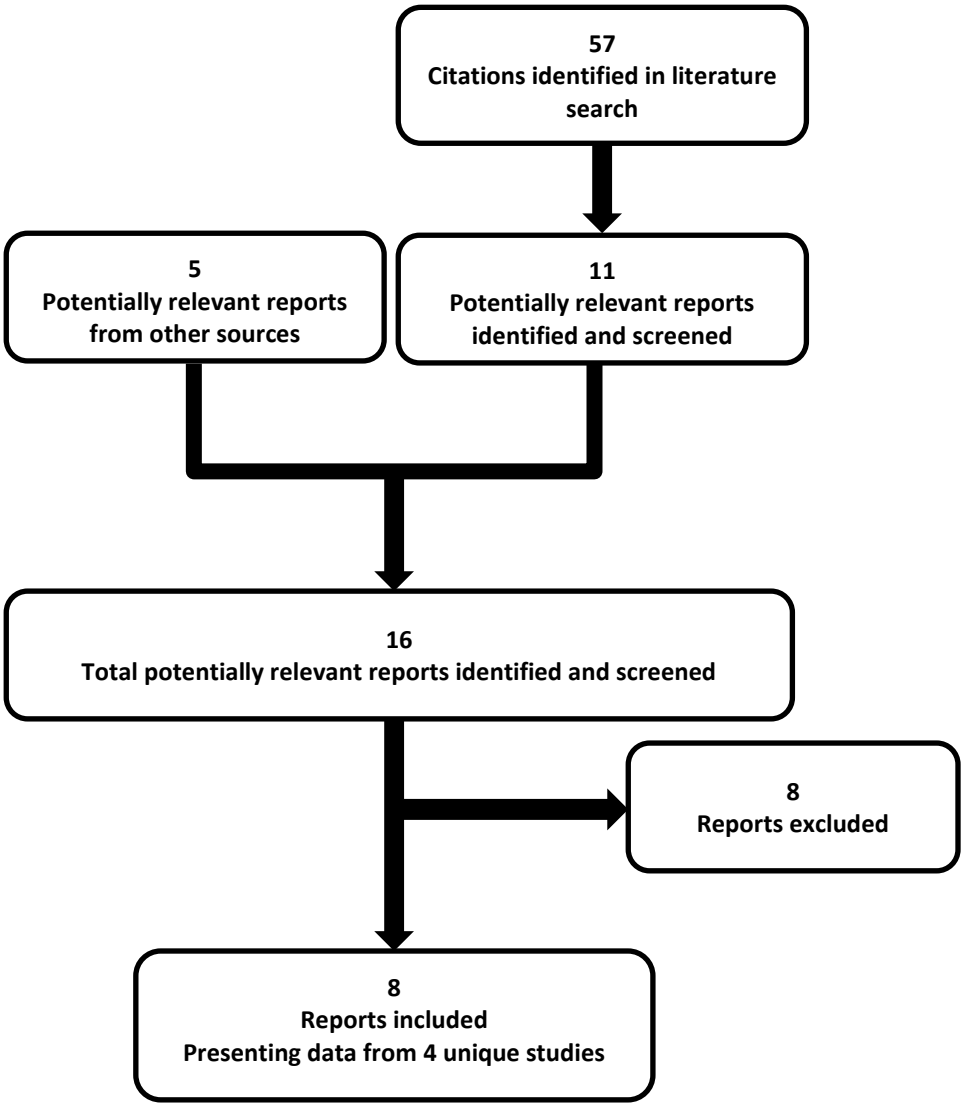


TABLE 4: DETAILS OF INCLUDED STUDIES

		Study MP4002[15]	Study MP4004[16]	Study MP4006[17]	Study MP4001[18]
DESIGNS & POPULATIONS	**Study Design**	Phase 3, DB RCT, parallel-group			
	Locations	US			
	Number of Sites	44	41	49	6
	Randomized (N)	832	779	1,801	607
	Inclusion Criteria	• Aged ≥ 12 years with a minimum 2-year history of moderate-to-severe SAR and a positive skin test to a local spring pollen during the previous year. • 12-hour rTNSS (a.m. or p.m.) ≥ 8/12, and 12-hour reflective nasal congestion score of 2 or 3 on 3 separate symptom assessments.	Similar to those in study MP4002, with the exception of testing positive for local fall pollen.	• Aged ≥ 12 years with a minimum 2-year history of moderate-to-severe SAR and a positive skin test to a prevailing individual seasonal pollen during the previous year. • Participants in early trials (i.e., MP4001, MP4002, or MP4004) were permitted to participate in this trial (17.7%). • Screening visit: had 12-hour reflective TNSS ≥ 8/12 and congestion score of 2 or 3. • Randomization visit: For the 3 days prior to randomization and on morning of randomization, the sum of the 7 consecutive reflective a.m. and p.m. TNSS assessments were ≥ 56, with nasal congestion score ≥ 14. • Randomization visit: Had an instantaneous TNSS ≥ 8 and a congestion score ≥ 2 at time point 0, just prior to beginning the onset of action assessment.	Similar to those in study MP4002 and MP4004, with the exception of testing positive for Texas mountain cedar pollen.
	Exclusion Criteria	• Nasal mucosal erosion, ulceration, or septal perforation (Grade 1b-4), or other nasal diseases • Asthma • Pulmonary or cardiac disease			

		Study MP4002[15]	Study MP4004[16]	Study MP4006[17]	Study MP4001[18]
		• Glaucoma • Pregnant or nursing women • Use of allergy and asthma medications (previous 5 to 15 days), oral corticosteroids (previous 30 days), tricyclic antidepressants (30 days), monoamine oxidase inhibitors (14 days), immunosuppressives or modulators (30 days), and immunoglobulin E antagonist (130 days) • Patients participate in MP4001.			
DRUGS	**Intervention**	AZE/FP — nasal spray containing 0.1% (w/w) AZE and 0.037% (w/w) FP • One spray per nostril, twice daily (a.m. and p.m.) Total daily dose of 548 mcg AZE and 200 mcg FP			
	Comparator(s)	• Azelastine nasal spray[a] (one spray per nostril, twice daily, total 548 mcg) • Fluticasone nasal spray[a] (one spray per nostril, twice daily, total 200 mcg) • Placebo nasal spray[a] (one spray per nostril, twice daily)			Marketed azelastine nasal spray 0.1% (Astelin)[b] Marketed fluticasone nasal spray 0.037% (Flonase)[b] Placebo nasal spray[a]
DURATION	**Phase**				
	Run-in	7 days			
	Double-blind	14 days			
	Follow-up	None			
OUTCOMES	**Primary End Point**	Change from baseline in 12-hour reflective TNSS			
	Other End Points	• Change from baseline in 12-hour reflective individual TNSS (including postnasal drip) • Change from baseline in the 12-hour reflective and instantaneous TNSS for the 14-day study period • Onset of action — change from baseline in instantaneous TNSS over the 4-hour period following initial administration of study drugs • Change from baseline in 12-hour reflective and individual TOSS • Change from baseline in the RQLQ, including overall score and 7 individual domains, in patients aged ≥ 18 years			Same as for studies MP4002, MP4004, and MP4006, except that the onset of action was not assessed in this study
NOTES	**Publications**	Carr et al. 2012[19]	Carr et al. 2012[19] Meltzer et al. 2012[20]	Carr et al. 2012[19]	Meltzer et al. 2013[21]

a.m. = morning; AZE = azelastine hydrochloride; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; DB = double-blind; FP = fluticasone propionate; p.m. = evening; RCT = randomized controlled trial; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; rTNSS = reflective total nasal symptom scores; SAR = seasonal allergic rhinitis; TNSS = total nasal symptom scores; TOSS = total ocular symptom scores.

[a] Same formulation as AZE/FP.

[b] Different formulation from AZE/FP.

Additional references: CADTH Common Drug Review submission,[22] FDA medical and statistical reviews,[23,24] Health Canada reviewer's report.[2]

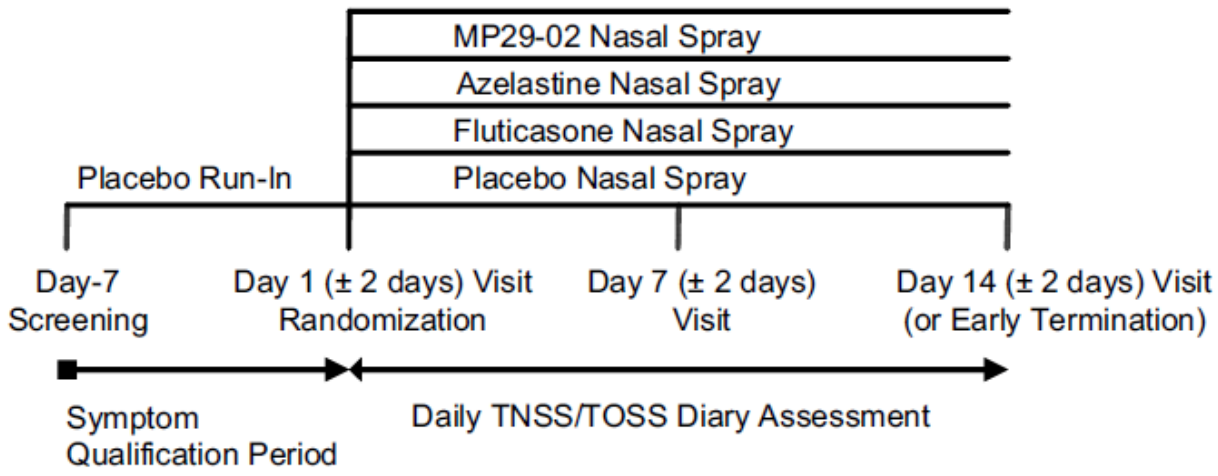
3.2 Included Studies

3.2.1 Description of Studies

Four studies — MP4002, MP4004, MP4006, and MP4001 — were similar in general design (Figure 2). The studies evaluated the safety and efficacy of AZE/FP (fixed dose combination of azelastine hydrochloride and fluticasone propionate) versus its monotherapy components and placebo. All were phase 3, randomized, double-blind, placebo controlled, parallel group, 14-day studies in patients with SAR. The studies began with a seven-day, single-blind, placebo lead-in period, one spray per nostril twice daily, in the morning and evening. On day 1, patients who met all of the study inclusion or exclusion criteria were randomized in a 1:1:1:1 ratio to receive one spray per nostril twice daily of AZE/FP, azelastine hydrochloride, fluticasone propionate, or placebo nasal spray. Randomization was stratified based on age, gender, race, and ethnicity. The use of concomitant medication was discouraged, unless those medications would not interfere with the study medications. The design of the study is shown in Figure 2.

Of note, in MP4001, AZE/FP was compared with marketed azelastine (Astelin) and commercially available generic fluticasone propionate; both were formulated with a different vehicle than AZE/FP (Table 4). Therefore, Health Canada and the US Food and Drug Administration (FDA) considered MP4001 to be a non-pivotal trial, the results of which were viewed as a secondary support for efficacy and safety.

FIGURE 2: STUDY DESIGN OF MP4002, MP4004, MP4006, AND MP4001



TNSS = total nasal symptom scores; TOSS = total ocular symptom scores.
Source: Clinical Study Report of MP4002, MP4004, MP4006, MP4001, p. 25.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The inclusion and exclusion criteria of MP4002, MP4004, MP4006, and MP4001 are listed in Table 4. Patients (aged 12 years and older) had at least a two-year history of moderate-to-severe SAR, assessed by positive skin test, and had a baseline 12-hour rTNSS (morning [a.m.] or evening [p.m.]) of at least 8 over a maximum score of 12, and a baseline 12-hour reflective nasal congestion score of 2 or 3 over a maximum score of 9. Baseline rTOSS was not a criterion employed in the included studies.
The inclusion criteria of MP4006 were slightly stricter than those of the other studies (i.e., for the three days prior to randomization and on the morning of randomization, the sum of the seven consecutive

reflective a.m. and p.m. TNSS assessments was ≥ 56, with nasal congestion score ≥ 14). In MP4006, a total of 318 (17.7%) of patients who had participated in a previous trial (MP4001, MP4002, or MP4004) were allowed to enrol.[2] It was therefore unclear to what extent the presence of those patients might affect the efficacy and safety results, although effort was made to ensure that sites had no more than 50% of patients who had participated in previous studies.

Patients who had nose and eye diseases, pregnant or nursing women, and those who had used corticosteroids, antidepressants, monoamine oxidase inhibitors, immunosuppressives or immunomodulators, and immunoglobulin E antagonists for a specific time period (ranging from five days to six months) prior to screening were excluded.

b) Baseline Characteristics

Table 5 presents the summary of baseline characteristics of the study MP4001 and the pooled results of studies MP4002, MP4004, and MP4006. The baseline characteristics of each individual study — MP4002, MP4004, and MP4006 — are presented in Table 11, Table 12, and Table 13, respectively. Baseline characteristics were generally well balanced between groups in all studies. Patients were predominantly female (61% to 68%) and Caucasian (78% to 89%), with a mean age of 40 years and a mean duration of SAR history of 20 years. All the studies included approximately 10% of adolescents and fewer than 5% of elderly patients. Mean total daily rTNSS was approximately 19 over a maximum score of 24, and mean total daily rTOSS was approximately 12 over a maximum score of 19. Common concomitant medications included ibuprofen, multivitamins, paracetamol, salbutamol, and acetylsalicylic acid. None of these concomitant medications are indicated for treatment of rhinitis and would be expected to affect study results. Quality of life was assessed in patients aged 18 years or older using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Overall score at baseline was approximately 3.9 over a maximum score of 6.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Category	Pooled ITT Population of Studies MP4002, MP4004, and MP4006				Study MP4001			
	AZE/FP (N = 848)	Azelastine (N = 847)	Fluticasone (N = 846)	Placebo (N = 857)	AZE/FP (N = 153)	Azelastine (N = 152)	Fluticasone (N = 151)	Placebo (N = 151)
Age (years) — mean (SD)	37 (14)	37 (15)	36 (14)	36 (14)	40 (14)	40 (14)	38 (14)	40 (15)
Age — n (%)								
12 to < 18	88 (10)	78 (9)	85 (10)	99 (12)	9 (6)	11 (7)	10 (7)	13 (9)
18 to < 65	741 (87)	740 (87)	747 (88)	733 (86)	136 (89)	132 (87)	137 (91)	131 (87)
≥ 65	19 (2)	29 (3)	14 (2)	25 (3)	8 (5)	9 (6)	4 (3)	7 (5)
Sex — n (%)								
Male	303 (36)	318 (38)	318 (38)	337 (39)	56 (37)	55 (36)	51 (34)	49 (33)
Female	545 (64)	529 (63)	528 (62)	520 (61)	97 (63)	97 (64)	100 (66)	102 (68)
Race — n (%)								
Caucasian	680 (80)	672 (79)	657 (78)	681 (80)	132 (86)	135 (89)	130 (86)	131 (87)
Black	134 (16)	134 (16)	149 (18)	132 (15)	15 (10)	15 (10)	16 (11)	17 (11)
Asian	18 (2)	17 (2)	16 (2)	19 (2)	4 (3)	0 (0)	3 (3)	2 (1)
Others	16 (2)	24 (3)	24 (3)	25 (3)	2 (1.3)	2 (1.3)	2 (1.4)	1 (0.7)
Total daily rTNSS — mean (SD)	18.8 (2.9)	19.0 (2.8)	19.0 (3.0)	18.9 (2.8)	18.8 (3.1)	18.1 (3.7)	18.3 (3.5)	18.7 (3.5)
Total daily rTOSS — mean (SD)	11.9 (3.9)	11.5 (4.5)	11.4 (4.4)	12.1 (4.3)	12.3 (4.0)	11.8 (4.2)	11.8 (4.3)	12.2 (4.3)
Duration of SAR (years) — mean (SD)	21 (13)	20.1 (13)	20 (13)	20.3 (13)	19 (12)	19 (13)	18 (12)	18 (12)
Concomitant medications — n (%)								
Ibuprofen	188 (22)	168 (20)	173 (20)	175 (20)	24 (16)	30 (20)	33 (22)	28 (19)
Multivitamins	116 (14)	130 (15)	138 (16)	133 (16)	22 (14)	19 (13)	18 (12)	19 (13)
Paracetamol	88 (10)	100 (12)	116 (14)	97 (11)	15 (10)	12 (8)	23 (15)	22 (15)
Salbutamol	66 (8)	81 (10)	60 (7)	73 (9)	10 (7)	9 (6)	10 (7)	4 (3)
Acetylsalicylic acid	33 (4)	38 (4)	40 (5)	31 (4)	10 (7)	12 (8)	8 (5)	6 (4)

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; rTNSS = reflective total nasal symptom score; rTOSS = reflective total ocular symptom score; SAR = seasonal allergic rhinitis; SD = standard deviation.

Source: Pooled data of MP4002, MP4004, and MP4006: Table 7, p. 39 of the US Food and Drug Administration Clinical Review.[23] MP4002: Table 14 (p. 46), Table 14.3.6 (p. 339) of the Clinical Study Report (CSR); MP4004: Table 14 (p. 46), Table 14.3.6 of CSR; MP4006: Table 13 (p. 46), Table 14.3.6 (p. 440) of CSR; MP4001: Table 12 (p. 44), Table 14.3.6 of CSR.

3.2.3 Interventions

AZE/FP, a nasal spray suspension containing 0.1% azelastine hydrochloride (w/w) and 0.037% fluticasone propionate (w/w), was approved for use in Canada in October 2014. Each spray contains 138 mcg azelastine hydrochloride and 50 mcg fluticasone propionate. The recommended dose of AZE/FP for patients aged 12 years and older is one spray in each nostril twice daily (morning and evening) for a total daily dose of 548 mcg azelastine hydrochloride and 200 mcg fluticasone propionate; this dosage was employed in all included trials.

Azelastine hydrochloride nasal spray has not been approved by Health Canada. In the included studies, azelastine was given as one spray per nostril, twice daily, for a total of 548 mcg.

Fluticasone propionate nasal spray has been authorized for use in Canada as Flonase since 1993. In the included studies, fluticasone was given as one spray per nostril, twice daily, for a total of 200 mcg.

The comparators azelastine, fluticasone, and placebo in studies MP4002, MP4004, and MP4006 had a similar formulation (vehicle) to AZE/FP.

In MP4001, the marketed azelastine (Astelin) and commercially available generic fluticasone propionate had different formulations from AZE/FP.

Prohibited concomitant medications included antihistamines, corticosteroids, decongestants, tricyclic antidepressants, monoamine oxidase inhibitors, leukotriene modifiers, immunosuppressives or immunomodulators, radiation therapy, immunoglobulin E inhibitor, initiation of immunotherapy, and any other drug that is used as a treatment of allergic rhinitis.

3.2.4 Outcomes

a) Efficacy Outcomes

All four included trials had similar primary efficacy end points and secondary end points.

Primary End Point:

- Change from baseline in 12-hour rTNSS for the entire 14-day study period.

Secondary End Points:

- Change from baseline in instantaneous TNSS (iTNSS) for the entire 14-day treatment period
- Daily scores — daily change from baseline in 12-hour rTNSS and iTNSS
- Change from baseline in the 12-hour reflective individual symptom scores (including postnasal drip) for the entire 14-day study period
- Onset of action (change from baseline in iTNSS over four-hour period following initial administration of trial drug) — for studies MP4002, MP4004, and MP4006
- Change from baseline in 12-hour reflective TOSS (rTOSS) and instantaneous TOSS (iTOSS), including individual ocular symptom scores, for the entire 14-day study period
- Change from baseline to day 14 in the RQLQ in patients aged 18 years and older.

Reflective symptom scores are used to evaluate symptom severity after a predefined period such as 12 hours (overall degree of effectiveness over a prespecified time interval).

Instantaneous symptom scores are used to evaluate symptom severity immediately before the next dose (effectiveness at the end-of-dosing interval). The measurement should be made at the morning evaluation.

This review of efficacy evaluated data for rTNSS, iTNSS, daily scores, individual symptom scores of TNSS (including postnasal drip), onset of action, rTOSS, and RQLQ.

The scoring systems for TNSS, TOSS, and RQLQ are presented below.

TNSS

TNSS symptoms (running nose, sneezing, itchy nose, and nasal congestion), as well as the symptom of postnasal drip, were graded twice daily and recorded in patients' diaries on the following 0- to 3-point scales:

0 = None — no symptoms present
1 = Mild — mild symptoms that are noticeable and do not interfere with any activity
2 = Moderate — symptoms that are slightly bothersome and slightly interfere with activity *or* nighttime sleep
3 = Severe — symptoms that are bothersome and interfere with activity *or* nighttime sleep.

The minimum and maximum possible scores are 0 and 12, respectively. The validated minimal clinically important difference (MCID) for TNSS has not been established.

Total Ocular Symptom Scores

TOSS symptoms (itchy eyes, watery eyes, and eye redness) were graded twice daily and recorded in patients' dairies on the following 0- to 3-point scales:

Severity scale for evaluation of itchy eyes and watery eyes:
0 = None — no symptoms present
1 = Mild — mild symptoms that are noticeable and do not interfere with any activity
2 = Moderate — symptoms that are slightly bothersome and slightly interfere with activity *or* nighttime sleep
3 = Severe — symptoms that are bothersome and interfere with activity *or* nighttime sleep.

Severity scale for evaluating eye redness:
0 = None — no redness present
1 = Mild — slightly dilated blood vessels and pinkish colour compared with patient's normal colour
2 = Moderate — more dilation of blood vessels and red colour compared with patient's normal colour
3 = Severe — large, numerous dilated blood vessels and deep red colour compared with patient's normal colour.

The minimum and maximum possible scores are 0 and 9, respectively. The validated MCID for TOSS has not been established.

Rhinoconjunctivitis Quality of Life Questionnaire

The RQLQ tool measures the subjective impact of SAR on patients' health-related quality of life. It consists of 28 items in seven domains (Activities [three items], Sleep [three], Non-nose/Eye Symptoms [seven], Practical Problems [three], Nasal Symptoms [four], Eye Symptoms [four], and Emotional [four]) that are rated on a 7-point scale in which 0 = not troubled by the allergy symptoms during the past week, and 6 = extremely troubled. The overall RQLQ score is the mean of all 28 responses, and the individual domain scores are the means of the questions in each domain — both range from 0 to 6. The RQLQ has been validated in adult patients with seasonal and perennial rhinoconjunctivitis.[25] The MCID is well established as 0.5 for the overall or individual domain scores.[26]

The RQLQ was completed by patients aged 18 years and older in the included studies.

c) Harm Outcomes

Safety outcomes including death, serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), nasal examination, eye examination, and special interest harm outcomes (dysgeusia, headache, somnolence, dry mouth) were assessed in this review.

TEAE was defined as any adverse event with an onset date on or after the first dose of study drug.

TRAE was defined as any adverse event that was considered by an investigator to be possibly or probably related to the study drug.

3.2.5 Statistical Analysis

Efficacy analyses were performed on the intention-to-treat (ITT) population, defined as all randomized patients with at least one post-baseline observation. A repeated-measures analysis was performed on the primary efficacy variable to include all absolute changes relative to baseline in combined (a.m. + p.m.) rTNSS on each day from day 2 to day 14 as repeated measures in an analysis for covariance (ANCOVA) model for the ITT population. The model contained study day as the within-subject effect, treatment group and site as the between-subject effect, and baseline as covariate. At day 1, only the post-dose p.m. score was available.

Baseline was defined as the average of all combined rTNSS scores over the entire seven-day placebo lead-in period, including the a.m. day 1 scores (pre-dosing).

Missing TNSS values were imputed using the last observation carried forward (LOCF) method. The same approach was employed for secondary analyses.

Analyses of secondary end points were also performed on the ITT population and employed the LOCF method. Scores over the 14-day period were compared using the ANCOVA model. The analyses were done for both the combined (a.m. + p.m.) and for the a.m. and p.m. scores separately.

To adjust for multiplicity, a gatekeeping strategy was employed for the primary end point rTNSS in studies MP4002, MP4004, MP4006, and MP4001, and for the secondary end point rTOSS in studies MP4004 and MP4006. No adjustment for multiplicity was done for other efficacy, safety, and quality of life end points.

In the gatekeeping strategy, the comparison between AZE/FP and placebo for rTNSS was first tested at the 0.05 significance level. If this was significant, then the AZE/FP and azelastine comparison was also done at the 0.05 level. If the AZE/FP and azelastine comparison was not significant at the 0.05 level, no comparison of AZE/FP and fluticasone was made; otherwise, comparison was made at the 0.05 level. When all these three test comparisons were shown to be significantly different in favour of AZE/FP, rTOSS was assessed in the same order as for TNSS.

Preliminary analyses of a proof-of-concept study[27] showed that the combination of azelastine (two sprays per nostril twice daily) with fluticasone propionate (two sprays per nostril once daily) resulted in a reduction of 14-day overall TNSS of –7.4 units. The sample sizes in the included studies were calculated using a 20% reduction value of –5.92 units, along with a two-tailed test with an alpha value of 0.05 and 90% power, and allowing for a 10% dropout rate.

a) Analysis Populations

For all included studies, the efficacy end points were analyzed in the ITT population, defined as all randomized patients with at least one post-baseline observation. The safety end points were analyzed in the randomized population. Actual numbers of each analysis population are presented in Table 6.

3.3 Patient Disposition

Patient disposition is summarized in Table 6. Pooled data of studies MP4002, MP4004, and MP4006 were obtained from the FDA clinical review[23] and are presented here, as the individual studies were similar in demographics, baseline characteristics, and patient disposition. Data from the individual studies MP4002, MP4004, and MP4006 are presented in Table 14, Table 15, and Table 16, respectively. The proportions of patients who discontinued from the studies were similar in all treatment groups: 4% to 5% from pooled data of studies MP4002, MP4004, and MP4006, and 5% to 6% in study MP4001.

