

Onset of action of loratadine/montelukast in seasonal allergic rhinitis subjects exposed to ragweed pollen in the Environmental Exposure Unit

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ABSTRACT

Onset of action is recognized as an important pharmacologic property of allergic rhinitis (AR) medications. This study was designed to evaluate the onset of action of loratadine/montelukast (L/M; 10 mg/10 mg) versus placebo in subjects with ragweed-induced seasonal AR (SAR). A single-center, double-blind, parallel-group study of ragweed-sensitive AR subjects ($n = 310$) was performed in the Environmental Exposure Unit (EEU). Subjects were exposed to ragweed pollen in the EEU and symptoms were recorded at 30, 60, 90, and 120 minutes before a single dose of L/M or placebo. After dosing, symptoms were recorded for 4 hours, at 15-minute intervals for the first 2 hours and at 30-minute intervals for the final 2 hours. The primary end point was time to onset of action of L/M, defined as the first time point at which the mean change from baseline in total symptom score (TSS) for L/M became and remained significantly better than placebo. Secondary end points included nasal congestion scores and peak nasal inspiratory flow (PNIF). The onset of action of L/M for TSS was 1 hour and 15 minutes ($p = 0.005$ versus placebo). L/M reduced nasal congestion as indicated by significant improvements in both the nasal congestion score ($p = 0.011$) and the PNIF measurements ($p = 0.007$) within 1 hour and 15 minutes postdose. The incidence of treatment-emergent adverse events was similar between groups. The onset of action after treatment with L/M was 1 hour and 15 minutes for TSS, as well as nasal congestion. L/M was well tolerated.

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Key words: Allergen challenge, allergic rhinitis, antihistamine, antileukotriene, Environmental Exposure Unit, loratadine/montelukast, nasal congestion, onset of action, peak nasal inspiratory flow, total symptom score

The prevalence of allergic disease has increased dramatically in the developed world during the second half of the 20th century and is emerging as the most common chronic illness in childhood.^{1,2} Evaluations of the various antiallergic medications available to patients provide important information for physicians allowing them to make informed decisions about the most suitable treatment. Such evaluations are best conducted using placebo-controlled, randomized controlled trials (RCTs), which remain the gold standard

for evidence-based medical evaluations of all pharmaceuticals.

The Allergic Rhinitis and Its Impact on Asthma and the European Academy of Allergy and Clinical Immunology workshop group have identified rapid onset of action and duration of effect long enough to allow for once-daily dosing as critical properties for allergic rhinitis (AR) treatments.³ Traditional RCTs of AR medications conducted under the everyday conditions of the symptomatic population provide information on efficacy and safety of therapies but do not adequately determine certain pharmacodynamic properties, including onset of action. Confounding factors, such as changes in environmental allergen levels, subject exposure to these allergens as well as compliance to the study dosing regimen and timing of symptom recordings, are inherent in the traditional AR clinical study setting and do not allow for the precise measurements required for onset of action studies.^{4,5}

Studies undertaken in the Environmental Exposure Unit (EEU), a model of controlled allergen challenge, provide for the precise determination of pharmacodynamic properties of AR medication using a controlled setting that eliminates environmental variability, inconsistencies in allergen exposure, recall bias in symptom recording, and treatment nonadherence.^{4–7} Stud-

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ies conducted in the EEU include a priming phase that reproduces the natural process whereby subjects become more reactive to a specific allergen over time,⁵ a phenomenon that is thought to be caused by the increase in nasal membrane reactivity after repeated exposure to an allergen.⁸ Priming also helps to ensure that subjects participating in the clinical trial have sufficient symptom levels to reliably assess the effect of the treatment they are evaluating.⁵

In addition to early onset and 24-hour duration of efficacy, broad relief of nasal symptoms (such as nasal congestion) and nonnasal symptoms (such as itching or tearing eyes) are considered an essential quality of medications used to treat AR.^{3,5} In the Allergies in America survey conducted among 2500 U.S. adults with AR,⁹ a broad range of nasal and nonnasal symptoms, including nasal congestion, rhinorrhea, nasal itching, sneezing, and ocular symptoms such as itchy and watery eyes, were graded as moderately or extremely bothersome by >50% of participants. Nasal congestion was rated as the most bothersome symptom of AR by the subjects in this study.⁹

Loratadine/montelukast (L/M) is a fixed-dose oral tablet containing 10 mg of loratadine and 10 mg of montelukast. Loratadine is a nonsedating, selective peripheral H₁-receptor antagonist widely used for relieving AR symptoms. Montelukast is a selective cysteinyl leukotriene CysLT₁ receptor antagonist approved for the treatment of AR. L/M targets two major mediators of the allergic cascade to provide relief of a broad range of AR symptoms, including the particularly bothersome symptom of nasal congestion.^{10,11} Previously, L/M has been shown to provide 24-hour relief of AR symptoms and objective end points of nasal obstruction/congestion as assessed by peak nasal inspiratory flow (PNIF).^{12,13} The current study was designed to evaluate the onset of action of once-daily L/M versus placebo in subjects with seasonal AR (SAR) exposed to short-ragweed pollen in the EEU.