TABLE 6: PATIENT DISPOSITION

Disposition Summary	Pooled ITT Population of Studies MP4002, MP4004, and MP4006				Study MP4001			
	AZE/FP	Azelastine	Fluticasone	Placebo	AZE/FP	Azelastine	Fluticasone	Placebo
Randomized, N	853	851	846	862	153	153	153	151
Completed Study, N (%)	815 (95.5)	813 (95.5)	811 (95.9)	826 (95.8)	145 (94.8)	144 (94.1)	144 (94.1)	144 (95.4)
Discontinued, N (%)	38 (4.5)	38 (4.5)	35 (4.1)	36 (4.2)	8 (5.2)	9 (5.9)	9 (5.9)	7 (4.6)
Adverse Events	10 (1.2)	6 (0.7)	4 (0.5)	9 (1.0)	1 (0.7)	3 (2.0)	1 (0.7)	1 (0.7)
Treatment Failure	1 (0.1)	1 (0.1)	2 (0.2)	5 (0.6)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
Protocol Violation	8 (0.9)	14 (1.6)	6 (0.7)	8 (0.9)	---	---	---	---
Non-compliance	1 (0.1)	4 (0.5)	10 (1.2)	4 (0.5)	3 (2.0)	2 (1.3)	3 (2.0)	1 (0.7)
Patient Withdrew Consent	3 (0.4)	3 (0.4)	3 (0.4)	2 (0.2)	1 (0.7)	1 (0.7)	2 (1.3)	2 (1.3)
Lost to Follow-up	6 (0.7)	3 (0.4)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
ITT, N (%)	848 (99.4)	847 (99.5)	846 (100.0)	857 (99.4)	153 (100.0)	152 (99.3)	151 (98.7)	151 (100.0)
Safety, N (%)	853 (100.0)	851 (100.0)	846 (100.0)	861 (99.9)	153 (100.0)	152 (99.3)	153 (100.0)	151 (100.0)
≥ 80% Compliance Overall, N (%)[a]	839 (98.9)	837 (98.9)	838 (97.0)	850 (99.2)	152 (99.3)	152 (100.0)	149 (97.4)	148 (98.0)

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to treat.
[a] Compliance = (total number of doses)/(duration of exposure x 2) from diary entries for each patient.
Source: Pooled data of MP4002, MP4004, and MP4006: Table 8 (p. 41) of the US Food and Drug Administration Clinical Review;[23] MP4001: Table 10 (p. 41) of Clinical Study Report (CSR). Compliance: Table 15 (p. 48) of CSR of MP4002; Table 15 (p. 48) of CSR of MP4004; Table 14 (p. 48) of CSR of MP4006; Table 13 (p. 46) of CSR of MP4001.

3.4 Exposure to Study Treatments

Patients recorded the number of sprays (doses) twice daily in their diary. Unused medication was returned on days 1, 7, and 14 to the study staff. The amount of medication returned and patient diary were reviewed to determine treatment compliance. Treatment adherence was ≥ 97% for all treatment groups.

The mean duration of exposure (≥ 14 days) and the mean total number of doses taken (≥ 27) were comparable among groups in all studies.

3.5 Critical Appraisal

3.5.1 Internal Validity

a) MP4002, MP4004, and MP4006

The study design was consistent with recommendations provided in the Health Canada guidance document[28] and the FDA guidance document[29] for clinical development of drug products for allergic rhinitis. The studies followed the recommendations in trial design, inclusion and exclusion criteria, blinding, formulations and dosage regimens, evaluation, and data analyses. Randomization method, allocation concealment, and blinding were appropriate. Patients went through a placebo lead-in period of seven days prior to being randomized and receiving study medication. This period appears to be sufficient to wash out any effect of the previous therapy of antihistamines or nasal corticosteroids.

The monotherapy components and placebo were formulated in the same vehicle as AZE/FP; all were administered intranasally. As such, these studies were considered to be pivotal by Health Canada and the FDA.

The studies were powered, and study sample sizes were determined using the results of a previous proof-of-concept study,[27] in which the combination of azelastine (two sprays per nostril twice daily) and fluticasone (two sprays per nostril once daily) resulted in a reduction of 7.4 units of the overall 14-day TNSS.

The validated MCIDs for TNSS and TOSS have not been established. It is therefore unclear whether the effect sizes for the treatment difference between AZE/FP and individual component are clinically significant. The MCID for RQLQ is 0.5 points.

Efficacy analyses for primary and secondary end points were performed on the modified ITT population of all randomized patients with at least one post-baseline observation. The randomized and modified ITT populations were almost identical. Adjustment for multiplicity using a gatekeeping strategy was employed for the primary end point rTNSS in studies MP4002, MP4004, MP4006, and MP4001, and for the secondary end point rTOSS in studies MP4004 and MP4006. No adjustment for multiplicity was done for other efficacy, safety, and quality of life end points. Therefore, the results in those cases were likely to be exploratory.

Missing values were imputed using the LOCF method. In this approach, patients who dropped out due to adverse events might have good scores carried forward despite unsuccessful treatment. A repeated-measures analysis was performed on the primary and secondary efficacy variables. The FDA statistical review noted that "the application of LOCF method together with repeated-measures analysis is problematic."[24] In the LOCF approach, patients who dropped out due to adverse events would have good scores carried forward despite unsuccessful treatment. Both the FDA and the manufacturer performed the analyses based on the imputed and non-imputed approaches, and the results of both

approaches were similar.[24] This was due to small dropout rates. Indeed, patient compliance was high (≥ 97%) and dropout rates were low (≤ 5%).

b) MP4001

All were similar to studies MP4002, MP4004, and MP4006, except that AZE/FP was compared with marketed azelastine hydrochloride (Astelin) and generic fluticasone propionate, which were formulated with different vehicles than AZE/FP.

3.5.2 External Validity

Patients from each of the included studies were recruited from multiple centres in the USA. Patients were aged 12 years or older with SAR from local spring pollen (MP4002), local fall pollen (MP4004), seasonal pollen (MP4006), and Texas mountain cedar pollen (MP4001). Although none of the studies were conducted in Canada, the study population may represent the North American population, including Canada. The clinical expert consulted by CDR felt that the patient population in the included studies was generalizable to the Canadian population.

All studies included small numbers of adolescents (10%) and geriatrics (4%). The clinical efficacy and safety in those populations were therefore not well established. However, treatment efficacy would not be expected to differ by age or gender.

The included patients had moderate-to-severe SAR, characterized by positive skin test and a baseline 12-hour rTNSS (morning [a.m.] or evening [p.m.]) of at least 8 over maximum score of 12, and a baseline 12-hour reflective nasal congestion score of 2 or 3 over maximum score of 9. Supportive statistical analysis provided by the manufacturer indicates that about 40% and 19% of patient in three pivotal studies (MP4002, MP4004, and MP4006) had inadequate response to antihistamines and intranasal corticosteroids, respectively. Treatment differences between AZE/FP and the individual components in those patient populations were statistically significant.

The outcome measures were appropriate and reflected both efficacy and harms. They were consistent with recommendations provided in the Health Canada guidance document[28] and the FDA guidance document[29] for clinical development of drug products for allergic rhinitis.

All studies had a study duration of 14 days, which is approximately the duration of seasonal allergy. However, patients may suffer from seasonal allergy for a longer period of time.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in section 2.2, Table 3). The results of key efficacy outcomes are presented in Table 7, Table 8, and Table 9.

3.6.1 Reflective Total Nasal Symptom Scores (rTNSS) — Overall Change

The results of combined rTNSS (a.m. + p.m.) over the 14-day treatment are presented in Table 7. The validated MCID for TNSS has not been established.

a) Studies MP4002, MP4004, and MP4006

AZE/FP showed a statistically significant difference in rTNSS compared with azelastine, fluticasone, and placebo. The treatment effects expressed by actual unit scores between AZE/FP and azelastine ranged from 0.7 to 1.4 points with baseline score of 18 points (maximum 24 points). The benefit of AZE/FP over fluticasone ranged from 0.6 to 1.0 points. The benefit of AZE/FP over placebo ranged from 2.1 to 2.7

points. When expressed as a percentage difference, the benefit of AZE/FP over azelastine ranged from 4% to 8%, the benefit of AZE/FP over fluticasone ranged from 3% to 6%, and the benefit of AZE/FP over placebo ranged from 11% to 15%.

b) Studies MP4001

Similar results were obtained in Study MP4001, except that the treatment effects were larger than those in studies MP4002, MP4004, and MP4006. AZE/FP was statistically significant better than azelastine by 2 points (12%), better than fluticasone by 1.5 points (8%), and better than placebo by 3 points (17%).

TABLE 7: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE TNSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION)

Study	Parameters	AZE/FP	Azelastine	Fluticasone	Placebo
MP4002	n	207	208	207	209
	LS mean baseline (SD)[a]	18.27 (3.04)	18.26 (3.54)	18.22 (3.23)	18.61 (3.18)
	LS mean (SD) change from baseline[b]	–5.61 (5.24)	–4.23 (4.63)	–4.71 (4.68)	–2.92 (3.92)
	Δ (95% CI)[c]; *P* value	---	–1.38 (–2.22 to –0.54); **0.001**	–0.9 (–1.74 to –0.07); **0.034**	–2.69 (–3.48 to –1.91); **< 0.001**
	LS mean (SD) % change from baseline[b]	–31.01 (28.21)	–22.87 (28.22)	–25.72 (25.50)	–15.61 (22.04)
	% Δ (95% CI)[c]; *P* value	---	–8.14 (–13.00 to –3.28); **0.001**	–5.29 (–10.03 to –0.57); **0.028**	–15.40 (–19.78 to –11.03); **< 0.001**
MP4004	n	193	193	188	199
	LS mean baseline (SD)[a]	18.28 (3.34)	18.54 (3.15)	18.64 (2.92)	18.24 (3.07)
	LS mean (SD) change from baseline[b]	–5.54 (5.18)	–4.54 (4.62)	–4.55 (5.15)	–3.03 (3.93)
	Δ (95% CI)[c]; *P* value	---	–1.00 (–1.90 to –0.09); **0.032**	–0.99 (–1.91 to –0.05); **0.038**	–2.51 (–3.33 to –1.67); **< 0.001**
	LS mean (SD) % change from baseline[b]	–30.71 (28.32)	–25.13 (25.08)	–24.92 (27.24)	–16.75 (22.35)
	% Δ (95% CI)[c]; *P* value	---	–5.58 (–10.55 to –0.60); **0.028**	–5.79 (–10.84 to –0.74); **0.025**	–13.96 (–18.59 to –9.32); **< 0.001**
MP4006	n	448	445	450	448
	LS mean baseline (SD)[a]	19.34 (2.43)	19.47 (2.52)	19.41 (2.38)	19.44 (2.36)
	LS mean (SD) change from baseline[b]	–5.53 (5.18)	–4.82 (4.76)	–4.89 (4.66)	–3.40 (4.34)
	Δ (95% CI)[c]; *P* value	---	–0.71 (–1.30 to –0.13); **0.016**	–0.64 (–1.22 to – 0.07); **0.029**	–2.13 (–2.70 to –1.57); **< 0.001**
	LS mean (SD) % change from baseline[b]	–28.16 (26.63)	–24.43 (24.16)	–24.92 (23.75)	–17.08 (22.03)
	% Δ (95% CI)[c]; *P* value	---	–3.73 (–6.81 to	–3.24 (–6.28 to	–11.08 (–14.06 to

Study	Parameters	AZE/FP	Azelastine	Fluticasone	Placebo
			–0.64); **0.018**	–0.19); **0.037**	–8.09); **< 0.001**
MP4001	n	153	152	151	150
	LS mean baseline (SD)[a]	18.64 (3.11)	17.87 (3.66)	18.12 (3.47)	18.49 (3.45)
	LS mean (SD) change from baseline[b]	–5.31 (5.08)	–3.25 (4.16)	–3.84 (4.76)	–2.20 (4.16)
	Δ (95% CI)[c]; *P* value	---	–2.06 (–2.98 to –1.14); **< 0.001**	–1.47 (–2.44 to –0.50); **0.003**	–3.11 (–4.03 to –2.19); **< 0.001**
	LS mean (SD) % change from baseline[b]	–28.35 (26.90)	–16.37 (24.06)	–20.42 (27.04)	–11.17 (25.27)
	% Δ (95% CI)[c]; *P* value	--	–11.98 (–17.13 to –6.82); **< 0.001**	–7.93 (–13.36 to –2.48); **0.004**	–17.18 (–22.41 to –11.94); **< 0.001**

a.m. = morning; ANOVA = analysis of variance; ANCOVA = analysis of covariance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; Δ = treatment difference; ITT = intention-to-treat; LS = least square; p.m. = afternoon; rTNSS = reflective total nasal symptom score; SD = standard deviation; TNSS = total nasal symptom score.

[a] Baseline includes rTNSS scores over a 7-day lead-in period, including day 1 a.m. LS mean was obtained from an ANOVA model for baseline containing treatment group and site as fixed effects.

[b] Obtained from a repeated-measures ANCOVA model for overall absolute change containing study day (2 through 14) as the within-subject effect, treatment group and site as the between-subject effects, and baseline as a covariate.

[c] CI for treatment differences is specified as AZE/FP treatment LS mean change (or % LS mean change) minus the indicated comparator LS mean change (or % LS mean change).

Source: MP4002: Table 16 (p. 49) of Clinical Study Report (CSR); MP4004: Table 16 (p. 49) of CSR; MP4006: Table 15 (p. 49) of CSR; MP4001: Table 14 (p. 48) of CSR.

3.6.2 Reflective Total Ocular Symptom Scores — Overall Change

The results of combined rTOSS (a.m. + p.m.) over the 14-day treatment are presented in Table 8. The validated MCID for TOSS has not been established.

a) Studies MP4002, MP4004, and MP4006

AZE/FP demonstrated a statistically significant difference in rTOSS compared with placebo in all three studies, and demonstrated a statistically significant difference to fluticasone in MP4004 only, but it failed to show a statistically significant difference to azelastine in all three studies. However, the significance of the difference of AZE/FP over fluticasone (*P* = 0.009) in study MP4004 is uncertain due to violation of the hierarchical statistical testing plan. The treatment effects between AZE/FP and placebo ranged from 1.0 to 1.5 points, with a baseline score of 12 (maximum of 18 points).

b) Study MP4001

In this study, AZE/FP showed a statistically significant difference compared with placebo (by 2 points) and fluticasone (by 1.2 points), but not to azelastine. Again, the significance of the difference of AZE/FP over fluticasone (*P* = 0.002) is uncertain due to the lack of hierarchical statistical testing in this study.

TABLE 8: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE TOSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION)

Study	Parameters	AZE/FP	Azelastine	Fluticasone	Placebo
MP4002	N	207	208	207	209
	LS mean baseline (SD)[a]	11.88 (3.90)	11.49 (4.54)	11.41 (4.42)	12.07 (4.28)
	LS mean (SD) change from baseline[b]	–3.07 (3.99)	–2.82 (3.82)	–2.55 (3.45)	–1.90 (3.26)
	Δ (95% CI)[c]; *P* value	---	–0.25 (–0.90 to 0.41); 0.457	–0.52 (–1.14 to 0.10); 0.097	–1.17 (–1.77 to –0.57); **< 0.001**
	LS mean (SD) % change from baseline[b]	–25.30 (35.32)	–23.47 (127.81)	–20.27 (41.20)	–15.55 (40.42)
	% Δ (95% CI)[c]; *P* value	---	–1.83 (–9.06 to 5.39); 0.618	–5.03 (–11.56 to 1.50); 0.131	–9.75 (–15.70 to –3.80); **0.001**
MP4004	N	193	192	188	199
	LS mean baseline (SD)[a]	11.70 (4.16)	11.78 (3.89)	12.01 (3.80)	11.56 (4.14)
	LS mean (SD) change from baseline[b]	–3.56 (3.86)	–2.96 (3.31)	–2.68 (3.57)	–2.02 (3.06)
	Δ (95% CI)[c]; *P* value	---	–0.60 (–1.25 to 0.05); 0.069	-0.88 (–1.54 to –0.23); **0.009**[d]	–1.54 (–2.16 to –0.92); **< 0.001**
	LS mean (SD) % change from baseline[b]	–30.12 (38.79)	–26.34 (31.80)	–21.55 (45.11)	–17.81 (30.71)
	% Δ (95% CI)[c]; *P* value	---	–3.78 (–10.03 to 2.47); 0.235	-8.57 (–14.95 to –2.19); **0.009**[d]	–12.31 (–18.54 to –6.08); **< 0.001**
MP4006	N	448	443	450	448
	LS mean baseline (SD)[a]	12.29 (4.01)	12.40 (3.99)	12.29 (3.62)	12.22 (3.72)
	LS mean (SD) change from baseline[b]	–3.02 (3.97)	–2.99 (3.81)	–2.76 (3.52)	–1.95 (3.49)
	Δ (95% CI)[c]; *P* value	---	–0.03 (–0.47 to 0.42); 0.912	–0.26 (–0.69 to 0.18); 0.247	–1.07 (–1.50 to –0.64); **< 0.001**
	LS mean (SD) % change from baseline[b]	–23.62 (42.00)	–22.90 (102.10)	–22.45 (33.49)	–13.96 (35.51)
	% Δ (95% CI)[c]; *P* value	---	–0.72 (–5.12 to 3.67); 0.746	–1.17 (–5.56 to 3.22); 0.600	–9.66 (–14.10 to –5.22); **< 0.001**
MP4001	N	153	152	151	150
	LS mean baseline (SD)[a]	12.06 (4.03)	11.55 (4.21)	11.50 (4.27)	11.92 (4.35)
	LS mean (SD) change from baseline[b]	–3.33 (4.06)	–2.62 (3.75)	–2.17 (3.71)	–1.32 (2.89)
	Δ (95% CI)[c]; *P* value	---	–0.71 (–1.49 to 0.06); 0.071	–1.16 (–1.91 to –0.42); **0.002**[e]	–2.01 (–2.70 to –1.33); **< 0.001**

Study	Parameters	AZE/FP	Azelastine	Fluticasone	Placebo
	LS mean (SD) % change from baseline[b]	–26.63 (39.34)	–21.21 (35.84)	–17.53 (39.27)	–10.53 (33.81)
	% Δ (95% CI)[c]; *P* value	---	–-5.42 (–12.42 to 1.57); 0.128	–9.10 (–16.39 to –1.81); **0.015**[e]	–16.10 (–22.86 to –9.33); **< 0.001**

ANCOVA = covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; Δ = treatment difference; ITT = intention-to-treat; LS = least-squares; rTOSS = reflective total ocular symptom score; SD = standard deviation; TOSS = total ocular symptom score.
[a] Baseline includes rTOSS scores over 7-day lead-in period, including day 1 a.m. LS mean was obtained from an ANOVA model for baseline containing treatment group and site as fixed effects.
[b] Obtained from a repeated-measures ANCOVA model for overall absolute change containing study day (2 through 14) as the within-subject effect, treatment group and site as the between-subject effects, and baseline as a covariate.
[c] The CI for treatment differences is specified as AZE/FP treatment LS mean change (or % LS mean change) minus the indicated comparator LS mean change (or % LS mean change).
[d] The significance is uncertain due to violation of the hierarchical statistical testing plan.
[e] The significance is uncertain because no adjustments for multiple comparisons were conducted.
Source: MP4002: Table 21 (p. 56) of Clinical Study Report (CSR); MP4004: Table 21 (p. 56) of CSR; MP4006: Table 20 (p. 56) of CSR; MP4001: Table 18 (p. 55) of CSR.

3.6.3 Rhinoconjunctivitis Quality of Life Questionnaire

The results of the RQLQ for studies MP4002, MP4004, MP4006, and MP4001 are presented in Table 9. Detailed data with baseline overall scores and change from baseline values of each treatment group are shown in Table 17 of APPENDIX 4. The MCID for RQLQ is 0.5 points.

In each of the included studies, AZE/FP demonstrated a statistically significant improvement of RQLQ total scores after 14-day treatment compared with azelastine and placebo, but not to fluticasone in patients aged 18 years and older. Treatment difference in the overall RQLQ score between AZE/FP and placebo ranged from 0.56 to 0.79 points, which met the MCID of 0.5 points. However, treatment difference between AZE/FP and azelastine, ranging from 0.17 to 0.43 points, did not meet the MCID.

Results of the RQLQ individual domains are in Table 18 of APPENDIX 4.

- **MP4002:** The benefit of AZE/FP over azelastine was found in three out of seven domains (Sleep, Practical Problems, and Nasal Symptoms).
- **MP4004:** The benefit of AZE/FP over azelastine was found in three out of seven domains (Sleep, Non-nose/Eye Symptoms, and Nasal Symptoms).
- **MP4006:** The benefit of AZE/FP over azelastine was found in three out of seven domains (Activity, Practical Problems, and Nasal Symptoms).
- **MP4001:** The benefit of AZE/FP over azelastine was found in five out of seven domains (Sleep, Non-nose/Eye Symptoms, Practical Problems, Nasal Symptoms, and Emotional).

TABLE 9: RQLQ IN PATIENTS AGED ≥ 18 YEARS (ITT POPULATION) — CHANGE FROM BASELINE IN OVERALL SCORE

Study	AZE/FP vs. Azelastine Δ LS Mean; *P* Value (Day 14)[a]	AZE/FP vs. Fluticasone Δ LS Mean; *P* Value (Day 14)[a]	AZE/FP vs. Placebo Δ LS Mean; *P* Value (Day 14)[a]
MP4002	–0.28; **0.029**	–0.01; 0.907	–0.79; **< 0.001**
MP4004	–0.28; **0.031**	–0.20; 0.123	–0.71; **< 0.001**
MP4006	–0.17; **0.043**	–0.04; 0.629	–0.56; **< 0.001**
MP4001	–0.43; **0.005**	–0.17; 0.286	–0.59; **< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; Δ = treatment difference; ITT = intention-to-treat; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.

[a] *P* value for between-treatment group comparison, except baseline, was based on ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate. For baseline, the *P* value was based on an ANOVA model containing treatment group and site as fixed effects.

Source: MP4002: Table 25 (p. 60) of Clinical Study Report (CSR); MP4004: Table 25 (p. 60) of CSR; MP4006: Table 24 (p. 60) of CSR; MP4001: Table 20 (p. 57) of CSR.

3.6.4 Other Efficacy Outcomes

a) Reflective Individual Nasal Symptom Scores

The nasal symptoms under investigation were itchy nose, nasal congestion, runny nose, and sneezing. The results in change from baseline in 12-hour reflective individual nasal symptoms scores over the 14-day treatment period are shown in Table 19,

Table 20, Table 21, and Table 22 of APPENDIX 4 for studies MP4002, MP4004, MP4006, and MP4001, respectively.

- **MP4002:** AZE/FP was statistically significantly better than azelastine for all nasal symptoms. When compared with fluticasone, AZE/FP was statistically significantly better for runny nose only.
- **MP4004:** AZE/FP was statistically significantly better than azelastine for nasal congestion only. When compared with fluticasone, AZE/FP was statistically significantly better for sneezing only.
- **MP4006:** AZE/FP was statistically significantly better than azelastine for three out of four nasal symptoms (nasal congestion, runny nose, and sneezing). When compared with fluticasone, AZE/FP was statistically significantly better for sneezing only.
- **MP4001:** AZE/FP was statistically significantly better than azelastine for all nasal symptoms. When compared with fluticasone, AZE/FP was statistically significantly better for three out of four nasal symptoms (itchy nose, nasal congestion, and sneezing).

b) Reflective Postnasal Drip Score

The results of postnasal drip scores are presented in Table 23 of APPENDIX 4.

AZE/FP demonstrated a statistically significantly greater reduction in reflective postnasal drip score compared with azelastine in studies MP4002, MP4006, and MP4001, but not in MP4004. Compared with fluticasone, AZE/FP was statistically significantly better in study MP4006 only.

c) Reflective Total Nasal Symptom Scores — Change by Day

The results of change from baseline in rTNSS in each day over the 14-day treatment period are presented in Table 24, Table 25, Table 26, and Table 27 of APPENDIX 4: DETAILED OUTCOME DATA for studies MP4002, MP4004, MP4006, and MP4001, respectively.

MP4002: Compared with azelastine, AZE/FP demonstrated a statistically significant improvement in overall rTNSS score and in all daily scores from day 2 to day 14. However, AZE/FP was statistically significantly better than fluticasone for the overall score and for scores of day 2 and day 3 only, while it failed to show a significant difference from day 4 to day 14.

MP4004: Compared with azelastine, AZE/FP demonstrated a statistically significant improvement in overall rTNSS score and in daily scores starting from day 4, but not at day 2 and day 3. However, AZE/FP failed to show a significant difference compared with fluticasone for any day, from day 2 to day 14. Although the change in the overall score between AZE/FP and fluticasone was statistically significant (*P* = 0.038), all daily scores were not.

MP4006: Compared with azelastine, AZE/FP demonstrated a statistically significant improvement in overall rTNSS score and in daily scores starting from day 4, but not at day 2 and day 3. However, AZE/FP was statistically significantly better than fluticasone for the overall score and for scores of day 2 and day 5 only, while it failed to show a significant difference for all the other days.

MP4001: Compared with azelastine, AZE/FP demonstrated a statistically significant improvement in overall rTNSS score and in all daily scores from day 2 to day 14. In addition, AZE/FP was statistically significantly better than fluticasone for the overall score and for all daily scores, except for day 10 and day 11.

d) Instantaneous Total Nasal Symptom Scores — Overall Change

The results of change from baseline in iTNSS over the 14-day treatment period are presented in Table 28, Table 29, Table 30, and Table 31 of APPENDIX 4 for studies MP4002, MP4004, MP4006, and MP4001, respectively.

MP4002: Compared with azelastine, AZE/FP demonstrated a statistically significant improvement in overall iTNSS score and in all daily scores from day 2 to day 14. However, AZE/FP did not show any significant benefit compared with fluticasone for overall score or any daily score.

MP4004: Compared with azelastine, AZE/FP demonstrated a statistically significant improvement in overall iTNSS score and in all daily scores, except on day 2 and day 3. AZE/FP was statistically significantly better than fluticasone for the overall score (*P* = 0.049), which resulted from a significant difference on day 2 only (*P* = 0.020), but not for the rest of the daily scores from day 3 to day 14.

MP4006: Compared with azelastine, AZE/FP demonstrated a statistically significant improvement in overall iTNSS score and in daily scores from day 5 to day 14, but not from day 2 to day 4. Similar to study MP4002, AZE/FP did not show any significant benefit compared with fluticasone for overall score or any daily score.

MP4001: Compared with azelastine, AZE/FP demonstrated a statistically significant improvement in overall iTNSS score and in all daily scores from day 2 to day 14. In this study, AZE/FP was statistically significantly better than fluticasone in overall iTNSS score and in many daily scores.

e) Onset of Action

Onset of action was assessed by measuring iTNSS during the four-hour period following the initial dose of study medication. The results are presented in Table 32, Table 33, and Table 34 of APPENDIX 4 for studies MP4002, MP4004, and MP4006, respectively. Onset of action was not reported in study MP4001.

In studies MP4002 and MP4004, there was no statistically significant difference between AZE/FP and azelastine ($P > 0.05$) or between AZE/FP and fluticasone ($P > 0.05$) in all time points from 15 to 240 minutes.

In study MP4006, AZE/FP also had no statistically significant advantage over azelastine ($P > 0.05$). AZE/FP was statistically significantly better than fluticasone with respect to time to onset of action after 30 minutes ($P < 0.05$).

f) Reflective Individual Ocular Symptom Scores

Individual ocular symptoms included itchy eyes, watery eyes, and eye redness. The results are presented in Table 35, Table 36, Table 37, and Table 38 of APPENDIX 4 for studies MP4002, MP4004, MP4006, and MP4001.

MP4002: AZE/FP was not statistically significantly different compared with azelastine for all three ocular symptoms ($P > 0.05$). If the gatekeeping strategy was applied, AZE/FP should not have been compared with fluticasone if the AZE/FP–azelastine comparison was not significant at the 0.05 level. However, the study reported that AZE/FP was superior to fluticasone for the symptom of itchy eye ($P = 0.031$).

MP4004: AZE/FP was statistically significantly different compared with azelastine for the symptom of watery eyes only ($P = 0.026$) and was statistically significantly different compared with fluticasone for symptoms of itchy eyes ($P = 0.004$) and watery eyes ($P = 0.002$). Again, it appears that the gatekeeping strategy was not applied (i.e., for the symptom of itchy eyes).

MP4006: There was no statistically significant difference between AZE/FP and azelastine ($P > 0.05$), or between AZE/FP and fluticasone ($P > 0.05$) for any individual ocular symptoms.

MP4001: AZE/FP was statistically significantly different compared with azelastine for the symptoms of itchy eyes ($P = 0.013$) and eye redness ($P = 0.037$), and was statistically significantly different compared with fluticasone for all three ocular symptoms ($P < 0.05$).

g) Subgroup Analyses

No subgroup analyses were conducted in any of the included studies.

The Health Canada[2] and FDA[23] clinical reviews reported the subgroup analyses based on age, gender, race, and ethnicity from pooled data across four studies (MP4002, MP4004, MP4006, and MP4001) for rTNSS. This review focus on the results of subgroup analyses for age only (Table 39).

The proportion of adolescents and patients older than 65 years was 10% and 3%, respectively, of the combined total number of the four studies. In the adolescents, AZE/FP was superior to placebo and azelastine, but the difference did not reach statistical significance against fluticasone (mean difference [MD] –0.98; 95% CI, –2.08 to 0.13). In patients older than 65 years, the difference did not reach statistical significance against azelastine (MD –2.54; 95% CI, –5.19 to 0.12).

3.7 Harms

Only those harms identified in the review protocol are reported below (see section 2.2: Methods). See Table 40 of APPENDIX 4 for detailed safety data from the individual studies. Table 10 presents the safety data of study MP4001 and pooled data from studies MP4002, MP4004, and MP4006.

3.7.1 Adverse Events

TEAEs and TRAEs from three pivotal studies were slightly higher in AZE/FP (16% and 10%, respectively) and azelastine (15% and 11%, respectively) groups compared with fluticasone (13% and 6%, respectively) and placebo (12% and 4%, respectively) groups. The majority (69%) of TRAEs were mild in nature. A mild adverse event was defined as meaning that the sign and symptom was easily tolerated, caused minimal discomfort, or was of no clinical consequence.

3.7.2 Serious Adverse Events

SAEs were rare and there were no notable differences between groups in each of the included studies. In study MP4004, only one SAE in the AZE/FP group was identified; the patient was diagnosed with hepatitis C three weeks after the end of the study. In study MP4006, two SAEs were identified: one in the AZE/FP group and one in the placebo group. In the AZE/FP group, the patient sustained a lacerated right hand seven days after initiating treatment. In the placebo group, the patient had pyogenic arthritis of the right elbow one day after treatment and had surgery for septic olecranon bursitis. It is unlikely that those SAEs were treatment related. There were no SAEs in study MP4002 or MP4001.

3.7.3 Withdrawals Due to Adverse Events

The proportions of patients who withdrew due to adverse events were low (approximately 1%), and were comparable between treatment groups. The reasons for discontinuation varied among patients. The adverse events that the investigator considered to be related to AZE/FP treatment included chronic cough, mucosal erosion, nausea, and epistaxis. Those related to azelastine treatment included headache, postnasal drip, abdominal discomfort, dysgeusia, mucosal excoriation, nasal mucosal disorder, and acute sinusitis. Those related to fluticasone included mucosal erosion. Those related to placebo included septal ulceration, mucosal erosion, and severe nausea.

3.7.4 Mortality

There were no deaths in any of the included studies.

3.7.5 Notable Harms

In each of the included studies, dysgeusia was one of the most common TRAEs in AZE/FP (2.1% to 7.2%) and in azelastine (2.0% to 7.2%). Epistaxis (1.0% to 4.0%) and headache (0.5% to 3.3%) were similar in all three active treatment groups. There were no differences between groups for somnolence, mucosal erosion, and infections.

TABLE 10: HARMS (SAFETY POPULATION)

Pooled Data of Studies MP4002, MP4004, and MP4006				
	AZE/FP (N = 853)	Azelastine (N = 851)	Fluticasone (N = 846)	Placebo (N = 861)
Treatment-emergent AEs, n (%)	136 (15.9)	124 (14.6)	111 (13.1)	99 (11.5)
Treatment-related AEs, n (%)	87 (10.2)	90 (10.6)	52 (6.1)	35 (4.1)
Dysgeusia	30 (3.5)	44 (5.2)	4 (0.5)	2 (0.2)
Epistaxis	15 (1.8)	12 (1.4)	13 (1.5)	15 (1.7)
Headache	12 (1.4)	14 (1.6)	15 (1.8)	6 (0.7)
Somnolence	5 (0.6)	3 (0.4)	1 (0.1)	1 (0.1)
Mucosal erosion	5 (0.6)	0 (0.0)	6 (0.7)	1 (0.1)
Infections	5 (0.6)	1 (0.1)	1 (0.1)	1 (0.1)
Serious AEs, n (%)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)

Pooled Data of Studies MP4002, MP4004, and MP4006				
	AZE/FP (N = 853)	**Azelastine (N = 851)**	**Fluticasone (N = 846)**	**Placebo (N = 861)**
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation, n (%)	10 (1.2)	6 (0.7)	4 (0.5)	9 (1.0)
TRAEs by maximum severity, n (%)				
Mild	60 (7.0)	58 (6.8)	42 (5.0)	29 (3.4)
Moderate	24 (2.8)	27 (3.2)	10 (1.2)	5 (0.6)
Severe	3 (0.4)	5 (0.6)	0 (0.0)	1 (0.1)
Study MP4001				
	AZE/FP (N = 153)	**Azelastine (N = 152)**	**Fluticasone (N = 153)**	**Placebo (N = 151)**
TEAEs, n (%)	29 (19.0)	23 (15.1)	22 (14.4)	18 (11.9)
TRAEs, n (%)	21 (13.7)	12 (7.9)	14 (9.2)	14 (9.3)
Dysgeusia	11 (7.2)	3 (2.0)	0 (0.0)	0 (0.0)
Epistaxis	6 (3.9)	3 (2.0)	6 (3.9)	5 (3.3)
Headache	3 (2.0)	1 (0.7)	5 (3.3)	1 (0.7)
Somnolence	1 (0.7)	1 (0.7)	1 (0.7)	0 (0.0)
Mucosal erosion	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
Infections	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Serious AEs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation, n (%)	1 (0.7)	2 (1.3)	1 (0.7)	1 (0.7)
TRAEs by maximum severity, n (%)				
Mild	16 (10.5)	9 (5.9)	9 (5.9)	11 (7.3)
Moderate	4 (2.6)	3 (2.0)	4 (2.6)	2 (1.3)
Severe	1 (0.7)	0 (0.0)	1 (0.7)	1 (0.7)

AE = adverse event; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event.
Source: Pooled data of MP4002, MP 4004, and MP4006: done by CADTH clinical reviewer. MP4001: Table 22 (p. 63), Table 24 (p. 65), and Table 14.3.1.7 of Clinical Study Report.

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was derived from four phase 3 (MP4002, MP4004, MP4006, and MP4001), randomized, double-blind, placebo-controlled, parallel-group, 14-day-long studies of patients with moderate-to-severe SAR. The objective of each study was to test the superiority of AZE/FP for reducing the symptoms of SAR, measured using the combined daily rTNSS score, compared with placebo and the individual components, azelastine hydrochloride (an antihistamine) and fluticasone propionate (a corticosteroid). A total of 4,022 adults and adolescents aged 12 years and older were randomized in a 1:1:1:1 ratio to receive one spray per nostril twice daily of AZE/FP, azelastine hydrochloride, fluticasone propionate, or placebo nasal spray. Although all studies were conducted in the US, the clinical expert consulted by CDR felt that the overall study population was representative of the Canadian allergic rhinitis population, with the exception of the underrepresentation of adolescents.

4.2 Interpretation of Results

4.2.1 Efficacy

The study design and the outcome measures for efficacy and harms were consistent with recommendations provided by Health Canada[28] and the FDA[29] for clinical development of drug products for allergic rhinitis.

In three pivotal studies (MP4002, MP4004, and MP4006), each monotherapy component was formulated in the same vehicle as AZE/FP, while in study MP4001, AZE/FP was compared with Astelin (the form of azelastine marketed in the US) and commercially available generic fluticasone propionate, each of which were formulated in a different vehicle than AZE/FP. It is unclear how the different vehicles used would have affected the relative effects of AZE/FP compared with the other drugs; nevertheless, it is worth noting that the treatment effect of AZE/FP was relatively greater in study MP4001, in which different vehicles were used, than in the three pivotal studies, in which an identical vehicle was used for all drugs. As the different vehicles used in study MP4001 reflect the commercial availability of the individual components, particularly fluticasone, in Canada, the results of this study likely better reflect the real-world relative efficacy of AZE/FP than the results of the pivotal trials.

AZE/FP treatment was associated with a statistically significant improvement in overall rTNSS relative to baseline compared with the individual components, azelastine and fluticasone. For overall rTOSS, there was no significant difference between AZE/FP and azelastine in any of the included studies. Similarly, there was no significant difference between AZE/FP and fluticasone for rTOSS in studies MP4002 and MP4006, although the significant improvement for AZE/FP in study MP4004 is uncertain, due to a failure in the hierarchical statistical analysis plan, which increased the risk of a type I error for this metric. The clinical expert consulted by CDR felt that the resolution of nasal symptoms, as reflected by the rTNSS, is more important than the ocular symptoms captured by the rTOSS. This is in line with the recommendation by Health Canada and the FDA[28,29] that rTNSS be used as the primary efficacy end point in clinical studies of allergic rhinitis.

For rTNSS in the three pivotal studies, the relative benefit of AZE/FP over azelastine ranged from 0.71 to 1.38 points (4% to 8%), and over fluticasone ranged from 0.64 to 0.99 points (3% to 6%). In study MP4001, rTNSS scores in AZE/FP-treated patients were greater than the scores of patients treated with azelastine by 2.06 points (12%) and fluticasone by 1.47 points (8%). The MCID for rTNSS has not been established definitively, although it is thought to lie between 0.5 and 7.2 points on the 24-point rTNSS

scale (see Table 41 and APPENDIX 5). The clinical expert consulted by CDR stated that an MCID of 1 to 2 points for the rTNSS reflects a clinically meaningful improvement in nasal symptoms in clinical practice in Canada. With an MCID of at least 1 point, the relative effects for AZE/FP on rTNSS compared with azelastine reached clinically meaningful improvement in two out of three pivotal trials (MP4002 and MP4004), but not in study MP4006. There was a lack of clinically meaningful improvement of AZE/FP over fluticasone in all three pivotal trials, as the relative effects were less than 1 point. By contrast, AZE/FP did appear to meet the threshold for clinically meaningful improvement over azelastine and fluticasone alone in study MP4001. Therefore, the results of the included studies provide some evidence to suggest that AZE/FP treatment can produce a clinically meaningful improvement in nasal symptoms compared with treatment with an intranasal antihistamine alone, and suggest that AZE/FP treatment does not produce a clinically meaningful improvement in nasal symptoms compared with fluticasone alone.

Patient input received by CDR indicated than one feature of a medication for SAR would be a rapid onset of action. The onset of action for AZE/FP was not statistically significantly different compared with either azelastine (in all three pivotal studies) or fluticasone (in studies MP4002 and MP4004). CDR found evidence in the literature that intranasal azelastine has a faster onset of action compared with oral antihistamines, but does not have a more rapid onset of action compared with the intranasal antihistamine, levocabastine. Therefore, there does not appear to be any clear evidence that AZE/FP would produce more rapid relief from SAR symptoms compared with administration of the individual components.

In each of the included studies, AZE/FP significantly improved RQLQ compared with azelastine, but not with fluticasone in patients aged 18 years and older. The benefit of AZE/FP over azelastine was found in three to five domains (of a total of seven domains), including Sleep. According to the clinical expert consulted by CDR, sleep is an important component to patients and sleeplessness is one of the most frequent complaints. Indeed, patient input received by CDR described a substantial impact of allergy symptoms on sleep, as well as on daily activities and workplace productivity. Therefore, the apparent improvement in sleep attributable to AZE/FP versus azelastine would appear to meet the needs of patients who are being treated with an antihistamine alone, but there is a lack of evidence to show the benefit related to sleep for AZE/FP in patients being treated with fluticasone alone. An important limitation with the apparent improvement in sleep for AZE/FP compared with azelastine is the fact that the difference between these treatments of 0.17 to 0.43 RQLQ points, while statistically significant, failed to exceed the MCID of 0.5 points. Therefore, any apparent effects between AZE/FP and azelastine with respect to RQLQ, including sleep, would likely not be clinically meaningful.

No subgroup analyses were conducted in any of the included studies. Nevertheless, the Health Canada review included a meta-analyses of rTNSS based on age subgroups using pooled data from all of the included studies.[2] This analysis showed that AZE/FP did not reach statistically significant difference compared with fluticasone (MD –0.98; 95% CI, –2.08 to 0.13; *P* = 0.0819) in patients between 12 and 17 years of age, and compared with azelastine (MD –2.54; 95% CI, –5.19 to 0.12; *P* = 0.0604) in patients older than 65 years.[2] However, treatment efficacy of AZE/FP would not be expected to differ by age or gender, but the effectiveness could be influenced by lower compliance with a nasal corticosteroid alone in children, according to the clinical expert consulted by CDR.

4.2.2 Harms

There were no notable concerns with respect to the safety profile of AZE/FP, which was comparable to individual components, which suggests that the combined use of the individual components may not be associated with an increase in harms. Only 12% of patients treated with AZE/FP reported any TRAEs, which were mostly mild-to-moderate in nature. There were no deaths, and SAEs were rare. The most common TRAEs reported for AZE/FP were dysgeusia (5%), epistaxis (3%), and headache (2%). Dysgeusia was caused mainly by azelastine, while epistaxis and headache were present in both azelastine and fluticasone groups.

The long-term safety and tolerability of AZE/FP was tested in study MP4000, conducted in India, in which patients with chronic allergic or vasomotor non-allergic rhinitis were randomized in an open-label manner to the AZE/FP group (N = 404) and to commercially available generic fluticasone propionate (N = 207) for more than one year of use. Study MP4000 was excluded from the review because this study involved patients with a different indication (i.e., chronic rhinitis or vasomotor non-allergic rhinitis). The results are summarized in APPENDIX 8. Briefly, TEAEs and TRAEs were mostly mild and moderate, and similar between treatment groups. The adverse event profile was similar to that observed in the studies included in this review.

4.3 Other Considerations

Overall, there is a paucity of convincing evidence to suggest notable differences in efficacy and safety between various intranasal corticosteroids, as well as between various intranasal antihistamines. Intranasal antihistamines appear to be more efficacious than oral antihistamines for SAR. Based on limited evidence from randomized controlled trials, there is no difference in the efficacy outcomes (TNSS, onset of action, or RQLQ) of the intranasal antihistamines levocabastine and olopatadine compared with azelastine (see APPENDIX 6). Conversely, evidence supports the superior efficacy of intranasal antihistamines versus oral antihistamines. From a safety perspective, higher rates of taste disturbance with the use of azelastine and higher rates of somnolence with the use of oral antihistamines have been observed and in some cases have led to higher rates of withdrawal. No additional safety concerns attributable to specific intranasal or oral antihistamines have been observed.

Based on limited evidence from two systematic reviews, there is no difference in the efficacy of various intranasal corticosteroids (see APPENDIX 7). Data were not available for fluticasone furoate, ciclesonide, or flunisolide. As such, any conclusions do not apply to these products and further research is needed to discern any efficacy or safety differences. In addition, no data were reported for ocular symptom scores. It has been suggested that fluticasone furoate may have superior efficacy in reducing ocular symptoms. Limited safety data were presented that suggested similar tolerability in terms of withdrawals due to adverse events, headache, and epistaxis. No data were presented on other relevant safety outcomes; therefore, tolerability with respect to overall and SAEs and infection is unclear.

The results of an online survey of 51 members of the National Asthma Patient Alliance are summarized in APPENDIX 1. The majority of these patients had been diagnosed with SAR, and experienced year-round symptoms. With regard to the drug being reviewed, none of the patients surveyed had had any experience with AZE/FP. However, they were informed that there could be potential for more rapid treatment onset and greater symptom reduction with AZE/FP. They also expressed interest in treatment that could provide specific benefits, such as improved nasal breathing and sleep. The current review of AZE/FP efficacy and safety meets the patient expectations as indicated above; as compared with placebo, AZE/FP demonstrated a meaningful clinical benefit in all outcomes including time to onset of action. Compared with individual components, however, AZE/FP provided better symptom relief than

azelastine, but was not better than fluticasone in providing symptom relief. Therefore, AZE/FP would likely not meet the expectations for improved symptom relief of patients who are already being treated with fluticasone. However, AZE/FP could potentially improve symptoms in patients being treated with an antihistamine alone, and would represent a more convenient option for patients being treated with both an antihistamine and an intranasal corticosteroid.

5. CONCLUSIONS

The results of four studies (MP4002 [N = 832], MP4004 [N = 779], MP4006 [N = 1,801], and MP4001 [N = 610]) indicate that treatment of SAR patients for 14 days with AZE/FP, a fixed-dose combination nasal spray of azelastine (an antihistamine) and fluticasone (a corticosteroid), provides superior relief of nasal (rTNSS) and ocular (rTOSS) symptoms, as well as quality of life (RQLQ) compared with placebo. Compared with azelastine, AZE/FP was associated with superior nasal symptom relief and improved quality of life, but did not provide superior ocular symptom relief in all studies. Compared with fluticasone, AZE/FP was associated with superior nasal symptom relief, but did not provide consistently greater relief from ocular symptoms or a greater improvement in quality of life. It is unclear whether any of the aforementioned differences between AZE/FP and the individual active components were clinically meaningful. The onset of action of AZE/FP (within 30 to 45 minutes of treatment) was faster than placebo, but was not significantly different compared with the onset of action of intranasal azelastine or fluticasone alone. The safety profile for AZE/FP was similar across each of the four included studies. There were no deaths or SAEs in any of the studies, and most TEAEs and TRAEs were mild in nature. Collectively, these results suggest that the combination therapy with AZE/FP provides better nasal symptom relief than monotherapy with an inhaled antihistamine or corticosteroid, but that this difference may not be clinically important compared with fluticasone alone. The evidence with respect to the relative benefit on ocular symptoms and quality of life does not support the conclusion that combination therapy with AZE/FP is better than monotherapy with an inhaled antihistamine or corticosteroid.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review staff, based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input
One patient group representing people with allergic rhinitis provided input.

The National Asthma Patient Alliance (NAPA) is a patient group associated with the Asthma Society of Canada (ASC), comprising more than 5,000 allergy and asthma patients who share information and engage in advocacy. The ASC is a national organization committed to enhancing the quality of life and health of people living with asthma and associated allergies by enabling patients to take control of symptoms through effective-self management. They operate through evidence-based health education and disease management programs; collaboration with policy-makers, researchers, and health care providers; provision of education and counselling; and advocacy. The ASC receives approximately 20% of its revenue from unrestricted grants, consulting fees, and fee-for-service contracts. Multiple drug companies provide the ASC with funding, excluding Meda Pharmaceuticals.

2. Condition and Current Therapy-Related Information
It is estimated that between 20% and 25% of adults in Canada suffer from respiratory allergies, often manifested as seasonal allergic rhinitis (SAR; also known as hay fever). Grass, tree, and other plant pollens and some fungi elicit SAR symptoms. Despite trigger management and allergen avoidance measures, complete allergen avoidance is rarely possible for most Canadians with allergic rhinitis. Thus, medical treatment is necessary to regain normal function.

The following information was generated through an online survey regarding respiratory allergies that was completed by NAPA members (n = 51), the majority of whom had been diagnosed with SAR (and concurrent asthma, in some cases) and experience year-round symptoms. In addition, information was pulled from two 2013 surveys, one on severe asthma patients (n = 24) and one concerning sublingual immunotherapy treatment for allergies (n = not reported).

Patients reported a persistent year-round impact of allergic rhinitis on day-to-day quality of life, with the frequency of symptoms and medication use increasing during the spring and fall months. The majority of surveyed patients experienced undesirable symptoms. When asked to rate the severity of symptoms during their most severe episodes, patients reported the worst symptom to be nasal congestion, followed by itchy eyes, moderate or severe runny nose, sneezing, watery eyes, itchy nose, and eye redness. It was reported that the average patient experiences multiple allergic rhinitis episodes annually, each lasting two weeks on average.

Patients noted a substantial impact of allergy symptoms on sleep, daily activities (including leisure and sport), and workplace productivity. Substantial time spent missing work to seek health care (including hospital visits and admissions) was reported, and treatment requirements necessitated changes to daily routines. Multiple annual visits to health care providers were noted, with more than half specifically attributed to dissatisfaction with current medications. Patients also found it challenging to obtain a referral to an allergist and perceived their family physicians to be lacking in knowledge of their condition.

Negative experiences for caregivers included coping with adverse patient side effects, time spent off work to support the patient or attend medical appointments, and sharing the financial burden of treatment. The greatest overall burden on caregivers was reported to be the need to rearrange daily routines to accommodate patient needs.

Current available treatments include prescription oral antihistamines, intranasal corticosteroids, antihistamine drops, and over-the-counter products (e.g., oral antihistamines). Allergy shots performed in a physician's office are the current standard of care in Canada for people with more severe SAR and were received by approximately one-quarter of surveyed patients. In addition, a small number of patients use sublingual immunotherapy, although it is not widely available. Almost all patients use medication to treat allergic rhinitis symptoms at least once per day for approximately 31 days each episode. Treatments used by the surveyed patients, in the order of frequency, include prescription nasal sprays (i.e., Nasonex, Avamys, Flonase, Omnaris, or Nasacort AQ), oral medications (i.e., acrivastine [Benadryl Allergy], loratadine [Claritin], Tylenol Sinus, Aerius, and Sudafed), and eye drops. A combination of all three is typically used. Patients also report using over-the-counter products, nasal rinses, and asthma medication. Almost all patients reuse leftover medication across symptom episodes. A financial burden of medication requirements was noted. Approximately half the surveyed patients were very satisfied or somewhat satisfied with current treatment effectiveness.

Approximately half the surveyed patients were either somewhat or very unsatisfied with their treatment. Patients reported that current available options do not address all nasal symptoms effectively, and that additional treatment is needed for ocular symptoms. In addition, the onset of action is not quick enough (often reported as at least three to 14 days) and other medications are often required for more immediate symptom relief. Fewer than a third of patients reported no side effects. Side effects included (in order of frequency) nosebleed, drowsiness, headache, bitter taste, dry nose, throat irritation, asthma attacks, cough, and mood changes. Asthma attacks, nosebleed, blocked nose, fatigue, cough, mood swings, and headache were symptoms patients were most interested in reducing, in order of priority.

3. Related Information About the Drug Being Reviewed

No patients surveyed had any experience with AZE/FP and patients who had taken part in clinical trials were not accessible for this submission. Almost all patients were interested in trying a new treatment when they were informed there could be potential for more rapid treatment onset and greater symptom reduction. Patients felt that quicker symptom relief would be most important in a new treatment, followed by relief of all allergy symptoms (i.e., runny rose, sneezing, itchy and watery eyes, postnasal drip, and nasal congestion), treatment safety, time to achieve maximum relief, and sustained treatment effects. Patients were interested in a treatment that could provide specific benefits, such as improved nasal breathing and sleep. In addition, they were interested in reduced nasal congestion; throat irritation; persistent coughing; itchy eyes, nose, and throat; watery eyes; loss of sense of taste and smell; and fatigue. Patients were also interested in the potential reduction in frequency and severity of asthma attacks and use of rescue medications, as upper and lower airway diseases were perceived to be one disease. Intolerable side effects were listed as severe sore throat, increased mucus production, long-lasting swollen tongue or lips, increased drowsiness, and increased number and severity of asthma attacks.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 29, 2015
Alerts:	Weekly search updates until (May 20, 2015 CDEC meeting)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt .po	Publication type Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY				
Select	**#**	**Searches**	**Results**	**Search Type**
	1	(Dymista* or Dylastine or Dymistin or MP29-02 or MP2902 or MP 2902 or MP 29-02).ti,ab,ot,sh,hw,rn,nm.	86	Advanced
	2	(azelastine* adj3 fluticasone*).ti,ab,ot,sh,hw,rn,nm.	481	Advanced
	3	(azelastine* and fluticasone*).ti,ab,ot,sh,hw,rn,nm.	493	Advanced
	6	azelastine plus fluticasone propionate/	38	Advanced
-	5	1417803-89-4.rn,nm.	0	Advanced
	6	1 or 2 or 3 or 4 or 5	498	Advanced
	7	limit 6 to human	466	Advanced
	8	*Azelastine/ and *fluticasone/	4	Advanced
	9	(Dymista* or Dylastine or Dymistin or MP29-02 or MP2902 or MP 2902 or MP 29-02).ti,ab.	83	Advanced
	10	8 or 9	87	Advanced
	11	remove duplicates from 10	78	Advanced
	12	remove duplicates from 7	436	Advanced

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.
CINAHL (EBSCO interface)	Same keywords and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform.

Grey Literature

Dates for Search:	February 2015
Keywords:	Included terms for single use medical devices, reuse, and reprocessing.
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey matters: a practical tool for evidence-based searching* (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

- Health technology assessment agencies
- Health economics
- Clinical practice guidelines
- Databases (free)
- Internet search
- Open access journals.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Ratner PH, Hampel F, Van BJ, Amar NJ, Daftary P, Wheeler W, et al. Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2008 Jan; 100(1):74-81.	Individual components in the combination therapy were administered separately.
LaForce CF, Carr W, Tilles SA, Chipps BE, Storms W, Meltzer EO, et al. Evaluation of olopatadine hydrochloride nasal spray, 0.6%, used in combination with an intranasal corticosteroid in seasonal allergic rhinitis. Allergy Asthma Proc. 2010 Mar;31(2):132-40.	Individual components in the combination therapy were administered separately.
Erratum: Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device (Ann Allergy Asthma Immunol. (2010) 105 (168-173)). Annals of Allergy, Asthma and Immunology. 2010;105(6):497.	Erratum.
Price D, Shah S, Bhatia S, Bachert C, Berger W, Bousquet J, et al. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. J Investig Allergol Clin Immunol. 2013;23(7):495-503.	Inappropriate population (i.e., chronic and non-allergic rhinitis).
Berger WE, Shah S, Lieberman P, Hadley J, Price D, Munzel U, et al. Long-term, randomized safety study of MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in an advanced delivery system) in subjects with chronic rhinitis. J Allergy Clin Immunol Pract. 2014 Mar;2(2):179-85.	Inappropriate population (i.e., chronic rhinitis).
Derendorf H, Meltzer EO, Hermann R, Canonica GW. Clinical development of an advanced intranasal delivery system of azelastine hydrochloride and fluticasone propionate. Drugs Today (Barc). 2014 Jan;50(1):15-31.	Review article.
Devillier P, Dreyfus JF, Demoly P, Calderon MA. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. Bmc med [Internet]. 2014 [cited 2015 Jan 30];12:71. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4101870/pdf/1741-7015-12-71.pdf	Duplicate of Carr et al.
Clinical Study Report: MP4000. Active-controlled trial of the safety and tolerability of MP29-02 in subjects with chronic allergic or nonallergic rhinitis [CONFIDENTIAL internal manufacturer's report], Somerset (NJ): Meda Pharmaceuticals; 2010	Inappropriate population (i.e., chronic and vasomotor rhinitis).

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 11: BASELINE CHARACTERISTICS OF INTENTION-TO-TREAT POPULATION — MP4002

Category	AZE/FP (N = 207)	Azelastine (N = 208)	Fluticasone (N = 207)	Placebo (N = 209)
Age (years) — mean (SD)	37.3 (14.07)	36.2 (14.56)	38.6 (14.14)	37.3 (16.01)
Age — n (%)				
12 to < 18	19 (9.2)	28 (13.5)	15 (7.2)	36 (17.2)
18 to < 65	183 (88.4)	172 (82.7)	185 (89.4)	165 (78.9)
≥ 65	5 (2.4)	8 (3.8)	7 (3.4)	8 (3.8)
Sex — n (%)				
Male	65 (31.4)	78 (37.5)	80 (38.6)	77 (36.8)
Female	142 (68.6)	130 (62.5)	127 (61.4)	132 (63.2)
Race — n (%)				
Caucasian	162 (78.3)	162 (77.9)	161 (77.8)	169 (80.9)
Black	34 (16.4)	37 (17.8)	38 (18.4)	32 (15.3)
Asian	5 (2.4)	2 (1.0)	4 (1.9)	3 (1.4)
Others	6 (2.9)	7 (3.4)	4 (1.9)	5 (2.4)
Total daily rTNSS — mean (SD)	18.3 (3.04)	18.2 (3.54)	18.2 (3.23)	18.6 (3.17)
Total daily rTOSS — mean (SD)	11.9 (3.90)	11.5 (4.54)	11.4 (4.42)	12.1 (4.28)
Duration of SAR (years) —mean (SD)	21.7 (13.24)	21.6 (13.61)	21.3 (13.46)	21.2 (14.03)
Concomitant medications — n (%)				
Ibuprofen	37 (17.9)	32 (15.4)	41 (19.8)	39 (18.6)
Multivitamins	33 (15.9)	32 (15.4)	45 (21.7)	37 (17.6)
Paracetamol	23 (11.1)	17 (8.2)	18 (8.7)	24 (11.4)
Salbutamol	22 (10.6)	25 (12.0)	15 (7.2)	19 (9.0)
Acetylsalicylic acid	11 (5.3)	9 (4.3)	10 (4.8)	10 (4.8)

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; rTNSS = reflective total nasal symptom score; rTOSS = reflective total ocular symptom score; SAR = seasonal allergic rhinitis; SD = standard deviation.
Source: Table 14 (p. 46) of Clinical Study Report (CSR); Table 14.3.6 (p. 339) of CSR.

TABLE 12: BASELINE CHARACTERISTICS OF INTENTION-TO-TREAT POPULATION — MP4004

Category	AZE/FP (N = 193)	Azelastine (N = 194)	Fluticasone (N = 189)	Placebo (N = 200)
Age (years) — mean (SD)	38.8 (14.08)	38.2 (13.49)	37.0 (13.63)	37.2 (13.03)
Age — n (%)				
12 to < 18	12 (6.2)	12 (6.2)	14 (7.4)	17 (8.5)
18 to < 65	176 (91.2)	178 (91.8)	172 (91.0)	181 (90.5)
≥ 65	5 (2.6)	4 (2.1)	3 (1.6)	2 (1.0)
Sex — n (%)				
Male	67 (34.7)	66 (34.0)	68 (36.0)	81 (40.5)
Female	126 (65.3)	128 (66.0)	121 (64.0)	119 (59.5)
Race — n (%)				
Caucasian	154 (79.8)	153 (78.9)	140 (74.1)	164 (82.0)

Category	AZE/FP (N = 193)	Azelastine (N = 194)	Fluticasone (N = 189)	Placebo (N = 200)
Black	30 (15.5)	35 (18.0)	38 (20.1)	25 (12.5)
Asian	5 (2.6)	3 (1.5)	4 (2.1)	6 (3.0)
Others	4 (2.1)	3 (1.5)	7 (3.7)	5 (2.5)
Total daily rTNSS — mean (SD)	18.2 (3.34)	18.5 (3.15)	18.6 (2.92)	18.2 (3.07)
Total daily rTOSS — mean (SD)	11.7 (1.46)	11.8 (3.9)	12.0 (3.8)	11.6 (4.1)
Duration of SAR (years) —mean (SD)	21.5 (13.51)	19.7 (13.05)	21.1 (13.65)	21.0 (12.82)
Concomitant medications — n (%)				
Ibuprofen	40 (20.5)	40 (20.6)	33 (17.5)	27 (13.5)
Multivitamins	24 (12.3)	32 (16.5)	29 (15.3)	34 (17.0)
Paracetamol	8 (4.1)	20 (10.3)	24 (12.7)	17 (8.5)
Salbutamol	13 (6.7)	16 (8.2)	11 (5.8)	12 (6.0)
Acetylsalicylic acid	7 (3.6)	8 (4.1)	10 (5.3)	8 (4.0)

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; rTNSS = reflective total nasal symptom score; rTOSS = reflective total ocular symptom score; SAR = seasonal allergic rhinitis; SD = standard deviation.
Source: Table 14 (p. 46) of Clinical Study Report (CSR); Table 14.3.6 (p. 339) of CSR.

TABLE 13: BASELINE CHARACTERISTICS OF INTENTION-TO-TREAT POPULATION — MP4006

Category	AZE/FP (N = 448)	Azelastine (N = 445)	Fluticasone (N = 450)	Placebo (N = 448)
Age (years) — mean (SD)	35.6 (14.53)	36.4 (14.83)	34.2 (14.45)	34.7 (14.05)
Age — n (%)				
12 to < 18	57 (12.7)	38 (8.5)	56 (12.4)	46 (10.3)
18 to < 65	382 (85.3)	390 (87.6)	390 (86.7)	387 (86.4)
≥ 65	9 (2.0)	17 (3.8)	4 (0.9)	15 (3.3)
Sex — n (%)				
Male	171 (38.2)	174 (39.1)	170 (37.8)	179 (40.0)
Female	277 (61.8)	271 (60.9)	280 (62.2)	269 (60.0)
Race — n (%)				
Caucasian	364 (81.3)	357 (80.2)	356 (79.1)	348 (77.7)
Black	70 (15.6)	62 (13.9)	73 (16.2)	75 (16.7)
Asian	8 (1.8)	12 (2.7)	8 (1.8)	10 (2.2)
Others	6 (1.3)	14 (3.1)	13 (2.9)	15 (3.3)
Total daily rTNSS — mean (SD)	19.4 (2.43)	19.5 (2.52)	19.4 (2.38)	19.5 (2.36)
Total daily rTOSS — mean (SD)	12.3 (4.01)	12.4 (3.99)	12.3 (3.62)	12.2 (3.72)
Duration of SAR (years) —mean (SD)	20.4 (13.04)	19.5 (12.88)	19.6 (12.45)	19.6 (12.39)
Concomitant medications — n (%)				
Ibuprofen	111 (24.6)	96 (21.4)	99 (22.0)	109 (24.2)
Multivitamins	59 (13.1)	66 (14.7)	64 (14.2)	62 (13.7)
Paracetamol	57 (12.6)	63 (14.0)	74 (16.4)	56 (12.4)

Category	AZE/FP (N = 448)	Azelastine (N = 445)	Fluticasone (N = 450)	Placebo (N = 448)
Salbutamol	31 (6.9)	40 (8.9)	34 (7.6)	42 (9.3)
Acetylsalicylic acid	15 (3.3)	21 (4.7)	20 (4.4)	13 (2.9)

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; rTNSS = reflective total nasal symptom score; rTOSS = reflective total ocular symptom score; SAR = seasonal allergic rhinitis; SD = standard deviation.
Source: Table 14 (p. 46) of Clinical Study Report (CSR); Table 14.3.6 (p. 440) of CSR.

TABLE 14: PATIENT DISPOSITION — MP4002

Disposition Summary	AZE/FP	Azelastine	Fluticasone	Placebo
Randomized, N	207	208	207	210
Completed study, N (%)	198 (95.7)	197 (94.7)	200 (96.6)	203 (96.7)
Discontinued, N (%)	9 (4.3)	11 (5.3)	7 (3.4)	7 (3.3)
Adverse events	4 (1.9)	1 (0.5)	0 (0.0)	1 (0.5)
Treatment failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	2 (1.0)	6 (2.9)	2 (1.0)	2 (1.0)
Patient withdrew consent	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)
Lost to follow-up	2 (1.0)	1 (0.5)	0 (0.0)	2 (1.0)
ITT, N (%)	207 (100.0)	208 (100.0)	207 (100.0)	209 (99.5)
Safety, N (%)	207 (100.0)	208 (100.0)	207 (100.0)	210 (100.0)
≥ 80% compliance overall, N (%)[a]	204 (98.6)	205 (98.6)	206 (9.5)	207 (98.6)

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to treat.
[a] Compliance = (total number of doses)/(duration of exposure x 2) from diary entries for each patient.
Source: Table 12 (p. 41) of Clinical Study Report (CSR); Table 15 (p. 48) of CSR.

TABLE 15: PATIENT DISPOSITION — MP4004

Disposition Summary	AZE/FP	Azelastine	Fluticasone	Placebo
Randomized, N	195	194	189	201
Completed study, N (%)	183 (93.8)	186 (95.9)	180 (95.2)	190 (94.5)
Discontinued, N (%)	12 (6.2)	8 (4.1)	9 (4.8)	11 (5.5)
Adverse events	3 (1.5)	1 (0.5)	1 (0.5)	3 (1.5)
Treatment failure	1 (0.5)	1 (0.5)	0 (0.0)	3 (1.5)
Protocol violation	0 (0.0)	1 (0.5)	0 (0.0)	2 (1.0)
Non-compliance	0 (0.0)	0 (0.0)	5 (2.6)	0 (0.0)
Patient withdrew consent	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Lost to follow-up	2 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)
ITT, N (%)	193 (99.0)	194 (100.0)	189 (100.0)	200 (99.5)
Safety, N (%)	195 (100.0)	194 (100.0)	189 (100.0)	200 (99.5)
≥ 80% compliance overall, N (%)[a]	190 (97.4)	190 (97.9)	185 (97.9)	197 (98.5)

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to treat.
[a] Compliance = (total number of doses)/(duration of exposure x 2) from diary entries for each patient.
Source: Table 12 (p. 41) of Clinical Study Report (CSR); Table 15 (p. 48) of CSR.

TABLE 16: PATIENT DISPOSITION — MP4006

Disposition Summary	AZE/FP	Azelastine	Fluticasone	Placebo
Randomized, N	451	449	450	451
Completed Study, N (%)	434 (96.2)	430 (95.8)	431 (95.8)	433 (96.0)
Discontinued, N (%)	17 (3.8)	19 (4.2)	19 (4.2)	18 (4.0)
Adverse Events	3 (0.7)	4 (0.9)	3 (0.7)	5 (1.1)
Treatment Failure	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)
Protocol Violation				
Non-Compliance	1 (0.2)	4 (0.9)	5 (1.1)	4 (0.9)
Patient Withdrew Consent	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)
Lost to Follow-up	2 (0.4)	1 (0.2)	1 (0.2)	0 (0.0)
ITT, N (%)	448 (99.3)	445 (99.1)	450 (100.0)	448 (99.3)
Safety, N (%)	451 (100.0)	449 (100.0)	450 (100.0)	451 (100.0)
≥80% Compliance Overall, N (%)[a]	445 (98.7)	442 (98.4)	447 (99.3)	446 (98.9)

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to treat.
[a] Compliance = (total number of doses)/(duration of exposure x 2) from diary entries for each patient.
Source: Table 12 (p. 43) of Clinical Study Report (CSR); Table 14 (p. 48) of CSR.

TABLE 17: OVERALL SCORES OF RQLQ IN PATIENTS AGED ≥ 18 YEARS (ITT POPULATION)

	MP4002	MP4004	MP4006	MP4001
Overall Baseline Score (LS Mean [SD])[a]				
AZE/FP	3.88 (0.90)	3.76 (0.99)	3.87 (0.96)	3.87 (1.06)
Azelastine	3.78 (0.96)	3.85 (0.93)	3.92 (1.02)	3.77 (1.04)
Fluticasone	3.76 (0.92)	3.78 (0.98)	3.88 (0.94)	3.76 (1.07)
Placebo	3.87 (0.98)	3.88 (0.97)	3.88 (0.97)	3.84 (1.17)
Change from Baseline in Overall Score (LS Mean [SD])[a]				
AZE/FP	–1.64 (1.39)	–1.68 (1.26)	–1.59 (1.30)	–1.60 (1.39)
Azelastine	–1.36 (1.13)	–1.40 (1.27)	–1.42 (1.30)	–1.17 (1.33)
Fluticasone	–1.63 (1.21)	–1.48 (1.34)	–1.55 (1.23)	–1.43 (1.39)
Placebo	–0.85 (1.07)	–0.97 (1.29)	–1.03 (1.23)	–1.01 (1.29)
Comparisons (Δ LS Mean; *P* Value [Day 14])[b]				
AZE/FP vs. azelastine	**–0.28;** 0.029	**–0.28;** 0.031	**–0.17;** 0.043	**–0.43;** 0.005
AZE/FP vs. fluticasone	–0.01; 0.907	–0.20; 0.123	–0.04; 0.629	–0.17; 0.286
AZE/FP vs. placebo	**–0.79;** < 0.001	**–0.71;** < 0.001	**–0.56;** < 0.001	**–0.59;** < 0.001

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; **Δ** = treatment difference; LS = least-squares; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SD = standard deviation.
[a] LS mean obtained from ANOVA.
[b] *P* value for between-treatment group comparison, except baseline, was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate. For baseline, the *P* value was based on an ANOVA model containing treatment group and site as fixed effects.
Source: MP4002: Table 14.2.15 (p. 286) of Clinical Study Report (CSR); MP4004: Table 14.2.15 (p. 368) of CSR; MP4006: Table 14.2.15 (p. 368) of CSR; MP4001: Table 14.2.23 of CSR.

TABLE 18: RQLQ *P* VALUES IN PATIENTS AGED ≥ 18 YEARS (ITT POPULATION)

Study	RQLQ Domains	AZE/FP vs. Azelastine *P* Value (Day 14)[a]	AZE/FP vs. Fluticasone *P* Value (Day 14)[a]	AZE/FP vs. Placebo *P* Value (Day 14)[a]
MP4002	Change from Baseline in Activity (Level)	0.055	0.413	**< 0.001**
	Change from Baseline in Sleep	**0.014**	0.549	**< 0.001**
	Change from Baseline in Non-nose/Eye Symptoms	0.210	0.178	**< 0.001**
	Change from Baseline in Practical Problems	**0.044**	0.991	**< 0.001**
	Change from Baseline in Nasal Symptoms	**0.021**	0.975	**< 0.001**
	Change from Baseline in Eye Symptoms	0.727	0.930	**< 0.001**
	Change from Baseline in Emotional	0.075	0.999	**< 0.001**
	Change from Baseline in Overall Score	**0.029**	0.907	**< 0.001**
MP4004	Change from Baseline in Activity (Level)	0.063	0.098	**< 0.001**
	Change from Baseline in Sleep	**0.022**	0.312	**< 0.001**
	Change from Baseline in Non-nose/Eye Symptoms	**0.021**	0.169	**< 0.001**
	Change from Baseline in Practical Problems	0.092	0.125	**< 0.001**
	Change from Baseline in Nasal Symptoms	**0.007**	0.173	**< 0.001**
	Change from Baseline in Eye Symptoms	0.097	**0.013**	**< 0.001**
	Change from Baseline in Emotional	0.144	0.550	**< 0.001**
	Change from Baseline in Overall Score	**0.031**	0.123	**< 0.001**
MP4006	Change from Baseline in Activity (Level)	**0.008**	0.291	**< 0.001**
	Change from Baseline in Sleep	0.131	0.959	**< 0.001**
	Change from Baseline in Non-nose/Eye Symptoms	0.341	0.658	**< 0.001**
	Change from Baseline in Practical Problems	**0.001**	0.269	**< 0.001**
	Change from Baseline in Nasal Symptoms	**0.001**	0.307	**< 0.001**
	Change from Baseline in Eye Symptoms	0.848	0.975	**< 0.001**

Study	RQLQ Domains	AZE/FP vs. Azelastine *P* Value (Day 14)[a]	AZE/FP vs. Fluticasone *P* Value (Day 14)[a]	AZE/FP vs. Placebo *P* Value (Day 14)[a]
	Change from Baseline in Emotional	0.176	0.644	**< 0.001**
	Change from Baseline in Overall Score	**0.043**	0.629	**< 0.001**
MP4001	Change from Baseline in Activity (Level)	0.057	0.528	**< 0.001**
	Change from Baseline in Sleep	**0.012**	0.575	**< 0.001**
	Change from Baseline in Non-nose/Eye Symptoms	**0.017**	0.611	**0.005**
	Change from Baseline in Practical Problems	**< 0.001**	0.169	**< 0.001**
	Change from Baseline in Nasal Symptoms	**< 0.001**	0.191	**< 0.001**
	Change from Baseline in Eye Symptoms	0.150	0.321	**0.010**
	Change from Baseline in Emotional	**0.003**	0.658	**0.005**
	Change from Baseline in Overall Score	**0.005**	0.286	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.
[a] *P* value for between-treatment group comparison, except baseline, was based on ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate. For baseline, the *P* value was based on an ANOVA model containing treatment group and site as fixed effects.
Source: MP4002: Table 25 (p. 60) of Clinical Study Report (CSR); MP4004: Table 25 (p. 60) of CSR; MP4006: Table 24 (p. 60) of CSR; MP4001: Table 20 (p. 57) of CSR.

TABLE 19: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE INDIVIDUAL NASAL SYMPTOM SCORES OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — STUDY MP4002

Comparison	LS Mean Difference (95% CI); *P* Value			
	Itchy Nose	Nasal Congestion	Runny Nose	Sneezing
AZE/FP vs. placebo	–0.62 (–0.85 to –0.40); **< 0.001**	–0.55 (–0.76 to –0.34); **< 0.001**	–0.76 (–0.99 to –0.53); **< 0.001**	–0.78 (–1.02 to –0.55); **< 0.001**
AZE/FP vs. azelastine	–0.30 (–0.54 to –0.06); **0.015**	–0.34 (–0.56 to –0.12); **0.003**	–0.41 (–0.66 to –0.17); **< 0.001**	–0.33 (–0.59 to –0.08); **0.010**
AZE/FP vs. fluticasone	–0.23 (–0.47 to 0.01); 0.058	–0.16 (–0.38 to 0.06); 0.163	–0.25 (–0.50 to –0.01); **0.043**	–0.19 (–0.44 to 0.06); 0.144

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; ITT = intention-to-treat; LS = least-squares.
Source: Table 19 (p. 53) of MP4002 Clinical Study Report.

TABLE 20: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE INDIVIDUAL NASAL SYMPTOM SCORES OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — STUDY MP4004

Comparison	LS Mean Difference (95% CI); *P* Value			
	Itchy Nose	Nasal Congestion	Runny Nose	Sneezing
AZE/FP vs. placebo	–0.62 (–0.86 to –0.38); **< 0.001**	–0.51 (–0.73 to –0.29); **< 0.001**	–0.60 (–0.84 to –0.35); **< 0.001**	–0.85 (–1.10 to –0.59); **< 0.001**
AZE/FP vs. azelastine	–0.22 (–0.47 to 0.04); 0.093	–0.36 (–0.60 to –0.14); **0.002**	–0.25 (–0.51 to 0.01); 0.058	–0.26 (–0.53 to 0.02); 0.066
AZE/FP vs. fluticasone	–0.24 (–0.50 to 0.02); 0.070	–0.28 (–0.52 to 0.04); 0.220	–0.15 (–0.41 to 0.12); 0.274	–0.29 (–0.56 to –0.01); **0.046**

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; ITT = intention-to-treat; LS = least-squares.
Source: Table 19 (p. 53) of MP4004 Clinical Study Report.

TABLE 21: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE INDIVIDUAL NASAL SYMPTOM SCORES OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — STUDY MP4006

Comparison	LS Mean Difference (95% CI); *P* Value			
	Itchy Nose	Nasal Congestion	Runny Nose	Sneezing
AZE/FP vs. placebo	–0.43 (–0.58 to –0.27); **< 0.001**	–0.45 (–0.60 to –0.30); **< 0.001**	–0.58 (–0.75 to –0.42); **< 0.001**	–0.75 (–0.92 to –0.58); **< 0.001**
AZE/FP vs. azelastine	–0.16 (–0.32 to 0.01); 0.065	–0.23 (–0.38 to –0.07); **0.004**	–0.24 (–0.41 to –0.07); **0.006**	–0.23 (–0.40 to –0.05); **0.012**
AZE/FP vs. fluticasone	–0.12 (–0.27 to 0.04); 0.142	–0.13 (–0.28 to 0.03); 0.106	–0.12 (–0.29 to 0.05); 0.170	–0.23 (–0.40 to –0.04); **0.014**

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; ITT = intention-to-treat; LS = least-squares.
Source: Table 18 (p. 52) of MP4006 Clinical Study Report.

TABLE 22: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE INDIVIDUAL NASAL SYMPTOM SCORES OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — STUDY MP4001

Comparison	LS Mean Difference (95% CI); *P* Value			
	Itchy Nose	Nasal Congestion	Runny Nose	Sneezing
AZE/FP vs. placebo	–0.71 (–0.97 to –0.44); **< 0.001**	–0.70 (–0.95 to –0.45); **< 0.001**	–0.84 (–1.10 to –0.56); **< 0.001**	–1.00 (–1.27 to –0.73); **< 0.001**
AZE/FP vs. azelastine	–0.40 (–0.67 to –0.13); **0.003**	–0.49 (–0.74 to –0.24); **< 0.001**	–0.55 (–0.80 to –0.28); **< 0.001**	–0.61 (–0.89 to –0.32); **< 0.001**
AZE/FP vs. fluticasone	–0.31 (–0.57 to –0.04); **0.024**	–0.38 (–0.65 to –0.13); **0.003**	–0.27 (–0.55 to 0.02); 0.068	–0.49 (–0.77 to –0.20); **< 0.001**

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; ITT = intention-to-treat; LS = least-squares.
Source: Table 17 (p. 53) of MP4001 Clinical Study Report.

TABLE 23: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE POSTNASAL DRIP SCORES OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION)

Study	Parameters	AZE/FP	Azelastine	Fluticasone	Placebo
MP4002	N	205	207	206	209
	LS mean baseline (SD)[a]	4.50 (1.28)	4.44 (1.45)	4.55 (1.40)	4.64 (1.34)
	LS mean (SD) change from baseline[b]	–1.12 (1.44)	–0.84 (1.28)	–0.89 (1.29)	–0.55 (0.16)
	Δ (95% CI)[c]; *P* value	---	–0.28 (–0.51 to –0.03); **0.025**	–0.23 (–0.47 to 0.01); 0.061	–0.57 (–0.80 to –0.34); **< 0.001**
MP4004	N	193	193	187	199
	LS mean baseline (SD)[a]	4.53 (1.38)	4.69 (1.29)	4.62 (1.21)	4.56 (1.34)
	LS mean (SD) change from baseline[b]	–1.00 (1.45)	–0.79 (1.36)	–0.87 (1.40)	–0.50 (1.15)
	Δ (95% CI)[c]; *P* value	---	–0.21 (–0.46 to 0.04); 0.102	–0.13 (–0.39 to 0.14); 0.335	–0.50 (–0.74 to –0.26); **< 0.001**
MP4006	N	447	442	450	448
	LS mean baseline (SD)[a]	4.68 (1.36)	4.74 (1.26)	4.62 (1.34)	4.69 (1.33)
	LS mean (SD) change from baseline[b]	–0.98 (1.54)	–0.81 (1.36)	–0.77 (1.31)	–0.55 (0.28)
	Δ (95% CI)[c]; *P* value	---	–0.17 (–0.34 to 0.00); **0.047**	–0.21 (–0.38 to –0.05); **0.009**	–0.43 (–0.60 to –0.27); **< 0.001**
MP4001	N	153	152	151	150
	LS mean baseline (SD)[a]	4.86 (1.19)	4.54 (1.27)	4.45 (1.26)	4.65 (1.24)
	LS mean (SD) change from baseline[b]	–0.99 (1.40)	–0.65 (1.15)	–0.79 (1.41)	–0.38 (1.13)
	Δ (95% CI)[c]; *P* value	---	–0.34 (–0.59 to –0.10); **0.005**	–0.20 (–0.47 to 0.07); 0.143	–0.61 (–0.85 to –0.38); **< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; Δ = treatment difference; ITT = intention-to-treat; LS = least-squares; rTNSS = reflective total nasal symptom score; rTOSS = reflective total ocular symptom score; SD = standard deviation.

[a] Baseline includes rTNSS scores over 7-day lead-in period, including day 1 a.m. LS mean obtained from an ANOVA model for baseline containing treatment group and site as fixed effects.

[b] Obtained from a repeated-measures ANCOVA model for overall absolute change containing study day (2 through 14) as the within-subject effect, treatment group and site as the between-subject effects, and baseline as a covariate.

[c] CI for treatment differences is specified as AZE/FP treatment LS mean change (or % LS mean change) minus the indicated comparator LS mean change (or % LS mean change).

Source: MP4002: Table 24 (p. 59) of Clinical Study Report (CSR); MP4004: Table 24 (p. 59) of CSR; MP4006: Table 23 (p. 59) of CSR; MP4001: Table 19 (p. 56) of CSR.

TABLE 24: CHANGE FROM BASELINE IN REFLECTIVE TNSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — MP4002

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	207	208	207	209
LS mean[b] (SD)	18.27 (3.04)	18.26 (3.54)	18.22 (3.23)	18.61 (3.18)
Overall,[c] N	207	208	207	209
LS mean (SD) change from baseline	–5.61 (5.24)	–4.23 (4.63)	–4.71 (4.68)	–2.92 (3.92)
P value[d]	---	**0.001**	**0.034**	**< 0.001**
Day 2, N	206	207	205	209
LS mean (SD) change from baseline	–4.22 (4.92)	–2.98 (4.52)	–3.10 (4.24)	–2.03 (3.96)
P value[d]	---	**0.007**	**0.013**	**< 0.001**
Day 3, N	207	208	207	209
LS mean (SD) change from baseline	–4.69 (5.31)	–3.35 (4.81)	–3.59 (4.56)	–2.33 (4.05)
P value[d]	---	**0.006**	**0.022**	**< 0.001**
Day 4, N	207	208	207	209
LS mean (SD) change from baseline	–5.04 (5.62)	–3.91 (5.04)	–4.25 (5.07)	–2.22 (4.36)
P value[d]	---	**0.028**	0.124	**< 0.001**
Day 5, N	207	208	207	209
LS mean (SD) change from baseline	–5.10 (5.81)	–4.20 (5.24)	–4.42 (5.47)	–2.78 (4.59)
P value[d]	---	0.095	0.210	**< 0.001**
Day 6, N	207	208	207	209
LS mean (SD) change from baseline	–5.51 (5.95)	–4.05 (5.34)	–4.42 (5.42)	–2.52 (4.46)
P value[d]	---	**0.008**	0.051	**< 0.001**
Day 7, n	207	208	207	209
LS mean (SD) change from baseline	–5.77 (5.94)	–4.06 (5.44)	–5.07 (5.64)	–2.43 (4.70)
P value[d]	---	**0.002**	0.216	**< 0.001**
Day 8, N	207	208	207	209
LS mean (SD) change from baseline	–5.81 (5.97)	–4.20 (5.27)	–5.35 (5.66)	–2.27 (4.77)
P value[d]	---	**0.003**	0.415	**< 0.001**
Day 9, N	207	208	207	209
LS mean (SD) change from baseline	–6.06 (5.74)	–4.39 (5.30)	–5.76 (5.60)	–2.80 (4.87)
P value[d]	---	**0.002**	0.576	**< 0.001**
Day 10, n	207	208	207	209
LS mean (SD) change from baseline	–6.22 (5.93)	–4.58 (5.29)	–6.08 (5.69)	–2.77 (4.75)
P value[d]	---	**0.002**	0.797	**< 0.001**

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Day 11, N	207	208	207	209
LS mean (SD) change from baseline	–6.32 (5.94)	–4.84 (5.46)	–6.31 (5.69)	–2.78 (4.78)
P value[d]	---	**0.007**	0.991	**< 0.001**
Day 12, N	207	208	207	209
LS mean (SD) change from baseline	–6.19 (6.33)	–5.02 (5.45)	–6.39 (5.42)	–3.08 (4.73)
P value[d]	---	**0.039**	0.719	**< 0.001**
Day 13, N	207	208	207	209
LS mean (SD) change from baseline	–6.25 (6.17)	–4.87 (5.62)	–6.16 (5.47)	–2.95 (4.79)
P value[d]	---	**0.013**	0.858	**< 0.001**
Day 14, N	207	208	207	209
LS mean (SD) change from baseline	–6.30 (6.09)	–4.90 (5.48)	–6.42 (5.39)	–3.02 (4.90)
P value[d]	---	**0.011**	0.832	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.

[a] Total number of intention-to-treat patients with available data.

[b] LS mean obtained from ANOVA.

[c] Baseline includes TNSS scores over the 7-day lead-in period, including day 1 a.m. Overall includes TNSS scores from day 1 p.m. to day 14 a.m.

[d] *P* value for between-treatment group comparison was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate.

Source: Table 14.2.1.2 (p. 85 to 92) of MP4002 Clinical Study Report.

TABLE 25: CHANGE FROM BASELINE IN REFLECTIVE TNSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — MP4004

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	193	194	189	199
LS mean[b] (SD)	18.28 (3.34)	18.54 (3.15)	18.64 (2.92)	18.24 (3.07)
Overall[c], N	193	193	188	199
LS mean (SD) change from baseline	–5.54 (5.18)	–4.54 (4.62)	–4.55 (5.15)	–3.03 (3.93)
P value[d]	---	**0.032**	**0.038**	**< 0.001**
Day 2, N	193	191	187	199
LS mean (SD) change from baseline	–4.25 (5.34)	–3.91 (4.94)	–3.31 (4.75)	–2.09 (3.89)
P value[d]	---	0.513	0.066	**< 0.001**
Day 3, N	193	192	187	199
LS mean (SD) change from baseline	–4.74 (5.16)	–3.95 (5.11)	–3.94 (4.96)	–2.53 (4.18)
P value[d]	---	0.125	0.119	**< 0.001**
Day 4, N	193	192	187	199
LS mean (SD) change from baseline	–5.30 (5.48)	–4.23 (5.02)	–4.29 (5.26)	–2.58 (4.41)
P value[d]	---	**0.042**	0.063	**< 0.001**
Day 5, N	193	192	187	199
LS mean (SD) change from baseline	–5.30 (5.66)	–3.97 (5.21)	–4.55 (5.74)	–2.61 (4.40)
P value[d]	---	**0.015**	0.186	**< 0.001**

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Day 6, N	193	193	187	199
LS mean (SD) change from baseline	–5.69 (5.68)	–3.99 (5.40)	–4.59 (5.97)	–2.79 (4.48)
P value[d]	---	**0.002**	0.062	**< 0.001**
Day 7, n	193	193	187	199
LS mean (SD) change from baseline	–5.54 (5.87)	–4.04 (5.39)	–4.82 (5.89)	–2.75 (4.52)
P value[d]	---	**0.008**	0.223	**< 0.001**
Day 8, N	193	193	187	199
LS mean (SD) change from baseline	–6.06 (5.77)	–4.12 (4.91)	–4.98 (5.74)	–2.83 (4.75)
P value[d]	---	**< 0.001**	0.064	**< 0.001**
Day 9, N	193	193	188	199
LS mean (SD) change from baseline	–6.02 (5.89)	–4.60 (5.22)	–5.57 (5.89)	–2.88 (4.75)
P value[d]	---	**0.010**	0.446	**< 0.001**
Day 10, n	193	193	188	199
LS mean (SD) change from baseline	–6.34 (5.93)	–4.78 (5.09)	–5.64 (6.05)	–3.24 (5.10)
P value[d]	---	**0.005**	0.245	**< 0.001**
Day 11, N	193	193	188	199
LS mean (SD) change from baseline	–6.46 (5.97)	–5.01 (5.40)	–5.78 (6.04)	–3.20 (5.05)
P value[d]	---	**0.011**	0.260	**< 0.001**
Day 12, N	193	193	188	199
LS mean (SD) change from baseline	–6.29 (5.95)	–5.05 (5.65)	–5.90 (6.07)	–3.27 (4.97)
P value[d]	---	**0.033**	0.516	**< 0.001**
Day 13, N	193	193	188	199
LS mean (SD) change from baseline	–6.50 (5.89)	–5.19 (5.62)	–6.12 (6.27)	–3.14 (4.89)
P value[d]	---	**0.022**	0.528	**< 0.001**
Day 14, N	193	193	188	199
LS mean (SD) change from baseline	–6.54 (5.74)	–5.36 (5.62)	–6.12 (6.36)	–3.15 (4.99)
P value[d]	---	**0.036**	0.483	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.
[a] Total number of ITT patients with available data.
[b] LS mean obtained from ANOVA.
[c] Baseline includes TNSS scores over the 7-day lead-in period, including day 1 a.m. Overall includes TNSS scores from day 1 p.m. to day 14 a.m.
[d] *P* value for between-treatment group comparison was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate.
Source: Table 14.2.1.2, MP4004 Clinical Study Report.

TABLE 26: CHANGE FROM BASELINE IN REFLECTIVE TNSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — MP4006

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	448	445	450	448
LS mean[b] (SD)	19.34 (2.43)	19.47 (2.52)	19.41 (2.38)	19.44 (2.36)
Overall,[c] N	448	443	450	448
LS mean (SD) change from baseline	–5.53 (5.18)	–4.82 (4.76)	–4.89 (4.66)	–3.40 (4.34)

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
P value[d]	---	**0.016**	**0.029**	**< 0.001**
Day 2, N	447	440	448	447
LS mean (SD) change from baseline	–4.12 (5.04)	–3.73 (4.80)	–3.31 (4.56)	–2.33 (4.48)
P value[d]	---	0.217	**0.009**	**< 0.001**
Day 3, N	448	443	450	448
LS mean (SD) change from baseline	–4.66 (5.24)	–4.10 (5.06)	–4.06 (4.81)	–2.59 (4.64)
P value[d]	---	0.089	0.063	**< 0.001**
Day 4, N	448	443	450	448
LS mean (SD) change from baseline	–4.77(5.41)	–4.10 (5.15)	–4.41 (5.03)	–2.72 (4.71)
P value[d]	---	**0.048**	0.278	**< 0.001**
Day 5, N	448	443	450	448
LS mean (SD) change from baseline	–5.22 (5.59)	–4.02 (5.19)	–4.49 (5.11)	–2.77 (4.95)
P value[d]	---	**< 0.001**	**0.033**	**< 0.001**
Day 6, N	448	443	450	448
LS mean (SD) change from baseline	–5.42 (5.54)	–4.13 (5.24)	–4.78 (5.14)	–2.96 (5.00)
P value[d]	---	**< 0.001**	0.062	**< 0.001**
Day 7, n	448	443	450	448
LS mean (SD) change from baseline	–5.55 (5.84)	–4.37 (5.30)	–5.17 (5.36)	–3.01 (5.07)
P value[d]	---	**< 0.001**	0.283	**< 0.001**
Day 8, N	448	443	450	448
LS mean (SD) change from baseline	–5.87 (5.67)	–4.57 (5.20)	–5.41 (5.30)	–3.35 (5.00)
P value[d]	---	**< 0.001**	0.190	**< 0.001**
Day 9, N	448	443	450	448
LS mean (SD) change from baseline	–6.01 (5.78)	–4.79 (5.41)	–5.68 (5.30)	–3.58 (5.16)
P value[d]	---	**< 0.001**	0.354	**< 0.001**
Day 10, n	448	443	450	448
LS mean (SD) change from baseline	–6.40 (5.90)	–5.08 (5.53)	–5.77 (5.58)	–3.69 (5.13)
P value[d]	---	**< 0.001**	0.086	**< 0.001**
Day 11, N	448	443	450	448
LS mean (SD) change from baseline	–6.53 (6.05)	–5.12 (5.60)	–5.92 (5.53)	–3.64 (4.96)
P value[d]	---	**< 0.001**	0.101	**< 0.001**
Day 12, N	448	443	450	448

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
LS mean (SD) change from baseline	–6.61 (6.14)	–5.32 (5.45)	–6.30 (5.61)	–3.69 (5.24)
P value[d]	---	**< 0.001**	0.405	**< 0.001**
Day 13, N	448	443	450	448
LS mean (SD) change from baseline	–6.73 (5.98)	–5.17 (5.72)	–6.43 (5.61)	–3.83 (5.35)
P value[d]	---	**< 0.001**	0.410	**< 0.001**
Day 14, N	448	443	450	448
LS mean (SD) change from baseline	–6.80 (6.23)	–5.40 (5.63)	–6.59 (5.68)	–3.93 (5.43)
P value[d]	---	**< 0.001**	0.584	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.
[a] Total number of ITT patients with available data.
[b] LS mean obtained from ANOVA.
[c] Baseline includes TNSS scores over the 7-day lead-in period, including day 1 a.m. Overall includes TNSS scores from day 1 p.m. to Day 14 a.m.
[d] *P* value for between-treatment group comparison was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate.
Source: Table 14.2.1.2 (p. 87 to 94) of MP4006 Clinical Study Report.

TABLE 27: CHANGE FROM BASELINE IN REFLECTIVE TNSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — MP4001

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	153	152	151	151
LS mean[b] (SD)	18.64	17.87	18.12	18.49
Overall,[c] N	153	152	151	150
LS mean (SD) change from baseline	–5.31 (5.08)	–3.25 (4.16)	–3.84 (4.76)	–2.20 (4.16)
P value[d]	---	**< 0.001**	**0.003**	**< 0.001**
Day 2, N	153	152	150	150
LS mean (SD) change from baseline	–3.40 (4.71)	–1.71 (4.39)	–2.13 (4.67)	–0.64 (4.33)
P value[d]	---	**< 0.001**	**0.015**	**< 0.001**
Day 3, N	153	152	151	150
LS mean (SD) change from baseline	–4.44 (5.09)	–2.37 (4.56)	–2.55 (4.72)	–1.17 (4.84)
P value[d]	---	**< 0.001**	**< 0.001**	**< 0.001**
Day 4, N	153	152	151	150
LS mean (SD) change from baseline	–4.55 (5.65)	–3.05 (4.88)	–2.74 (5.20)	–1.69 (4.66)
P value[d]	---	**0.012**	**0.003**	**< 0.001**
Day 5, N	153	152	151	150
LS mean (SD) change from baseline	–5.02 (5.76)	–2.94 (5.07)	–3.49 (5.38)	–1.55 (5.00)
P value[d]	---	**< 0.001**	**0.015**	**< 0.001**

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Day 6, N	153	152	151	150
LS mean (SD) change from baseline	–5.25 (5.96)	–2.85 (5.09)	–3.57 (5.42)	–1.92 (4.75)
P value[d]	---	**< 0.001**	**0.010**	**< 0.001**
Day 7, n	153	152	151	150
LS mean (SD) change from baseline	–5.25 (6.07)	–3.29 (5.10)	–3.89 (5.67)	–1.84 (5.04)
P value[d]	---	**0.002**	**0.040**	**< 0.001**
Day 8, N	153	152	151	150
LS mean (SD) change from baseline	–5.70 (5.92)	–3.17 (5.19)	–4.10 (5.49)	–2.05 (4.63)
P value[d]	---	**< 0.001**	**0.013**	**< 0.001**
Day 9, N	153	152	151	150
LS mean (SD) change from baseline	–6.03 (5.88)	–3.77 (5.23)	–4.37 (5.39)	–2.15 (5.15)
P value[d]	---	**< 0.001**	**0.010**	**< 0.001**
Day 10, n	153	152	151	150
LS mean (SD) change from baseline	–5.92 (6.09)	–3.70 (5.28)	–4.86 (5.35)	–2.18 (5.60)
P value[d]	---	**< 0.001**	0.103	**< 0.001**
Day 11, N	153	152	151	150
LS mean (SD) change from baseline	–6.32 (6.06)	–3.89 (5.68)	–5.10 (5.77)	–2.34 (5.77)
P value[d]	---	**< 0.001**	0.070	**< 0.001**
Day 12, N	153	152	151	150
LS mean (SD) change from baseline	–6.56 (6.04)	–3.75 (5.55)	–4.95 (5.87)	–2.48 (5.84)
P value[d]	---	**< 0.001**	**0.017**	**< 0.001**
Day 13, N	153	152	151	150
LS mean (SD) change from baseline	–6.76 (6.07)	–3.88 (5.52)	–5.15 (5.92)	–2.48 (5.74)
P value[d]	---	**< 0.001**	**0.019**	**< 0.001**
Day 14, N	153	152	151	150
LS mean (SD) change from baseline	–6.65 (6.07)	–3.83 (5.65)	–5.06 (5.79)	–2.77 (5.62)
P value[d]	---	**< 0.001**	**0.018**	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.

[a] Total number of ITT patients with available data.

[b] LS mean obtained from ANOVA.

[c] Baseline includes TNSS scores over the 7-day lead-in period, including day 1 a.m. Overall includes TNSS scores from day 1 p.m. to day 14 a.m.

[d] *P* value for between-treatment group comparison was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate.

Source: Table 14.2.1.2, MP4001 Clinical Study Report.

TABLE 28: CHANGE FROM BASELINE IN INSTANTANEOUS TNSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — MP4002

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	207	208	207	209
LS mean[b] (SD)	17.16 (3.70)	16.84 (4.23)	16.84 (4.16)	17.26 (4.15)
Overall,[c] N	207	208	207	209
LS mean (SD) change from baseline	–5.21 (5.29)	–3.95 (4.67)	–4.51 (4.70)	–2.63 (4.08)
P value[d]	---	**0.003**	0.100	**< 0.001**
Day 2, N	205	207	205	207
LS mean (SD) change from baseline	–3.80 (5.17)	–2.58 (4.47)	–2.92 (4.26)	–1.58 (4.25)
P value[d]	---	**0.008**	0.052	**< 0.001**
Day 3, N	207	208	207	209
LS mean (SD) change from baseline	–4.24 (5.23	–3.09 (4.66)	–3.45 (4.52)	–1.86 (4.26)
P value[d]	---	**0.015**	0.094	**< 0.001**
Day 4, N	207	208	207	209
LS mean (SD) change from baseline	–4.59 (5.73)	–3.32 (5.08)	–3.98 (5.15)	–2.02 (4.41)
P value[d]	---	**0.013**	0.239	**< 0.001**
Day 5, N	207	208	207	209
LS mean (SD) change from baseline	–4.79 (5.94)	–3.93 (5.22)	–4.03 (5.40)	–2.25 (4.52)
P value[d]	---	0.107	0.163	**< 0.001**
Day 6, N	207	208	207	209
LS mean (SD) change from baseline	–5.01 (5.78)	–3.66 (5.26)	–4.28 (5.60)	–2.18 (4.75)
P value[d]	---	**0.011**	0.185	**< 0.001**
Day 7, n	207	208	207	209
LS mean (SD) change from baseline	–5.17 (5.87)	–3.64 (5.41)	–4.75 (5.54)	–2.23 (4.88)
P value[d]	---	**0.004**	0.437	**< 0.001**
Day 8, N	207	208	207	209
LS mean (SD) change from baseline	–5.34 (5.79)	–4.00 (5.23)	–5.17 (5.64)	–2.29 (5.03)
P value[d]	---	**0.011**	0.768	**< 0.001**
Day 9, N	207	208	207	209
LS mean (SD) change from baseline	–5.62 (5.96)	–3.99 (5.37)	–5.51 (5.37)	–2.41 (4.89)
P value[d]	---	**0.002**	0.846	**< 0.001**
Day 10, n	207	208	207	209
LS mean (SD) change from baseline	–5.91 (6.03)	–4.26 (5.57)	–5.73 (5.53)	–2.46 (4.98)
P value[d]	---	**0.002**	0.742	**< 0.001**

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Day 11, N	207	208	207	209
LS mean (SD) change from baseline	–5.82 (6.08)	–4.28 (5.58)	–5.91 (5.55)	–2.64 (4.95)
P value[d]	---	**0.005**	0.873	**< 0.001**
Day 12, N	207	208	207	209
LS mean (SD) change from baseline	–5.98 (6.31)	–4.66 (5.64)	–5.78 (5.38)	–2.99 (5.02)
P value[d]	---	**0.018**	0.717	**< 0.001**
Day 13, N	207	208	207	209
LS mean (SD) change from baseline	–6.07 (6.16)	–4.41 (5.63)	–5.75 (5.45)	–2.85 (5.09)
P value[d]	---	**0.003**	0.556	**< 0.001**
Day 14, N	207	208	207	209
LS mean (SD) change from baseline	–6.11 (6.14)	–4.27 (5.73)	–6.07 (5.55)	–2.83 (4.97)
P value[d]	---	**0.001**	0.946	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.
[a] Total number of ITT patients with available data.
[b] LS mean obtained from ANOVA.
[c] Baseline includes TNSS scores over the 7-day lead-in period, including day 1 a.m. Overall includes TNSS scores from day 1 p.m. to day 14 a.m.
[d] *P* value for between-treatment group comparison was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate.
Source: Table 14.2.7.2 (p. 176) MP4002 Clinical Study Report.

TABLE 29: CHANGE FROM BASELINE IN INSTANTANEOUS TNSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — MP4004

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	193	194	189	199
LS mean[b] (SD)	17.16 (4.09)	17.28 (4.08)	17.19 (3.78)	16.84 (3.88)
Overall[c], N	193	193	188	199
LS mean (SD) change from baseline	–5.23 (5.30)	–4.23 (4.63)	–4.29 (5.16)	–2.45 (4.15)
P value[d]	---	**0.029**	**0.049**	**< 0.001**
Day 2, N	192	191	187	198
LS mean (SD) change from baseline	–4.22 (5.31)	–3.50 (4.72)	–3.03 (4.89)	–1.65 (4.26)
P value[d]	---	0.150	**0.020**	**< 0.001**
Day 3, N	193	191	188	199
LS mean (SD) change from baseline	–4.60 (5.31)	–3.64 (5.10)	–4.07 (5.13)	–1.91 (4.34)
P value[d]	---	0.063	0.308	**< 0.001**
Day 4, N	193	191	188	199
LS mean (SD) change from baseline	–5.07 (5.66)	–3.69 (5.10)	–4.30 (5.16)	–2.06 (4.64)
P value[d]	---	**0.010**	0.153	**< 0.001**

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Day 5, N	193	191	188	199
LS mean (SD) change from baseline	–5.00 (6.02)	–3.62 (5.26)	–4.45 (5.65)	–2.12 (4.47)
P value[d]	---	**0.014**	0.346	**< 0.001**
Day 6, N	193	192	188	199
LS mean (SD) change from baseline	–5.26 (5.87)	–3.45 (5.35)	–4.68 (5.81)	–2.26 (4.62)
P value[d]	---	**0.001**	0.325	**< 0.001**
Day 7, n	193	192	188	199
LS mean (SD) change from baseline	–5.43 (5.98)	–3.38 (5.22)	–4.63 (6.03)	–2.49 (4.70)
P value[d]	---	**< 0.001**	0.183	**< 0.001**
Day 8, N	193	192	188	199
LS mean (SD) change from baseline	–5.55 (5.77)	–3.80 (5.09)	–4.63 (5.78)	–2.51 (4.99)
P value[d]	---	**0.001**	0.106	**< 0.001**
Day 9, N	193	192	188	199
LS mean (SD) change from baseline	–5.55 (5.94)	–4.11 (5.22)	–4.89 (5.77)	–2.54 (4.95)
P value[d]	---	**0.009**	0.257	**< 0.001**
Day 10, n	193	192	188	199
LS mean (SD) change from baseline	–6.10 (6.06)	–4.27 (5.15)	–5.09 (5.91)	–2.52 (5.42)
P value[d]	---	**0.001**	0.087	**< 0.001**
Day 11, N	193	193	188	199
LS mean (SD) change from baseline	–5.99 (6.01)	–4.40 (5.38)	–5.29 (6.06)	–2.55 (5.31)
P value[d]	---	**0.004**	0.236	**< 0.001**
Day 12, N	193	193	188	199
LS mean (SD) change from baseline	–6.03 (5.98)	–4.38 (5.63)	–5.37 (6.03)	–2.76 (4.92)
P value[d]	---	**0.004**	0.271	**< 0.001**
Day 13, N	193	193	188	199
LS mean (SD) change from baseline	–6.11 (6.00)	–4.47 (5.53)	–5.50 (6.24)	–2.54 (4.99)
P value[d]	---	**0.004**	0.309	**< 0.001**
Day 14, N	193	193	188	199
LS mean (SD) change from baseline	–6.02 (5.78)	–4.74 (5.49)	–5.60 (6.21)	–2.55 (4.95)
P value[d]	---	**0.022**	0.476	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.

[a] Total number of ITT patients with available data.

[b] LS mean obtained from ANOVA.

[c] Baseline includes TNSS scores over the 7-day lead-in period, including day 1 a.m. Overall includes TNSS scores from day 1 p.m. to day 14 a.m.

[d] *P* value for between-treatment group comparison was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate.

Source: Table 14.2.7.2, MP4004 Clinical Study Report.

TABLE 30: CHANGE FROM BASELINE IN INSTANTANEOUS TNSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — MP4006

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	448	445	450	448
LS mean[b] (SD)	17.91 (3.52)	18.00 (3.73)	17.82 (3.37)	17.90 (3.52)
Overall,[c] N	448	443	450	448
LS mean (SD) change from baseline	–5.00 (5.30)	–4.34 (4.89)	–4.72 (4.88)	–3.08 (4.41)
P value[d]	---	**0.026**	0.348	**< 0.001**
Day 2, N	445	438	447	448
LS mean (SD) change from baseline	–3.53 (5.20)	–3.21 (4.93)	–3.12 (4.84)	–2.02 (4.67)
P value[d]	---	0.306	0.196	**< 0.001**
Day 3, N	448	443	450	448
LS mean (SD) change from baseline	–4.12 (5.33)	–3.63 (5.27)	–3.95 (5.26)	–2.30 (4.72)
P value[d]	---	0.133	0.595	**< 0.001**
Day 4, N	448	443	450	448
LS mean (SD) change from baseline	–4.29 (5.63)	–3.69 (5.28)	–4.25 (5.26)	–2.43 (4.68)
P value[d]	---	0.077	0.917	**< 0.001**
Day 5, N	448	443	450	448
LS mean (SD) change from baseline	–4.47 (5.71)	–3.69 (5.37)	–4.30 (5.35)	–2.45 (4.89)
P value[d]	---	**0.025**	0.634	**< 0.001**
Day 6, N	448	443	450	448
LS mean (SD) change from baseline	–4.62 (5.64)	–3.75 (5.36)	–4.39 (5.50)	–2.56 (4.99)
P value[d]	---	**0.013**	0.521	**< 0.001**
Day 7, n	448	443	450	448
LS mean (SD) change from baseline	–4.95 (5.90)	–4.10 (5.57)	–4.86 (5.44)	–2.65 (4.94)
P value[d]	---	**0.018**	0.821	**< 0.001**
Day 8, N	448	443	450	448
LS mean (SD) change from baseline	–5.21 (5.87)	–4.10 (5.25)	–5.14 (5.47)	–2.95 (4.94)
P value[d]	---	**0.001**	0.837	**< 0.001**
Day 9, N	448	443	450	448
LS mean (SD) change from baseline	–5.51 (5.87)	–4.39 (5.47)	–5.35 (5.55)	–3.24 (5.29)
P value[d]	---	**0.001**	0.655	**< 0.001**
Day 10, n	448	443	450	448
LS mean (SD) change from baseline	–5.81 (6.11)	–4.85 (5.65)	–5.64 (5.57)	–3.44 (5.17)
P value[d]	---	**0.008**	0.644	**< 0.001**
Day 11, N	448	443	450	448

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
LS mean (SD) change from baseline	–5.80 (6.17)	–4.74 (5.59)	–5.82 (5.59)	–3.34 (5.19)
P value[d]	---	**0.004**	0.941	**< 0.001**
Day 12, N	448	443	450	448
LS mean (SD) change from baseline	–5.95 (6.14)	–5.00 (5.71)	–5.96 (5.78)	–3.48 (5.36)
P value[d]	---	**0.009**	0.979	**< 0.001**
Day 13, N	448	443	450	448
LS mean (SD) change from baseline	–6.20 (6.03)	–5.00 (5.78)	–6.07 (5.68)	–3.51 (5.46)
P value[d]	---	**0.001**	0.737	**< 0.001**
Day 14, N	448	443	450	448
LS mean (SD) change from baseline	–6.29 (6.30)	–5.07 (5.60)	–6.23 (5.77)	–3.58 (6.62)
P value[d]	---	**0.001**	0.879	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.

[a] Total number of ITT patients with available data.

[b] LS mean obtained from ANOVA.

[c] Baseline includes TNSS scores over the 7-day lead-in period, including day 1 a.m. Overall includes TNSS scores from day 1 p.m. to day 14 a.m.

[d] *P* value for between-treatment group comparison was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate.

Source: Table 14.2.7.2 (p. 206) of MP4006 Clinical Study Report.

TABLE 31: CHANGE FROM BASELINE IN INSTANTANEOUS TNSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — MP4001

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	153	152	151	151
LS mean[b] (SD)	17.14 (4.15)	16.54 (4.54)	16.85 (4.43)	17.54 (4.08)
Overall,[c] N	153	152	151	150
LS mean (SD) change from baseline	–4.44 (5.21)	–3.02 (4.50)	–3.46 (4.81)	–1.68 (4.17)
P value[d]	---	**0.003**	**0.043**	**< 0.001**
Day 2, N	153	151	150	150
LS mean (SD) change from baseline	–2.58 (4.61)	–1.73 (4.71)	–1.98 (4.58)	–0.47 (4.54)
P value[d]	---	0.102	0.229	**< 0.001**
Day 3, N	153	152	151	150
LS mean (SD) change from baseline	–3.58 (5.15)	–2.36 (4.89)	–2.17 (4.92)	–0.98 (5.25)
P value[d]	---	**0.028**	**0.011**	**< 0.001**
Day 4, N	153	152	151	150
LS mean (SD) change from baseline	–3.96 (5.66)	–2.35 (5.09)	–2.54 (5.33)	–1.27 (4.77)
P value[d]	---	**0.008**	**0.019**	**< 0.001**
Day 5, N	153	152	151	150
LS mean (SD) change from baseline	–4.27 (5.71)	–2.55 (5.14)	–3.13 (5.69)	–1.14 (4.84)
P value[d]	---	**0.004**	0.069	**< 0.001**

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Day 6, N	153	152	151	150
LS mean (SD) change from baseline	–4.40 (6.14)	–2.70 (5.33)	–3.00 (5.64)	–1.36 (4.81)
P value[d]	---	**0.007**	**0.034**	**< 0.001**
Day 7, n	153	152	151	150
LS mean (SD) change from baseline	–4.80 (6.23)	–2.94 (5.33)	–3.53 (5.72)	–1.30 (4.98)
P value[d]	---	**0.004**	0.053	**< 0.001**
Day 8, N	153	152	151	150
LS mean (SD) change from baseline	–5.21 (5.81)	–2.93 (5.35)	–3.64 (5.36)	–1.47 (4.62)
P value[d]	---	**< 0.001**	**0.011**	**< 0.001**
Day 9, N	153	152	151	150
LS mean (SD) change from baseline	–5.46 (5.78)	–3.15 (5.25)	–4.00 (5.22)	–1.93 (5.05)
P value[d]	---	**< 0.001**	**0.018**	**< 0.001**
Day 10, n	153	152	151	150
LS mean (SD) change from baseline	–5.25 (6.13)	–2.98 (5.79)	–4.46 (5.36)	–1.64 (5.46)
P value[d]	---	**< 0.001**	0.213	< 0.001
Day 11, N	153	152	151	150
LS mean (SD) change from baseline	–5.48 (6.21)	–3.34 (5.77)	–4.41 (5.80)	–2.06 (5.57)
P value[d]	---	**0.001**	0.109	**< 0.001**
Day 12, N	153	152	151	150
LS mean (SD) change from baseline	–5.60 (6.09)	–3.39 (6.32)	–4.46 (5.85)	–1.80 (5.74)
P value[d]	---	**0.001**	0.080	**< 0.001**
Day 13, N	153	152	151	150
LS mean (SD) change from baseline	–5.76 (6.25)	–3.38 (6.17)	–4.43 (5.97)	–2.23 (5.86)
P value[d]	---	**< 0.001**	**0.048**	**< 0.001**
Day 14, N	153	152	151	150
LS mean (SD) change from baseline	–5.90 (6.03)	–3.54 (6.21)	–4.47 (5.71)	–2.43 (5.65)
P value[d]	---	**< 0.001**	**0.028**	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.

[a] Total number of ITT patients with available data.

[b] LS mean obtained from ANOVA.

[c] Baseline includes TNSS scores over the 7-day lead-in period, including day 1 a.m. Overall includes TNSS scores from day 1 p.m. to day 14 a.m.

[d] *P* value for between-treatment group comparison was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate.

Source: Table 14.2.6.2, MP4001 Clinical Study Report.

TABLE 32: CHANGE FROM BASELINE IN 4-HOUR INSTANTANEOUS TNSS: ONSET OF ACTION (ITT POPULATION) — STUDY MP4002

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	207	208	207	209
LS mean[b] (SD)	9.32 (1.35)	9.60 (1.36)	9.51 (1.36)	9.46 (1.31)
15 minutes, N	207	208	207	209
LS mean (SD) change from baseline	–1.12 (1.95)	–1.01 (2.06)	–1.31 (1.85)	–1.08 (1.72)
P value[c]	---	0.572	0.309	0.814
30 minutes, N	207	208	207	209
LS mean (SD) change from baseline	–2.01 (2.21)	–1.88 (2.28)	–2.03 (2.04)	–1.68 (1.94)
P value[c]	---	0.559	0.920	0.108
45 minutes, N	207	208	207	209
LS mean (SD) change from baseline	–2.78 (2.42)	–2.51 (2.47)	–2.59 (2.20)	–2.27 (2.09)
P value[c]	---	0.260	0.398	**0.021**
60 minutes, N	207	208	207	209
LS mean (SD) change from baseline	–3.29 (2.61)	–2.97 (2.61)	–3.02 (2.37)	–2.75 (2.21)
P value[c]	---	0.204	0.257	**0.021**
90 minutes, N	207	208	207	209
LS mean (SD) change from baseline	–3.80 (2.76)	–3.53 (2.81)	–3.38 (2.60)	–3.10 (2.35)
P value[c]	---	0.299	0.102	**0.005**
120 minutes, N	207	208	206	209
LS mean (SD) change from baseline	–4.12 (2.79)	–4.10 (2.90)	–3.87 (2.65)	–3.43 (2.47)
P value[c]	---	0.947	0.342	**0.007**
240 minutes, N	206	207	207	209
LS mean (SD) change from baseline	–5.01 (3.03)	–4.95 (2.98)	–4.60 (3.03)	–3.94 (2.68)
P value[c]	---	0.825	0.146	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.

[a] Total number of ITT patients with available data.

[b] LS mean obtained from ANOVA.

[c] *P* value for between-treatment group comparison, except baseline, was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate allowing for heterogeneous variances. For baseline, the *P* value was based on an ANOVA model containing treatment group and site as fixed effects.

Source: Table 14.2.6.2 (p. 167 to 170) of MP4002 Clinical Study Report.

TABLE 33: CHANGE FROM BASELINE IN 4-HOUR INSTANTANEOUS TNSS: ONSET OF ACTION (ITT POPULATION) — STUDY MP4004

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	192	192	187	200
LS mean[b] (SD)	9.51 (1.36)	9.57 (1.37)	9.49 (1.37)	9.63 (1.41)
15 minutes, N	192	192	187	199
LS mean (SD) change from baseline	–1.20 (1.90)	–1.49 (2.19)	–1.55 (2.00)	–1.20 (1.86)
P value[c]	---	0.156	0.072	0.993
30 minutes, N	192	192	186	199
LS mean (SD) change from baseline	–2.27 (2.27)	–2.30 (2.51)	–2.02 (2.29)	–1.80 (2.04)
P value[c]	---	0.915	0.279	**0.032**
45 minutes, N	192	192	187	199
LS mean (SD) change from baseline	–2.98 (2.60)	–3.02 (2.56)	–2.68 (2.45)	–2.34 (2.23)
P value[c]	---	0.889	0.229	**0.008**
60 minutes, N	192	192	187	198
LS mean (SD) change from baseline	–3.62 (2.75)	–3.46 (2.79)	–3.20 (2.69)	–2.98 (2.46)
P value[c]	---	0.569	0.123	**0.016**
90 minutes, N	191	192	187	198
LS mean (SD) change from baseline	–4.00 (2.82)	–3.88 (2.74)	–3.70 (2.77)	–3.28 (2.61)
P value[c]	---	0.664	0.275	**0.009**
120 minutes, N	192	192	187	199
LS mean (SD) change from baseline	–4.39 (2.67)	–4.52 (2.68)	–3.96 (2.81)	–3.62 (2.70)
P value[c]	---	0.634	0.110	**0.005**
240 minutes, N	192	190	185	199
LS mean (SD) change from baseline	–5.21 (3.06)	–5.23 (2.86)	–4.81 (3.04)	–4.23 (3.06)
P value[c]	---	0.924	0.189	**0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.

[a] Total number of ITT patients with available data.

[b] LS mean obtained from ANOVA.

[c] *P* value for between-treatment group comparison, except baseline, was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate allowing for heterogeneous variances. For baseline, the *P* value was based on an ANOVA model containing treatment group and site as fixed effects.

Source: Table 14.2.6.2, MP4004 Clinical Study Report.

TABLE 34: CHANGE FROM BASELINE IN 4-HOUR INSTANTANEOUS TNSS: ONSET OF ACTION (ITT POPULATION) – STUDY MP4006

Time Point	AZE/FP	Azelastine	Fluticasone	Placebo
Baseline, N[a]	445	444	450	447
LS mean[b] (SD)	9.65 (1.37)	9.59 (1.42)	9.64 (1.40)	9.55 (1.35)
15 minutes, N	444	443	448	446
LS mean (SD) change from baseline	–1.41(2.13)	–1.24 (1.96)	–1.30 (1.83)	–1.26 (1.88)
P value[c]	---	0.180	0.386	0.240
30 minutes, N	444	443	449	446
LS mean (SD) change from baseline	–2.20 (2.37)	–2.14 (2.34)	–1.91 (2.08)	–1.83 (2.08)
P value[c]	---	0.666	**0.037**	**0.008**
45 minutes, N	444	441	449	446
LS mean (SD) change from baseline	–2.87 (2.48)	–2.70 (2.43)	–2.51 (2.24)	–2.37 (2.21)
P value[c]	---	0.269	**0.014**	**< 0.001**
60 minutes, N	443	441	448	446
LS mean (SD) change from baseline	–3.40 (2.68)	–3.31 (2.55)	–3.07 (2.43)	–2.86 (2.40)
P value[c]	---	0.571	**0.038**	**< 0.001**
90 minutes, N	443	442	448	446
LS mean (SD) change from baseline	–3.80 (2.83)	–3.79 (2.60)	–3.37 (2.57)	–3.19 (2.45)
P value[c]	---	0.989	**0.013**	**< 0.001**
120 minutes, N	442	442	449	446
LS mean (SD) change from baseline	–4.15 (2.79)	–4.15 (2.72)	–3.78 (2.63)	–3.48 (2.54)
P value[c]	---	0.982	**0.032**	**< 0.001**
240 minutes, N	444	441	449	444
LS mean (SD) change from baseline	–5.01 (3.01)	–4.98 (2.93)	–4.54 (2.92)	–4.09 (2.90)
P value[c]	---	0.848	**0.013**	**< 0.001**

ANCOVA = analysis of covariance; ANOVA = analysis of variance; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; ITT = intention-to-treat; LS = least-squares; SD = standard deviation; TNSS = total nasal symptom score.
[a] Total number of ITT patients with available data.
[b] LS mean obtained from ANOVA.
[c] *P* value for between-treatment group comparison, except baseline, was based on an ANCOVA model containing treatment group and site as fixed effects and baseline as a covariate allowing for heterogeneous variances. For baseline, the *P* value was based on an ANOVA model containing treatment group and site as fixed effects.
Source: Table 14.2.6.2 (p. 193 to 198) of MP4006 Clinical Study Report.

TABLE 35: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE INDIVIDUAL OCULAR SYMPTOM SCORES OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — STUDY MP4002

Comparison	LS Mean Difference (95% CI); *P* Value		
	Itchy Eyes	Watery Eyes	Eye Redness
AZE/FP vs. placebo	–0.52 (–0.74 to –0.30); **< 0.001**	–0.40 (–0.62 to –0.17); **< 0.001**	–0.33 (–0.55 to –0.12); **0.002**
AZE/FP vs. azelastine	–0.07 (–0.31 to 0.17); 0.587	–0.08 (–0.31 to 0.16); 0.538	–0.13 (–0.37 to 0.09); 0.241
AZE/FP vs. fluticasone	–0.25 (–0.48 to –0.02); **0.031**	–0.11 (–0.34 to 0.12); 0.361	–0.12 (–0.34 to 0.08); 0.237

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; ITT = intention-to-treat; LS = least-squares; vs. = versus.
Source: Table 23 (p. 58) of MP4002 Clinical Study Report.

TABLE 36: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE INDIVIDUAL OCULAR SYMPTOM SCORES OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — STUDY MP4004

Comparison	LS Mean Difference (95% CI); *P* Value		
	Itchy Eyes	Watery Eyes	Eye Redness
AZE/FP vs. placebo	–0.58 (–0.82 to –0.34); **< 0.001**	–0.56 (–0.79 to –0.34); **< 0.001**	–0.45 (–0.66 to –0.23); **< 0.001**
AZE/FP vs. azelastine	–0.19 (–0.44 to 0.05); 0.126	–0.26 (–0.50 to –0.03); **0.026**	–0.17 (–0.39 to 0.05); 0.125
AZE/FP vs. fluticasone	–0.36 (–0.62 to –0.12); **0.004**	–0.38 (–0.63 to –0.14); **0.002**	–0.16 (–0.38 to 0.07); 0.180

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; ITT = intention-to-treat; LS = least-squares vs. = versus.
Source: Table 24 (p. 59) of MP4004 Clinical Study Report.

TABLE 37: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE INDIVIDUAL OCULAR SYMPTOM SCORES OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — STUDY MP4006

Comparison	LS Mean Difference (95% CI); *P* Value		
	Itchy Eyes	Watery Eyes	Eye Redness
AZE/FP vs. placebo	–0.41 (–0.58 to –0.25); **< 0.001**	–0.40 (–0.55 to –0.23); **< 0.001**	–0.31 (–0.46 to –0.16); **< 0.001**
AZE/FP vs. azelastine	–0.03 (–0.19 to 0.13); 0.723	–0.05 (–0.21 to 0.12); 0.619	0.01 (–0.14 to 0.17); 0.873
AZE/FP vs. fluticasone	–0.10 (–0.26 to 0.06); 0.217	–0.08 (–0.23 to 0.09); 0.372	–0.08 (–0.23 to 0.07); 0.279

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; ITT = intention-to-treat; LS = least-squares vs. = versus.
Source: Table 22 (p. 58) of MP4006 Clinical Study Report.

TABLE 38: CHANGE FROM BASELINE IN 12-HOUR REFLECTIVE INDIVIDUAL OCULAR SYMPTOM SCORES OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED (ITT POPULATION) — STUDY MP4001

Comparison	LS Mean Difference (95% CI); *P* Value		
	Itchy Eyes	Watery Eyes	Eye Redness
AZE/FP vs. placebo	–0.79 (–1.04 to –0.54); **< 0.001**	–0.61 (–0.86 to –0.35); **< 0.001**	–0.73 (–0.96 to –0.49); **< 0.001**
AZE/FP vs. azelastine	–0.35 (–0.63 to –0.08); **0.013**	–0.15 (–0.43 to 0.13); 0.292	–0.29 (–0.55 to –0.02); **0.037**
AZE/FP vs. fluticasone	–0.53 (–0.79 to –0.26); **< 0.001**	–0.31 (–0.59 to –0.05); **0.022**	–0.39 (–0.65 to –0.12); **0.004**

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; ITT = intention-to-treat; LS = least-squares; vs. = versus.
Source: Tables 14.2.13.1, 14.2.13.2, 14.2.13.3, 14.2.14.1, 14.2.14.2, 14.2.14.3 of MP4001 Clinical Study Report.

TABLE 39: CHANGE FROM BASELINE IN REFLECTIVE TNSS OVER THE 14-DAY TREATMENT PERIOD: A.M. AND P.M. COMBINED, POOLED ITT POPULATION BY AGE — MP4002, MP4004, MP4006, AND MP4001

Comparison	Treatment Difference, LS Mean (95% CI)		
	12 to < 18 years (N = 393)	18 to < 65 years (N = 3491)	≥ 65 years (N = 115)
AZE/FP vs. placebo	–2.22 (–3.23 to –1.22); **< 0.0001**	–2.40 (–2.81 to –1.99); **< 0.0001**	–3.42 (–6.12 to –0.71); **0.0144**
AZE/FP vs. azelastine	–1.79 (–2.88 to –0.69); **0.0015**	–1.02 (–1.45 to –0.60); **< 0.0001**	–2.54 (–5.19 to 0.12); 0.0604
AZE/FP vs. fluticasone	–0.98 (–2.08 to 0.13); **0.0819**	–0.86 (–1.28 to –0.44); **< 0.0001**	–3.42 (–6.55 to –0.29); **0.0328**

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; CI = confidence interval; ITT = intention-to-treat; LS = least-squares.
Source: Table 17, p. 51 of US Food and Drug Administration Clinical Review;[23] and Table 5, p. 111 of Health Canada Pharmaceutical Safety and Efficacy Assessment.[2]

TABLE 40: ADVERSE EVENTS (SAFETY POPULATION)

	Study MP4002			
	AZE/FP (N = 207)	Azelastine (N = 208)	Fluticasone (N = 207)	Placebo (N = 210)
Treatment-emergent AEs, n (%)	30 (14.5)	26 (12.5)	32 (15.5)	24 (11.4)
Treatment-related AEs, n (%)	17 (8.2)	16 (7.7)	14 (6.8)	8 (3.8)
Dysgeusia	5 (2.4)	7 (3.4)	2 (1.0)	1 (0.5)
Epistaxis	2 (1.0)	4 (1.9)	5 (2.4)	2 (1.0)
Headache	1 (0.5)	1 (0.5)	5 (2.4)	3 (1.4)
Somnolence	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Mucosal erosion	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Infections	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AEs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation, n (%)	4 (1.9)	1 (0.5)	0 (0.0)	1 (0.5)
Patients with TRAEs by maximum severity, n (%)				
Mild	10 (4.8)	8 (3.8)	10 (4.8)	6 (2.9)

Study MP4002				
	AZE/FP (N = 207)	Azelastine (N = 208)	Fluticasone (N = 207)	Placebo (N = 210)
Moderate	6 (2.9)	6 (2.9)	4 (1.9)	1 (0.5)
Severe	1 (0.5)	2 (1.0)	0 (0.0)	1 (0.5)
Study MP4004				
	AZE/FP (N = 195)	Azelastine (N = 194)	Fluticasone (N = 189)	Placebo (N = 200)
Treatment-emergent AEs, n (%)	31 (15.9)	35 (18.0)	24 (12.7)	20 (10.0)
Treatment-related AEs, n (%)	20 (10.3)	29 (14.9)	10 (5.3)	9 (4.5)
Dysgeusia	4 (2.1)	14 (7.2)	1 (0.5)	1 (0.5)
Epistaxis	3 (1.5)	3 (1.6)	3 (1.6)	5 (2.5)
Headache	5 (2.6)	4 (2.1)	4 (2.1)	1 (0.5)
Somnolence	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Mucosal erosion	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Serious AEs, n (%)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation, n (%)	3 (1.5)	1 (0.5)	1 (0.5)	3 (1.5)
Patients with TRAEs by maximum severity, n (%)				
Mild	16 (8.2)	17 (8.8)	7 (3.7)	7 (3.5)
Moderate	3 (1.5)	9 (4.6)	3 (1.6)	2 (1.0)
Severe	1 (0.5)	3 (1.5)	0 (0.0)	0 (0.0)
Study MP4006				
	AZE/FP (N = 451)	Azelastine (N = 449)	Fluticasone (N = 450)	Placebo (N = 451)
Treatment-emergent AEs, n (%)	75 (16.6)	63 (14.0)	55 (12.2)	55 (12.2)
Treatment-related AEs, n (%)	50 (11.1)	45 (10.0)	28 (6.2)	18 (4.0)
Dysgeusia	21 (4.7)	23 (5.1)	1 (0.2)	0 (0.0)
Epistaxis	8 (1.8)	5 (1.1)	5 (1.1)	8 (1.8)
Headache	6 (1.3)	9 (2.0)	6 (1.3)	2 (0.4)
Somnolence	5 (1.1)	2 (0.4)	0 (0.0)	1 (0.2)
Mucosal erosion	2 (0.4)	0 (0.0)	5 (1.1)	1 (0.2)
Infections	3 (0.7)	0 (0.0)	1 (0.2)	1 (0.2)
Serious AEs, n (%)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to discontinuation, n (%)	3 (0.7)	4 (0.9)	3 (0.7)	5 (1.1)
TRAEs by maximum severity, n (%)				
Mild	34 (7.5)	33 (7.3)	25 (5.6)	16 (3.5)
Moderate	15 (3.3)	12 (2.7)	3 (0.7)	2 (0.4)
Severe	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

AE = adverse event; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; TRAE = treatment-related adverse event.
Source: MP4002: Table 28 (p. 65), Table 30 (p. 67), and Table 14.3.1.7 (p. 318) of Clinical Study Report (CSR); MP4004: Table 28 (p. 66), Table 30 (p. 68), and Table 14.3.1.7 of CSR; MP4006: Table 27 (p. 65), Table 29 (p. 67), and Table 14.3.1.7 (p. 408) of CSR (pooled data of MP4002, MP4004, and MP4006: done by CADTH clinical reviewer). MP4001: Table 22 (p. 63), Table 24 (p. 65), and Table 14.3.1.7 of CSR.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To provide background information on and to summarize the validity of the following outcome measures included in randomized controlled trials in this review:

- Total nasal symptom score (TNSS)
- Total ocular symptom score (TOSS)
- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

Findings

The reviewed symptom and quality of life outcome measures are well established and comprise the gold standard for assessment of allergic rhinitis (AR) treatment. The minimal clinically important difference (MCID) is well established for the RQLQ but there is no accepted MCID for symptom scores.

Allergic Rhinitis Symptom Scores

Total Nasal Symptom Score

The reflective TNSS is the efficacy outcome recommended by Health Canada and the US Food and Drug Administration for seasonal AR (SAR) clinical development trials.[30] This score is a composite of four individual nasal symptoms (rhinorrhea, nasal congestion, nasal itching, sneezing). Individual scores of a maximum of 3 (Likert scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe) for each symptom contribute to a total maximum score of 12. An instantaneous (i.e., immediate) or reflective (over a set time period; e.g., 12 hours) score can be calculated. The reflective score can be assessed over 24 hours (i.e., a.m. and p.m.) for a combined maximum score of 24. The validity of the TNSS has not been formally assessed.

The MCID for the TNSS is unclear. A range of values have been proposed (Table 41). A report by the Agency for Healthcare Research and Quality (AHRQ) used a 30% MCID value based on concordance between empirical evidence[31] and expert opinion, but the authors commented that there is a lack of a well-defined MCID for symptom scales and suggested identification of an MCID as a research priority.[32] With regard to the 30% MCID used by the AHRQ, the manufacturer commented in its submission that "it is clear that this could apply only to individual patient responses" and that "this criterion is clearly too wide to compare means."[30] They propose that the use of this value would result in all active treatments being equivalent in efficacy to placebo.[30]

Total Ocular Symptom Score

The TOSS is a three-item scale used to collectively assess three symptoms of AR including tearing, itching or burning, and redness). The validity of this score has not been formally assessed. A collective score of 3 possible points per item for a total out of 9 is calculated. The validity of this scale has not been assessed. Similarly, MCID values have not been formally assessed. Experts involved in the generation of the AHRQ report proposed a 30% change to be clinically relevant.[32] This would require a change of 3 points on the 9-point scale (Table 41).

Other Combined Scoring Approaches

The four nasal symptoms of TNSS and two of three ocular symptoms (excluding eye redness) of the TOSS can be combined for the rhinitis total symptom score (RTSS). Alternatively, others have termed this approach the total symptom score with six individual symptoms (T6SS), and have further excluded an additional ocular symptom for the total symptom score with five individual symptoms (T5SS).[33] None of these measures were used in the trials assessed for this review. The MCIDs for these values are presented in Table 41.

TABLE 41: SUMMARY OF PROPOSED MINIMALLY CLINICALLY IMPORTANT DIFFERENCES FOR SYMPTOM SCORES

First Author, Publication Year	Analytical Method	MCID	Scale
TNSS			
Barnes, 2006[34] and 2010[35]	Distribution-based approach	0.59	0 to 12 interval
	Anchor-based approach	0.28	0 to 12 interval
Bousquet, 2009[31]	Responsiveness of VAS to interval scale	2.9	0 to 12 VAS
Malling, 2003[36]	Allergen-specific immunotherapy recommendation	30%[a]	Any scale
AHRQ, 2013[32]	Technical expert panel input (clinical opinion)	2 to 4	0 to 12 interval
TOSS			
AHRQ, 2013[32]	Expert input (clinical opinion)	3	0 to 9 interval
Individual Nasal Symptoms			
AHRQ, 2013[32]	Expert input (clinical opinion)	1	0 to 3 interval
RTSS			
Devillier, 2014[37]	Anchor-based approach (compared against GRCS and RQLQ) in 806 patients with grass pollen–induced AR (children, adolescents, and adults)	1.1 to 1.3	0 to 18 interval (RTSS)
Other Composite Scores of Nasal and Ocular Symptoms			
Higaki, 2013[33]	Anchor-based approach (compared against the JRQLQ) in 55 adult patients exposed to Japanese cedar pollen.	3.6	0 to 18 interval (T6SS[b])
		1.5	0 to 15 interval (T5SS[c])

AHRQ = Agency for Healthcare Research and Quality; AR = allergic rhinitis; GRCS = global rating of change scale; JRQLQ = Japanese Rhinoconjunctivitis Quality of Life Questionnaire; MCID = minimal clinically important difference; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; RTSS = rhinitis total symptom score; TNSS = total nasal symptom score; TOSS = total ocular symptom score; VAS = visual analogue scale.

Note: MCIDs have been partially adapted from the AHRQ report.[32]

[a] A 30% greater improvement compared with placebo in composite symptom or rescue medication use scores was proposed as minimally clinically meaningful.

[b] Total symptom score with 6 individual nasal and ocular symptoms (including all nasal symptoms).

[c] Total symptom score with 5 individual nasal and ocular symptoms (including all nasal symptoms).

Rhinoconjunctivitis Quality of Life Questionnaire

The RQLQ is an AR-specific self-administered questionnaire that serves to measure the impact of AR on day-to-day life.[38] It contains 28 questions in seven domains. These domains include Activity Limitation (three questions), Sleep Problems (three questions), Nose Symptoms (four questions), Eye Symptoms (four questions), Non-nose/Eye Symptoms (seven questions), Practical Problems (three questions), and Emotional Function (four questions). Scores for each question range from 0 (not troubled/none of the time) to 6 (extremely troubled/all of the time). The overall RQLQ score is the mean of all 28 responses, and the individual domain scores are the means of the questions in each domain — both range from 0 to 6. The RQLQ has been validated in adult patients with seasonal and perennial rhinoconjunctivitis.[25] The MCID is well established as 0.5 for the overall or individual domain scores.[26] Other versions of the RQLQ (including a standardized questionnaire, electronic, mini, and adolescent- and pediatric-specific versions) have been developed and validated, but the standard version of the RQLQ was used for all assessments in this review. Alternate MCID values (0.4 to 0.7)[35,39] have been proposed for the mini RQLQ.

Conclusion

Recommended and universally accepted outcome measures for SAR assessment in clinical trials include total nasal and ocular symptom scores to assess symptoms and the RQLQ to assess quality of life. There is a paucity of data on the validity of symptom scores. The appropriate MCID for AR symptom scores is unclear, although many possibilities have been proposed. The RQLQ is well established and has been well validated. The MCID for this questionnaire is 0.5.

APPENDIX 6: SUMMARY OF COMPARATIVE EFFICACY OF AZELASTINE VERSUS OTHER ANTIHISTAMINES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize the comparative clinical efficacy of azelastine nasal spray (AZE) versus other oral and intranasal antihistamines in the treatment of seasonal allergic rhinitis (SAR).

Key Findings

Based on limited evidence, there is no difference in the efficacy of intranasal antihistamines and AZE, but greater efficacy of AZE versus oral antihistamines in patients with SAR. Trends toward higher rates of somnolence with the use of oral antihistamines and higher rates of taste disturbance with the use of AZE were observed, but this was inconsistent across trials.

Background

Azelastine was approved in the United States in 1996,[40] but has not yet been approved in Canada. Therefore, it is of interest to understand the comparative clinical efficacy of azelastine versus antihistamine (intranasal and oral) products currently approved for use in Canada. There is particular interest in the comparative efficacy of AZE and levocabastine, as cost data for levocabastine were used in the manufacturer's economic submission due to the absence of Canadian cost data for AZE. As such, the results are presented for studies comparing AZE and levocabastine, followed by studies comparing AZE and other antihistamines.

Methods

A limited PubMed search of English-language articles was conducted from January 2010 to January 2015. Of 84 potentially relevant articles, three studies met the inclusion criteria. A further eight relevant studies outside of the date range were identified from reference lists. Overall, 11 studies were included in this summary. Two studies conducted in patients with perennial AR (PAR) as opposed to SAR were included.[41,42] Despite noted differences between SAR and PAR, studies on both populations were included due to the potential for co-presentation.[43] All trials comparing AZE with terfenadine were excluded, as this drug has been withdrawn from the market. One meta-analysis was identified[44] that compared AZE nasal spray to active comparators including oral and intranasal antihistamines and intranasal corticosteroids. Studies in the meta-analysis were pooled to compare AZE with any active comparator, but no subgroup analysis was conducted on antihistamines; therefore, this study was excluded and individual trials comparing AZE with antihistamines are presented.

Summary of Study Characteristics

Study characteristics and outcomes are summarized in Table 42. All studies were randomized controlled trials. Two short-term studies had a crossover design.[45,46] Three trials compared azelastine with levocabastine.[41,47,48] Azelastine nasal spray plus fluticasone nasal spray (FNS; separate treatment components) was compared with olopatadine nasal spray plus FNS.[49] The remaining trials compared AZE nasal spray alone with oral cetirizine,[42,45,50-52] olopatadine nasal spray,[53] oral desloratadine,[46] and oral loratadine.[45] Trial duration ranged from six hours[45] to 14 days.[45,49]

TABLE 42: SUMMARY OF STUDY CHARACTERISTICS FOR ALL TRIALS

Author, Publication Year, Country	Population, Sample Size	Study Design	Study Duration	Azelastine Group, Sample Size	Comparator, Sample Size
Livostin (Levocabastine)					
Perennial AR					
Han,[41] 2011, China	Patients (aged 18 to 65 years) with moderate-to-severe perennial AR, n = 75 *Note: Patients with SAR excluded*	Randomized, double-blind, placebo-controlled, parallel-group, multi-centre study	14 days	AZE (0.1%) nasal spray (1 spray twice daily [0.56 mg]), n = 112	Levocabastine hydrochloride (0.05%) nasal spray (2 sprays twice daily [0.40 mg/day]), n =112
SAR					
Mosges,[47] 1995, Germany and Belgium	Patients (aged 12 to 70 years) with clinically confirmed SAR, n = 242	Randomized, open-label, parallel-group, multi-centre study	7 days	AZE nasal spray (1 mg/mL, 1 puff twice daily), n = 119	Levocabastine nasal spray (0.5 mg/mL, 2 puffs twice daily), n = 123
Falser,[48] 2001, Germany	Patients (aged 18 to 65 years) with clinically confirmed SAR, n = 179 (intention-to-treat)	Randomized, double-blind, placebo-controlled, parallel-group, single-centre study	28 days	AZE nasal spray (0.14 mg/spray, 2 puffs twice daily [1.12 mg daily]), n = 89	Levocabastine hydrochloride nasal spray (0.05 mg/spray, 2 puffs twice daily [0.4 mg/day]), n = 90
Other Comparators					
Perennial AR					
Passali,[42] 1994, Italy	Patients (19 to 65 years) with 3- to 20-year history of perennial allergic rhinitis, n = 37 (per-protocol analysis)	Randomized, double-blind, double-dummy, parallel-group, single-centre study	8 weeks	AZE nasal spray (0.14 mg/spray, 2 puffs twice daily), n = 19	Oral cetirizine (10 mg) once daily, n = 18
SAR					
Ellis,[45] 2013, Canada	Patients (aged 18 to 65 years) with a 2-season history of clinically confirmed SAR exposed to pollen in an environmental exposure unit, n = 70 (intention-to-treat analysis), n = 66 (per-protocol analysis)	Randomized, double-blind, placebo-controlled, double-dummy, single-centre, 4-way crossover study (13-day washout between sessions)	8 hours	AZE nasal spray plus oral placebo, n = 66	Oral cetirizine plus placebo nasal spray, n = 66 Oral loratadine plus placebo nasal spray, n = 66

Author, Publication Year, Country	Population, Sample Size	Study Design	Study Duration	Azelastine Group, Sample Size	Comparator, Sample Size
LaForce,[49] 2010, US	Patients ≥ 12 years with 2-year history of clinically confirmed SAR, n = 135 (per-protocol analysis)	Randomized, double-blind, parallel-group, multi-centre study	14 days	AZE nasal spray (0.1%) + FNS (50 mcg) 2 sprays twice daily, n = 68	OLO nasal spray (0.6%) + FNS (50 mcg) 2 sprays twice daily, n = 67
Shah,[53] 2009, US	Patients ≥ 12 years with 2-year history of clinically confirmed SAR, n = 544 (per-protocol analysis)	Randomized, double-blind, placebo-controlled, parallel-group, multi-centre study	4 to 14 days	AZE nasal spray (0.1%) 2 sprays twice daily, n = 188	OLO nasal spray (0.6%) 2 sprays twice daily, n = 180
Berger,[50] 2006, US	Patients ≥ 12 years with 2-year history of clinically confirmed SAR, n = 342 (efficacy analysis)	Randomized, double-blind, parallel-group, multi-centre study	14 days	AZE nasal spray 2 sprays twice daily + oral placebo, n = 179	Oral cetirizine (10 mg) + placebo nasal spray, n = 175
Horak,[46] 2006	Patients (aged 18 to 55 years) with 2-year history of clinically confirmed SAR, n = 45 (per-protocol analysis)	Randomized, double-blind, placebo-controlled, double-dummy, single-centre, 3-way crossover study (12-day washout between sessions)	6 hours (treatment administered at hour 2)	AZE nasal spray (0.28 mg) 1 puff per nostril plus placebo tablet, n = 45	Oral desloratadine (5 mg) plus placebo nasal spray, n = 45
Corren,[52] 2005, US	Patients (≥ 12 years) with 2-year history of clinically confirmed SAR, n = 306 (efficacy analysis)	Randomized, double-blind, parallel-group, multi-centre study	14 days	AZE nasal spray (2 sprays twice daily) + oral placebo, n = 152	Oral cetirizine (10 mg) + placebo nasal spray, n = 155
Charpin,[51] 1995, France	Patients (12 to 60 years) with clinically confirmed SAR, n = 129 (efficacy analysis)	Randomized, double-blind, parallel-group, multi-centre study	14 days	AZE nasal spray twice daily (0.56 mg/day) + oral placebo, n = NR	Oral cetirizine (10 mg) + placebo nasal spray, n = NR

AR = allergic rhinitis; AZE = azelastine; FNS = fluticasone nasal spray; NR = not reported; OLO = olopatadine; SAR = seasonal allergic rhinitis.

Summary of Findings

Livostin (Levocabastine)

Efficacy

Detailed outcomes for trials comparing AZE and levocabastine nasal sprays are presented in Table 43. The two trials comparing AZE and levocabastine in SAR patients reported similar mean changes in total nasal symptom score (TNSS) and total symptom score (TSS) for both treatment groups.[47,48] Both studies reported similar proportions of good or very good physician-assessed therapeutic efficacy scores for both treatments.[47,48] One trial[47] reported similar proportions of excellent or good patient-assessed therapeutic efficacy scores, patient-reported relief of symptoms at 30 minutes, and symptom-free days in both treatment groups.

The single trial comparing treatments in PAR[41] reported no difference in mean change in TNSS between groups. However, the proportion of patients achieving symptom relief at 15 and 30 minutes was higher in the levocabastine group.[41] Onset of action for both groups was similar at two hours. Patient- and investigator-assessed therapeutic effect and total effective rate were not different between groups.[41]26

TABLE 43: SUMMARY OF EFFICACY DATA FOR LEVOCABASTINE TRIALS

	Azelastine	Levocabastine	*P* Value
SAR			
Mosges,[47] 1995, Germany and Belgium	**n = 119**	**n = 123**	
Mean Δ in TNSS from baseline Mean Δ in TSS from baseline	–3.2 –3.8	–3.1 –3.6	NS
Patient-assessed therapeutic efficacy (excellent or good)	61%	68%	NR
Investigator-assessed therapeutic efficacy (excellent or good)	63%	70%	NR
Patient-reported relief of symptoms within 30 minutes of drug application	54%	53%	NR
Symptom-free days[a]	9%	7%	NR
Falser,[48] 2001, Germany	**n = 89**	**n = 90**	
Mean Δ in TSS from baseline	–14.5	–11.9	NR
Mean Δ in nasal symptom sum score (sum of sneezing, itching of the nose, and rhinorrhea) at 4 weeks	–6.1	–5.0	NR
Physician-scored global efficacy assessment (good or very good)	90%	74%	NR
PAR			
Han,[41] 2011, China	**n = 122**	**n = 122**	
Mean Δ in TNSS from baseline (95% CI)	–3.21 (2.13)	–2.90 (1.90)	NS
Onset of action: 15 minutes 30 minutes 2 hours	 41% 65% 92%	 59% 80% 90%	 < 0.05 < 0.05 NR[b]
Patient-reported evaluation of therapeutic effect (positive)	91%	88%	NS
Investigator-reported evaluation of therapeutic effect (positive)	92%	95%	NS

	Azelastine	Levocabastine	*P* Value
Total effective rate	104 (93%)	103 (92%)	NR[b]

CI = confidence interval; Δ = treatment difference; PAR = perennial allergic rhinitis; NR = not reported; NS = not significant; SAR = seasonal allergic rhinitis; TNSS = total nasal symptom score, TSS = total symptom score.
[a] Based on investigator- and patient-assessed nasal and ocular symptoms.
[b] Reported in text as no significant differences between groups; no *P* values presented.

Safety

The two trials in SAR patients[47,48] reported good tolerance overall, with very low occurrence of serious adverse events (SAEs)[48] and withdrawal due to adverse events (WDAEs).[47] One study[47] reported a slightly higher AE rate in the AZE group, whereas another study[48] reported higher incidence of AE in the levocabastine group (significance not reported) with a significantly higher proportion of patients and investigators rating tolerance as very good or good in the AZE group. Mosges et al.[47] reported higher rates of taste disturbance in the AZE group.

The single PAR trial[41] reported no difference in the rate of AE, SAE, medication-related AE, and WDAE between groups and low AE rates overall (Table 44).

TABLE 44: SUMMARY OF SAFETY DATA FOR LEVOCABASTINE TRIALS

	Azelastine Group	Levocabastine	*P* Value
SAR			
Mosges,[47] 1995, Germany and Belgium	**n = 119**	**n = 123**	
Overall AE (%)	19.5%	10.8%	0.06
WDAE (%)	2.5%	< 1%	NR
Taste disturbances (%)	5%	0%	0.01
Falser,[48] 2001, Germany	n = 89	n = 90	
AE,[a] n	2	20	NR
Severe AE, n	1	19	NR
SAE, n	0	0	NR
% patient-rated tolerance (very good or good)	98%	70%	< 0.001
% patient-rated tolerance (insufficient)	1%	19%	NR
Investigator-rated tolerance (very good or good)	98%	78%	< 0.001
PAR			
Han,[41] 2011, China	**n = 112**	**n = 112**	
Overall (%)	3.3%	2.6%	NR*
Medication-related AE (%)	2.5%	0.9%	NR*
SAE (%)	0%	0%	NR*
WDAE (%)	0%	0%	NR*

AE = adverse event; NR = not reported; PAR = perennial allergic rhinitis; SAE = serious adverse event; SAR = seasonal allergic rhinitis; WDAE = withdrawal due to adverse event.
Note: Data reported as no significant differences between groups.
[a] All related to nasal symptoms.

Other Antihistamines

Detailed efficacy outcome data are presented for short-term trials of AZE versus oral antihistamines and longer-term trials of azelastine versus olopatadine nasal spray and oral antihistamines in Table 45 and Table 46, respectively. Safety data can be found in Table 47.

Olopatadine Hydrochloride[49]

Efficacy

Azelastine and FNP taken separately was not reported to be superior to OLO and FNP taken separately at reducing reflective TNSS (rTNSS) and instantaneous TNSS (iTNSS) over two weeks.[49] One trial reported that AZE was not superior to OLO for reduction of rTNSS and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score.[53]

Safety

Trials comparing AZE (with and without FNP separate therapy) to OLO (with and without FNP separate therapy)[49,53] reported good tolerability with no difference in overall AE, SAE, and severe AE (*P* values not reported).[49] One trial[53] reported higher rates of bitter taste in the AZE group (*P* = 0.05).

Oral Antihistamines[45]

Efficacy

Two short-term (≤ 1 day) trials conducted in environmental exposure units reported that azelastine was more effective than oral antihistamines (Table 45).[45,46] The Canadian study[45] reported superior efficacy of AZE nasal spray compared with oral cetirizine from 15 to 60 minutes post-dose (95% confidence interval [CI], ≤ –0.2) and compared with loratadine from 15 minutes to five hours post-dose (95% CI, ≤ –0.1). Overall efficacy was similar for AZE nasal spray and oral cetirizine[45] and greater for AZE nasal spray than oral loratadine[45] and oral desloratadine[46] (significance not reported). One trial reported earlier onset of action for AZE nasal spray versus oral desloratadine.[46]

TABLE 45: SUMMARY OF EFFICACY DATA FOR SHORT-TERM TRIALS

	Azelastine[a]	Comparator		*P* value
Ellis,[45] 2013, Canada	**AZE** n = 66	**Cetirizine** n = 66	**Loratadine** n = 66	
Mean Δ in TNSS from baseline	–1.5 to –4.3	–0.8 to –3.8	–0.7 to –3.4	NR
Patient-reported overall assessment of efficacy (good or very good)[b]	30*	34*	20†	NA
Horak,[46] 2006, Austria	**AZE** n = 45	**Desloratadine** n = 45		
MNSS Mean treatment difference at 4 to 6 hours (AZE vs. desloratadine)	-0.9 ± 2.1[c]	NA		0.005
Onset of action (minutes)	15	150		
Overall assessment of efficacy (% at least satisfactory rating)	73.9%	55.6%		NR

AZE = azelastine; Δ = treatment difference; MNSS = major nasal symptom score; NA = not applicable; NR = not reported; TNSS = total nasal symptom score.

Note: Placebo comparison data not included. See reference text for details.[45]

[a] Four-way crossover. Sample size for all groups, n = 66.

[b] Symbols indicate statistically significant groups at *P* < 0.05.

[c] Azelastine versus desloratadine.

For longer-term (> 1 day) studies, two studies[50,52] reported a greater percentage reduction in rTNSS and RQLQ scores for AZE nasal spray versus oral cetirizine in the treatment of SAR (Table 46). One study reported a greater onset of action for the AZE group at 60 and 40 minutes.[52] However, one study[51] reported no difference in mean change from baseline in investigator-scored total symptoms despite reporting increased patient-scored symptom reduction for nasal stuffiness and rhinorrhea. One study in PAR patients reported no differences in mean change in TNSS between treatment AZE and oral cetirizine groups.[42] In this study, physician-assessed global efficacy was good or excellent in a greater proportion of patients in the AZE group (significance not reported).

TABLE 46: SUMMARY OF EFFICACY DATA FOR TRIALS LONGER THAN ONE DAY

	AZE Group	Comparator	*P* Value
SAR			
LaForce,[49] 2010, US	**AZE+FNS (n = 68)**	**OLO+FNS (n = 67)**	
Mean Δ in rTNSS from baseline (averaged over 2 weeks)	–4.15	–4.28	0.8039
Mean percentage reduction in rTNSS from baseline	53.65%	47.95%	0.3688
Mean Δ in iTNSS from baseline (averaged over 2 weeks)	–4.04	–4.22	0.7339
Mean percentage reduction in iTNSS from baseline	57.15%	53.25%	0.4933
Shah,[53] 2009, US	**AZE (n = 188)**	**OLO (n = 180)**	
Mean percentage Δ in TNSS from baseline	~30%	~26%	0.278
Mean Δ in RQLQ score from baseline	~–12	~–10	0.684
Berger,[50] 2006, US	**AZE (n = 179)**	**Cetirizine (n = 175)**	
Mean Δ in rTNSS from baseline (averaged over 2 weeks)	–4.6 (± 4.2)	–3.8 (± 4.3)	0.09
Mean percentage reduction in rTNSS from baseline	24.2%	19.2%	0.046
Mean Δ in RQLQ score from baseline	~–1.5	~–1.25	< 0.01
Corren,[52] 2005, US	**AZE (n = 152)**	**Cetirizine (n = 155)**	
Mean Δ in rTNSS from baseline	–5.56 (4.68)	–4.32 (4.6)	0.015
Mean Δ in RQLQ score from baseline	–1.41 (1.25)	–1.11 (1.18)	0.049
Onset of action (iTNSS) 60 minutes 240 minutes	 ~3 ~4.5	 ~2.5 ~4.0	 0.040 0.040
Charpin,[51] 1995, France	**AZE (n = NR)**	**Cetirizine (n = NR)**	
	n = 129 total		
TSSI Mean percentage Δ from baseline at day 7 Mean percentage Δ from baseline at day 14	 47% 61%	 55% 67%	 0.66
Investigator-Scored TNSS Mean percentage Δ from baseline at day 7 Mean percentage Δ from baseline at day 14	 49.5% 60.2%	 50.8% 63.3%	0.69
Investigator-Scored TOSS Mean percentage Δ from baseline at day 7 Mean percentage Δ from baseline at day 14	 46.4% 65%	 60.8% 60.8%	0.7
Patients' VAS scores Nasal stuffiness Rhinorrhea	 –13.97 (± 1.15) –14.71 (± 0.79)	 –9.38 (±0.94) –11.74 (± 1.25)	 0.002 0.044

	AZE Group	Comparator	*P* Value
	n = 54	**n = 56**	
Investigator Global Assessment of treatment efficacy (highly satisfied), n	39	43	0.82
Patient Global Assessment of treatment efficacy (excellent or good), n	37	38	0.87
PAR			
Passali,[42] 1994, Italy	**AZE (n = 19)**	**Cetirizine (n = 18)**	
Mean percentage Δ in TNSS from baseline	NR	NR	NR[a]
Physician Global Assessment of efficacy (good or excellent)	74%	56%	NR

AZE = azelastine; Δ = treatment difference; FNS = fluticasone nasal spray; iTNSS = instantaneous total nasal symptom score; NR = not reported; OLO = olopatadine; PAR = perennial allergic rhinitis; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; rTNSS = reflective total nasal symptom score; SAR = seasonal allergic rhinitis; TNSS = total nasal symptom score; TOSS = total ocular symptom score; TSS = total symptom score; TSSI = total symptom score of investigator; VAS = visual analogue scale.
[a] Indicated in text that there were no differences between treatment groups.

Safety

The short-term trials[45,46] reported low AE rates overall with no differences in the rate of SAE,[45] WDAE,[45] and treatment-related AE between AZE and oral cetirizine, loratadine, and desloratadine (Table 47).[46]

Trials comparing AZE to oral cetirizine in SAR patients[50-52] reported good tolerability. Several trials reported higher rates of bitter taste,[45,50] and WDAE,[50,52] in the AZE group. One trial[51] reported no difference in overall AE[51] despite higher rates of treatment-related AE, and sleepiness in the cetirizine group. In general, statistical significance was not reported. The single trial in PAR patients[42] reported increased somnolence and WDAE and reduced physician-rated tolerance in the cetirizine group.

TABLE 47: SUMMARY OF SAFETY DATA

	Azelastine Group n (%)	Comparator n (%)		*P* Value
SAR				
LaForce,[49] 2010, US	**AZE+FNS (n = 68)**	**OLO+FNS (n = 67)**		
AE	16 (23.5%)	15 (22.4%)		NR
SAE	0 (0%)	0 (0%)		NR
Severe AE	4 (5.9%)	1 (1.5%)		NR
Ellis,[45] 2013, Canada[a]	**AZE (n = 66)**	**Cetirizine (n = 66)**	**Loratadine (n = 66)**	
SAE	1	1	0	NR
AE related to study medication	2	0	1	NR
WDAE	0	0	0	NR
Shah,[53] 2009, US	**AZE (n = 188)**	**OLO (n = 180)**		
Bitter taste	37 (19.7)	22 (12.2)		0.05
Nasal infection	0 (0%)	2 (1.1%)		NR
Epistaxis	2 (1.1%)	1 (0.6%)		NR
Nasal ulceration	1 (0.5%	0 (0%)		NR
Berger,[50] 2006, US	**AZE (n = 179)**	**Cetirizine (n = 175)**		

	Azelastine Group n (%)	Comparator n (%)	*P* Value
Bitter taste (%)	7.7%	< 2%	NR
Somnolence (%)	< 2%	< 2%	NR
WDAE	4	1	NR
Horak,[46] 2006, Austria[a]	**AZE (n = 45)**	**Desloratadine (n = 45)**	
Overall AE	6		NA
Treatment-related AE	1	1	NR
Corren,[52] 2005, US	**AZE (n = 152)**	**Cetirizine (n = 155)**	
WDAE	4	1	NR
Somnolence	1.3%	2.6%	NR
Bitter taste	3.3%	< 1%	NR
Charpin,[51] 1995, France	**AZE (n = 67)**	**Cetirizine (n = 69)**	
Overall AE	12 patients (16 AE)	20 patients (27 AE)	0.12
AE attributed to study medication	6	19	NR
Sleepiness	2	9	0.03
SAE	0	0	N/A
PAR			
Passali,[42] 1994, Italy	**AZE (n = 19)**	**Cetirizine (n = 18)**	
SAE	0	0	NR
WDAE	0	2	NR
Somnolence	NR	3	NR
Physician tolerance rating (good or excellent)	94.7%	83.3%	NR

AE = adverse event; AZE = azelastine; FNS = fluticasone nasal spray; NA = not available; NR = not reported; OLO = olopatadine; PAR = perennial allergic rhinitis; SAE = serious adverse event; SAR = seasonal allergic rhinitis; WDAE = withdrawal due to adverse event;
[a] Short-term (≤ 1 day) study.

Discussion

Based on the results of three trials,[41,47,48] there was no difference in efficacy measures, efficacy ratings, or onset of action of intranasal levocabastine and intranasal AZE in SAR[47,48] and PAR[41] patients. In addition, efficacy did not appear to vary based on condition (SAR versus PAR). Both medications showed good and similar tolerability. One trial[47] reported significantly increased taste disturbance due to AZE treatment, and one trial[48] reported higher rates of AE and lower tolerability in levocabastine patients.

Azelastine nasal spray (with and without fluticasone nasal spray) had comparable efficacy and tolerability to olopatadine nasal spray (OLO) (with and without FNP), with one trial[53] reporting higher rates of bitter taste in the AZE group. Compared with oral cetirizine, AZE treatment was more efficacious and resulted in greater improvements in quality of life[50,52] and patient-scored symptom reduction.[51] However, one study did not show a difference in investigator-rated efficacy[51] and there was no difference in efficacy between groups in PAR patients.[42] These results suggest a potential lesser benefit of oral cetirizine in PAR. Safety measures were similar between groups for oral antihistamines and AZE. Concerns to note were bitter taste in AZE groups[45,50] and somnolence or sedation in the oral antihistamine groups.[42,51]

While the trials were mostly well designed, in general there was poor reporting of measures of variance and statistical significance, especially for all safety data and levocabastine trials.[47,48] This introduced substantial uncertainty when interpreting comparative data. Also, it is possible that the limited search strategy may have resulted in exclusion of some relevant trials.

In conclusion, the identified studies provide mixed evidence to suggest superior efficacy of AZE versus oral antihistamines and do not provide sufficient evidence to suggest differences in efficacy and safety between AZE and other intranasal antihistamines. All studies reported good tolerability, with notable adverse effects including taste disturbance for AZE treatment and somnolence for oral antihistamines.

APPENDIX 7: SUMMARY OF COMPARATIVE EFFICACY OF INTRANASAL CORTICOSTEROIDS

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize the comparative clinical efficacy of various intranasal corticosteroids used for the treatment of seasonal allergic rhinitis (SAR).

Key Findings

Limited evidence from two systematic reviews[54,55] suggests equivalent efficacy and safety of intranasal corticosteroids (INCSs). No evidence was available regarding comparative efficacy of ciclesonide, or fluticasone furoate and several safety outcomes of interest (i.e., overall and serious adverse events and infection).

Background

Evidence suggests that INCSs are more effective for SAR than antihistamines when used as monotherapy.[56] Fluticasone propionate comprises the INCS component of AZE/FP (azelastine hydrochloride and fluticasone propionate fixed-dose combination). Many other INCSs are available on the market and may be prescribed more frequently.[57] In the United States, mometasone furoate and triamcinolone were the non-generic INCSs in most frequent use in 2007.[57] The delivery device, propellant, dose regimen,[58] and potency of these products is varied.[54] As such, it is of interest to assess the comparative efficacy and harms of available INCSs.

Methods

A limited PubMed search of English-language articles was conducted without date restrictions. Of 121 potentially relevant articles, 10 studies, including seven systematic reviews and three randomized controlled trials, were retrieved for full-text review.[55,59,59-66] One additional reference was retrieved from the grey literature.[54] Studies that did not present disaggregated results,[67] were narrative review articles,[62] were superseded by a more recent systematic review,[63] were included in a systematic review,[66] were conducted in perennial AR patients,[65] or did not include head-to-head comparisons of INCSs[60,61,64] were excluded. In addition, one systematic review was excluded due to substantial underreporting of individual trial information and exclusion of a complete reference list.[59] Ultimately, two systematic reviews[54,55] met the inclusion criteria and were included in this summary.

Summary of Study Characteristics

Study characteristics and outcomes are summarized in Table 48. Both studies were systematic reviews published between 2007 and 2008. One systematic review focused on individuals with SAR[54] and the other was inclusive of all AR patients.[55] Within these reviews, trials assessing the comparative efficacy and tolerability of beclomethasone, two formulations of flunisolide, triamcinolone, fluticasone propionate, mometasone furoate, and budesonide nasal sprays were included. There was substantial overlap among studies included in the systematic reviews and the methodology of one review[55] was unclear. As such, rather than repeat data, data from the more recent systematic review[54] are the focus of this supplemental issue and only the results of unique trials from Herman et al.[55] are presented.

TABLE 48: SUMMARY OF STUDY CHARACTERISTICS

First Author, Publication Year, Country	Population(s)	Sample Size	Individual Study Duration, Design	Intranasal Corticosteroids Assessed	Outcome(s)	Individual Study Quality
Systematic Reviews and Meta-Analyses						
Selover, 2008, United States[54]	Adult patients with clinically confirmed AR (subdivided by SAR and PAR)[a]	n = 15 studies	2 to 8 weeks, RCTs n = 8 studies were single-blind n = 7 studies double-blind	Beclomethasone, flunisolide (2 formulations), triamcinolone, fluticasone propionate, mometasone furoate, budesonide	TNSS, nasal index score, RQLQ, TOSS	All studies except one (rated poor) rated as fair quality
Herman, 2007, United States[55][b]	Patients with allergic rhinitis	n = 8 studies	1 week to 3 months, RCTs	Budesonide, fluticasone propionate, mometasone furoate, and triamcinolone	Reflective and instantaneous nasal symptom scores[c]	Not assessed

SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis; RCT = randomized controlled trial; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; TNSS = total nasal symptom score; TOSS = total ocular symptom score.
[a] With the exception of McArthur et al. and Langrick et al., 24-month history and positive skin prick tests were elements of the eligibility criteria.
[b] Data from one unique study are included in this report; all other studies overlap with Selover et al.
[c] Composite score of blocked nose, runny nose, sneezy itchy nose (maximum score = 9).

Summary of Findings

Efficacy

In adults, treatment with fluticasone propionate results in comparable reduction in total nasal symptom scores to beclomethasone, budesonide, and triamcinolone (Table 49). Similarly, mometasone and triamcinolone are equivalent in efficacy to beclomethasone, and mometasone furoate and budesonide.[55] Mometasone furoate was of equivalent efficacy to budesonide in children (Table 50).[54] No comparative evidence was available on fluticasone furoate, ciclesonide, or flunisolide. With regard to quality of life, RQLQ point reductions were similar between triamcinolone and beclomethasone and triamcinolone and fluticasone propionate groups. Data were not presented for TOSS. It was reported that there were no differences in ocular symptom score reduction between different INCSs.

TABLE 49: SUMMARY OF ADULT COMPARATIVE EFFICACY DATA FOR TOTAL AND INDIVIDUAL NASAL SYMPTOM SCORE(S) AND QUALITY OF LIFE

Outcome	Intervention, Value	Comparator, Value	*P* Value
Selover, 2008[54]			
Total Nasal Symptom Score, % change in total symptom score	FLUT 200 mcg twice daily mcg, –43% 200 mcg once daily, –53%	BEC 226 mcg, –32%	NS
	MOM 100 mcg, –53% 200 mcg, –59%	BEC 400 mcg, –59%	NS
	TRI AQ 220 mcg, –48	FLUT 200 mcg, –49.7	NS
	TRI AQ 220 mcg, –49.4%	FLUT 200 mcg, –52.7	NS
Nasal Index Score,[a] % change in total symptom score	TRI AQ 220 mcg, –42.9%	BEC 226 mcg, – 45.9%	NS
Combined Nasal Symptom Score, % change in total symptom score	BUD 128 mcg, –26.5% 256 mcg, –29.4%	FLUT 200 mcg, –29.4%	NS
RQLQ, point reductions	TRI AQ 220 mcg, –1.71	BEC 336 mcg, –1.79	NS
	TRI AQ 220 mcg, –2.4	FLUT 200 mcg, –2.5	NS
	TRI AQ 220 mcg, –2.4	FLUT 200 mcg, –2.5	NS
Herman, 2007[55,b]			
3 Instantaneous Nasal Symptoms (blocked nose, runny nose, sneezy itchy nose)	BUD (64 mcg or 256 mcg), NR	MOM 200 mcg, NR	NS
3 Reflective Nasal Symptoms (blocked nose, runny nose, sneezy itchy nose)	BUD (64 mcg or 256 mcg), NR	MOM 200 mcg, NR	NS

AQ = aqueous; BEC = beclomethasone; BUD = budesonide; FLUT = fluticasone propionate; MOM = mometasone furoate; NR = not reported; NS = not significant; TRI = triamcinolone.
[a] Composite of nasal discharge, stuffiness, and sneezing.
[b] Trial results only presented for trials not captured by the Selover et al. review.

TABLE 50: SUMMARY OF CHILD COMPARATIVE EFFICACY DATA FOR TOTAL AND INDIVIDUAL NASAL SYMPTOM SCORE(S) AND QUALITY OF LIFE

Outcomes	Intervention	Comparator	*P* Value
Selover, 2008[54]			
Physician-rated TNSS	Mometasone furoate (25 mcg, 100 mcg, or 200 mcg)	Beclomethasone (84 mcg)	NR[a]

NR = not reported; TNSS = total nasal symptom score.
[a] Results reported as not statistically significant for all comparisons up to day 16. Between day 16 and day 29, all treatments were superior to mometasone furoate 25 mcg.

Safety

None of the unique studies included in Herman et al. contained relevant safety data; therefore, only results from Selover et al.[54] are presented. Safety data from 28 trials was reported for withdrawals due to adverse events (WDAEs), headache, and epistaxis. Detailed data are presented in Table 51.

Comparisons were made between beclomethasone and flunisolide, fluticasone propionate, mometasone furoate, triamcinolone, and budesonide, as well as fluticasone propionate and budesonide and triamcinolone. WDAEs ranged from 0% to 7%. Headache rates ranged from 0% to 36% and only differed in one trial comparing mometasone furoate and beclomethasone (*P* = 0.02). Epistaxis (including bloody discharge) rates ranged from 0% to 8% and did not differ between groups. Overall, the evidence from this review does not suggest a substantial difference in safety outcomes between treatments for comparable treatments and doses.

TABLE 51: SUMMARY OF SAFETY DATA

First Author, Year	Intervention, Value	Comparator, Value	*P* Value
Selover, 2008			
Withdrawals due to adverse events	TRI AQ 220 mcg, 0%	FLUT 200 mcg, 0%	NS
	FLUN 200 mcg, 2.2%	BEC 400 mcg, 0%	NS
	MOM 200 mcg, 0.8%	BEC 336 mcg, 4.3%	NS
	TRI AQ 200 mcg, 1.2%	FLUT 200 mcg, 0%	NS
	MOM 100 mcg, 3% 200 mcg, 4%	BEC 400 mcg, 0%	NS
	FLUT 200 mcg twice daily, 0% 200 mcg one daily, 0%	BEC 336 mcg, 1.6%	NS
	FLUN 200 mcg, 0%	BEC 400 mcg, 0%	NS
	TRI AQ 220 mcg, 0%	BEC 336 mcg, 0%	NS
	BUD 200 mcg, 4%	BEC 200 mcg, 0%	NS
	FLUT 200 mcg, 0%	BEC 336, 1%	NS
	BUD 128 mcg, 0.5% 256 mcg, 0.5%	FLUT 200 mcg, 1.7%	NS
	FLUN 200 mcg, 6.7%	BEC 336 mcg, 0%	NS
Headache	TRI AQ 220 mcg, 6.8%	FLUT 200 mcg, 4.1%	NS
	FLUN 200 mcg, 10% 300 mcg, 10%	BEC 168 mcg, 12% 336 mcg, 10%	NS
	MOM 200 mcg, 36%	BEC 336, 22%	**0.02**
	TRI AQ 22 mcg, 11%	FLUT 200 mcg, 11.7%	NS
	MOM 100 mcg, 8% 200 mcg, 10%	BEC 400 mcg, 8%	NS
	FLUT 200 mcg twice daily, 4.7% 200 mcg one daily, 3.6%	BEC 336 mcg, 4.9%	NS
	BUD 200 mcg, 2%	BEC 200 mcg, 0%	NS
	FLUT 200 mcg, 0%	BEC 336 mcg, 1%	NS
	FLUN 200 mcg, 0%	BEC 336 mcg, 16.7%	0.0522
Epistaxis	TRI AQ 220 mcg, 2.7%	FLUT 200 mcg, 4.8%	NS
	FLUN 200 mcg, 8% 300 mcg, 8%	BEC 168 mcg, 7% 336 mcg, 8%	NS

First Author, Year	Intervention, Value	Comparator, Value	*P* Value
	MOM 100 mcg, 3% 200 mcg, 6%	BEC 400 mcg, 5%	NS
	FLUT 200 mcg twice daily, 0% 200 mcg one daily, 1.8%	BEC 336 mcg, 4.9%	NS
	BUD 200 mcg, 0%	BEC 200 mcg, 2.6%	NS
	FLUT 200 mcg, 3%	BEC 336 mcg, 2%	NS
	FLUN 200 mcg, 0%	BEC 336 mcg, 0%	NS

BEC = beclomethasone; BUD = budesonide; FLUN = flunisolide; FLUT = fluticasone propionate; MOM = mometasone furoate; NS = not significant; TRI = triamcinolone.

Limitations

The summarized evidence is only current up to 2008. No evidence published since 2008 was identified. Not all relevant safety outcomes were reported and could not be assessed. In particular, the data from one systematic review[54] did not include results on deaths, overall and serious adverse events, and infection. Evidence regarding the relevant active comparator fluticasone furoate was not available; therefore, the comparative efficacy of this treatment is unclear.

Discussion

Based on the results of the trials summarized within two systematic reviews[54,55] involving limited treatment comparisons, there was no difference in efficacy outcomes between INCS treatments in both adults and children with SAR. Of note, no evidence was retrieved on the comparative efficacy of fluticasone furoate, a treatment of interest. It has been reported that fluticasone furoate treatment is the only INCS to demonstrate a consistently greater reduction in ocular symptoms over placebo, but no head-to-head trials are available to support this suggestion.[61]

Limited safety data on three outcomes (WDAE, headache, and epistaxis) suggested similar tolerability between INCS treatment groups. One study reported higher rates of headache in mometasone- versus beclomethasone-treated patients, and another study showed a trend toward higher rates in beclomethasone patients versus flunisolide-treated patients. These outcomes were not corroborated by similar trials. In general, adverse event rates were low and suggest good tolerability.

The overall quality of the main review[54] was good — methodology and reporting were adequate. The quality of the majority of the individual included trials was rated as fair.[54] Some included trials were only single-blind, suggesting potential risk of performance and selection bias, especially due to the subjective nature of the symptom and quality of life scores. The comparative efficacy and safety of INCS treatments that were not assessed is unclear and possible differences cannot be ruled out. In the same vein, it is unclear whether several relevant safety outcomes vary by treatment due to underreporting. Finally, it is possible that the limited search strategy may have resulted in the exclusion of some relevant publications.

In conclusion, limited evidence suggests equivalent efficacy and safety of INCSs. Further research is needed to clarify several treatment comparisons and safety outcomes.

APPENDIX 8: SUMMARY OF STUDY MP4000

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To summarize data from a single long-term safety study (MP4000)[68] of AZE/FP (azelastine hydrochloride and fluticasone propionate fixed-dose combination) for allergic rhinitis (AR).

Findings

MP4000 was a randomized, multi-centre (37 sites), open-label, active-control, parallel-group, one-year-long study conducted in India, which aimed to evaluate the long-term safety and tolerability of AZE/FP in individuals with chronic allergic or vasomotor (VMR) non-allergic rhinitis. Patients aged 12 to 80 years with a history of chronic (allergic or non-allergic VMR) rhinitis and patients with seasonal rhinitis with significant symptoms outside allergy season were considered for entry. In order to be eligible for randomization, patients had to exhibit nasal symptoms of rhinitis on at least two out of seven days during the run-in period and not exhibit any clinically significant laboratory, electrocardiogram, or eye examination abnormalities. AZE/FP was compared against commercially available generic fluticasone propionate (FP). Patients were randomized 2:1 to AZE/FP (one spray, twice daily) or FP (two sprays, twice daily). Demographic and baseline characteristics were presented by treatment group. Baseline characteristics were well balanced between groups. An interim analysis was performed once all patients had completed their six-month visit. Overall, 612 patients were randomized (405 to AZE/FP and 207 to FP). At the end point, 464 (75.8%) patients completed the protocol as indicated and 139 (22.7%) discontinued.

The primary outcome of this trial was safety and tolerability. Detailed results are presented in Table 52. Adverse events were recorded, and direct visual nasal examination assessments, vital sign assessments, eye examinations, and laboratory assessments were conducted. Outcomes were assessed at five intervals (months 1, 3, 6, 9, and 12). A subset of patients (approximately one-third) underwent hypothalamic-pituitary-adrenal (HPA) axis testing at months 6 and 12. Treatment with AZE/FP was well tolerated overall. Less than 3% of patients discontinued do to an adverse event. Dysgeusia and epistaxis were the most common treatment-related adverse events and dysgeusia occurred more frequently in the AZE/FP group.

Efficacy (total nasal symptom score [TNSS] and the Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]) was assessed as a secondary outcome. The total ocular symptom score (TOSS) was not assessed; therefore, no conclusions can be made about the long-term efficacy of AZE/FP for reducing ocular symptoms. The TNSS was assessed over seven days at four-week intervals. The RQLQ was assessed at months 1, 3, 6, 9, and 12. Mean absolute changes from baseline in TNSS and RQLQ are presented in Table 53. A greater decrease from baseline in mean 12-hour reflective TNSS (rTNSS) was observed in the AZE/FP group compared with the FP group over the first week. TNSS scores decreased over the course of the trial in both groups with final recorded reductions at one year being greater in the AZE/FP group. Reductions in RQLQ were similar between groups and were consistently above the minimal clinically important difference (MCID) of 0.5.

TABLE 52: SUMMARY OF KEY SAFETY OUTCOMES FROM MP4000

Adverse Events, n (%)	AZE/FP (n = 404)	Fluticasone Propionate (n = 207)
SAE	3 (0.7)	1 (0.5)
AE leading to discontinuation	11 (2.7)	6 (2.9)
Deaths	0 (0)	0 (0)
Treatment-emergent AE	188 (45.65)	94 (44.4)
Treatment-related AE	38 (9.4)	23 (11.1)
Mild	29 (7.2)	16 (7.7)
Moderate	9 (2.2)	7 (3.4)
Severe	0 (0)	0 (0)
Dysgeusia	10 (2.5)	1 (0.5)
Epistaxis	5 (1.2)	1 (0.5)
Headache	4 (1.0)	9 (4.3)
Somnolence	1 (0.2)	1 (0.5)
Mucosal erosion	1 (0.2)	1 (0.6)
Infection	2 (0.5)	3 (1.4)
Blood cortisol, decreased	5 (1.2)	1 (0.5)
HPA axis test results (mean, SD)		
n	154	78
6-month change from baseline (mcg/dL)	–0.31 ± 5.14	–0.92 ± 5.319
n	137	73
12-month change from baseline	–0.08 ± 5.53	–1.04 ± 4.99

AE = adverse event; AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; HPA = hypothalamus-pituitary-adrenal; n = number of patients; SAE = serious adverse event; SD = standard deviation.
Note: Safety population assessed.
Source: MP4000 Clinical Study Report Table 19 (p. 66); 14.3.1.1; 14.3.1.5; 14.3.1.2.1.

TABLE 53: SUMMARY OF KEY EFFICACY OUTCOMES FROM MP4000

Outcome	AZE/FP (n = 388)	Fluticasone Propionate (n = 199)
TNSS (mean change from baseline in 12-hour rTNSS), mean (SD)		
n	379	194
Baseline score	3.84 (2.49)	3.87 (2.33)
n	370	187
Overall (days 1 to 7)	–1.55 (2.33)	–0.76 (2.11)
n	359	185
Day 7	–1.80 (2.68)	–1.03 (2.67)
n	372	188
Week 4[a]	–1.93 (2.83)	–1.36 (2.16)
n	295	148
Week 52[b]	–2.99 (2.59)	–2.88 (2.54)
n	378	191
End point	–2.99 (2.72)	–2.73 (2.75)
RQLQ (Mean change from baseline in adult RQLQ at 12 months), n (%)		
n[c]	191	97

Outcome	AZE/FP (n = 388)	Fluticasone Propionate (n = 199)
Baseline overall score	2.1 (1.05)	2.2 (1.06)
N	165	83
Overall score (Δ from baseline)	–1.5 (1.20)	–1.6 (1.24)
n	193	97
Baseline sleep	1.8 (1.62)	1.7 (1.36)
n	167	83
Sleep (Δ from baseline)	–1.3 (1.75)	–1.2 (1.46)
n	193	97
Baseline Non-nose/Eye Symptoms	2.1 (1.18)	2.0 (1.10)
n	167	83
Non-nose/Eye Symptoms (Δ from baseline)	–1.5 (1.22)	–1.4 (1.20)
n	193	97
Baseline Practical Problems	2.3 (1.43)	2.6 (1.50)
n	167	83
Practical Problems (Δ from baseline)	–1.8 (1.67)	–2.0 (1.64)
n	193	97
Baseline Nasal Symptoms	2.3 (1.25)	2.7 (1.26)
n	167	83
Nasal Symptoms (Δ from baseline)	–1.7 (1.47)	–2.0 (1.53)
n	193	97
Baseline Eye Symptoms	1.3 (1.17)	1.5 (1.33)
n	167	83
Eye Symptoms (Δ from baseline)	–0.8 (1.33)	–1.0 (1.48)
n	193	97
Baseline Emotional	2.2 (1.60)	2.3 (1.41)
n	167	83
Emotional (Δ from baseline)	–1.7 (1.60)	–1.8 (1.54)
n	191	97
Baseline Activity	2.8 (1.30)	3.1 (1.31)
n	165	83
Activity (Δ from baseline)	–2.1 (1.59)	–2.4 (1.63)

AZE/FP = azelastine hydrochloride and fluticasone propionate fixed-dose combination; Δ = treatment difference; n = number of patients; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; rTNSS = reflective TNSS; SD = standard deviation; TNSS = total nasal symptom score.

Note: Analyses were conducted in the intention-to-treat population.

[a] Includes p.m. TNSS scores from day 1 to 28.

[b] Includes p.m. TNSS scores from day 337 to 365.

[c] n = 297 did not complete RQLQ due to a) age < 18 years, b) language barrier, c) other reasons.

Source: Clinical Study Report MP4000 14.2.2; 14.2.1.

Limitations

The primary limitations of MP4000 are the open-label design and limited generalizability. Patient's awareness of treatment should be considered in the interpretation of outcome data due to the potential risk of performance bias. This is of particular concern due to the subjective nature of the outcome scores. For the RQLQ assessment, many patients were excluded due to language barriers. The long-term quality of life data are limited to adults and individuals able to communicate in English and Hindi, so confidence in this estimate is limited. Generalizability of these results to SAR patients is limited. Patients with SAR symptoms persistent in non-allergy season were included, but the distinction between persistent SAR and chronic AR was not clarified. Furthermore, the baseline TNSS values were substantially lower and history of suffering from AR was shorter (six years versus 20 years in the pivotal trials), suggesting less severe disease in the MP4000 patients. The setting (India) of the study may reduce generalizability to the North American setting, due to potential differences in offending allergens and climate, and between ethnic groups. Lastly, statistical significance of all comparisons was not reported, limiting confidence in the reported differences between groups.

Conclusion

MP4000 was a 52-week open-label study that enrolled 612 patients with chronic allergic or VMR non-allergic rhinitis. The efficacy results through week 52 were consistent with the two-week pivotal trials showing persistent reductions in TNSS and RQLQ. Long-term use of AZE/FP was not associated with any new safety concerns and overall tolerability was good. The only apparent difference between treatment groups was for rates of dysgeusia, consistent with the observations of the two-week trials. Rates of discontinuation were higher, as would be expected for a longer-term trial. Limitations of this these findings are mainly attributed to the generalizability of the patient population and setting in which the trial was conducted, and the open-label design. Overall, the long-term trial data are suggestive of long-term efficacy and safety of AZE/FP in patients with chronic allergic and VMR non-allergic rhinitis.

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