METHODS

Study Design

This phase III, double-blind, parallel-group, placebo-controlled study was conducted at a single center in Kingston, Ontario, Canada. All subjects (or guardians for those aged <18 years) provided written, informed consent before study entry. The trial protocol, amendments, and informed consent forms were approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board, and the study was conducted according to Good Clinical Practice standards and International Conference on Harmonization guidelines.

The study involved three phases, a screening visit (≤ 60 days before treatment), one to six priming visits (≤ 30 days before treatment), and a treatment visit (single day). During the screening visit, a skin-prick test (if not done within the past 12 months) was performed to confirm sensitivity to short-ragweed pollen; medical histories were taken including allergy history and medication use; subjects underwent a limited physical examination including eyes, ears, upper and lower respiratory tract, vital signs, laboratory testing, and serum pregnancy testing for women of childbearing potential; and medication washouts were reviewed to confirm subject eligibility. At each priming visit, subjects were exposed to short-ragweed pollen (*Ambrosia artemisiifolia*; Greer Laboratories, Lenoir, NC) for 3 hours in the EEU at a concentration of 3500 ± 500 grains/m³. Seven Rotorod samplers (Sampling Technologies, Inc., Minnetonka, MN) positioned throughout the subject seating area were used to monitor pollen levels every 30 minutes and adjust the pollen levels as required. During each priming visit, subjects were asked to record symptom scores on diary cards every 30 minutes. To qualify for the treatment visit, at any time point during the priming visit, subjects must have obtained a "minimum symptom score" (graded on a scale of 0–3: 0 = none, 1 = mild, 2 = moderate, and 3 = severe) as follows: a nasal congestion symptom score of ≥ 2 , total nasal symptom score (TNSS; the sum of symptom scores for rhinorrhea, stuffiness/nasal congestion, sneezing, and nasal itching) of ≥ 7 , total nonnasal symptom score (TNNSS; the sum of symptom scores for eye itching, eye tearing, and itching of the ears/palate) of ≥ 3 , and total symptom score (TSS; the sum of all 7 AR symptoms) of ≥ 10 . Subjects were also trained in the use of the PNIF meter at a priming visit.

On presentation at the treatment visit, subject eligibility and medication use were reviewed, subjects had their vital signs measured and female subjects of childbearing potential were required to have a negative urine pregnancy test to be eligible for randomization. Subjects were exposed to ragweed pollen in the EEU for 2 hours before dosing and recorded symptoms and PNIF results on diary cards at 30, 60, 90, and 120 minutes. Only subjects who met the minimum symptom score at the 90-minute symptom assessment were eligible to continue in the study, and results for the 120-minute symptom assessment were used as baseline symptom and PNIF measurements. Eligible subjects were randomized sequentially in a 1:1 ratio to receive a single dose of either L/M 10 mg/10 mg or matching placebo immediately after the 120-minute assessment. The investigator, subjects, and study center staff were blinded to treatment assignment.

Table 1 Subject demographics and baseline characteristics

Characteristic	L/M (n = 155)	Placebo (n = 155)
Age, mean yr	32.2	32.5
Sex, n (%)		
Female	87 (56)	95 (61)
Male	68 (44)	60 (39)
Race, n (%)		
White	146 (94)	149 (96)
Black	2 (1)	0
Hispanic	1 (<1)	1 (<1)
Asian	5 (3)	3 (2)
American Indian	0	1 (<1)
Other	1 (<1)	1 (<1)
Duration of SAR, mean yr	15.9	16.9
Perennial AR History, n (%)		
No	94 (61)	101 (65)
Yes	61 (39)	54 (35)
Symptom score, mean		
Total symptoms	17.63	17.46
Total nasal symptoms	10.46	10.47
Total nonnasal symptoms	7.17	6.99
Congestion	2.82	2.81
PNIF, mean L/min	88.10	85.00

L/M = loratadine/montelukast; PNIF = peak nasal inspiratory flow.

Subjects

Subjects were ≥ 16 years of age with a minimum 2-year history of AR and a positive skin-prick test within the past 12 months confirming hypersensitivity to short-ragweed pollen. Female subjects of childbearing potential could not be pregnant or nursing and must have been using a medically accepted method of birth control. Inclusion and exclusion criteria were reviewed to ensure subjects were in good health and free from any clinically significant disease that would interfere with the study schedule or procedures or compromise the subject's safety.

Potential subjects were excluded if they had a respiratory infection within the 2 weeks before their first priming visit or during the treatment visit, rhinitis medicamentosa, nasal structural abnormalities significantly impairing airflow, and other clinically significant medical conditions that might interfere with the study or require treatment. Subjects who were dependent on nasal, oral, or ocular decongestants; nasal topical antihistamines; or nasal steroids were also excluded. Medications used to treat inflammatory respiratory conditions and nasal and ocular allergy symptoms, including antihistamines, decongestants,

cromolyn sodium, all corticosteroids (except for low-potency topical corticosteroids), montelukast, and nasal and ocular saline, as well as oral anticholinergics, immunotherapy, and systemic antibiotics (unless on a stable dose for prophylaxis) required specific washout periods before the priming visit ranging from 12 hours to 3 months. Subjects who did not observe the prescribed washout periods for prohibited medications were ineligible for study participation.

Efficacy and Safety Assessments

The primary end point was the time to the onset of action of L/M for TSS, defined as the first time point at which the mean change from baseline in TSS became and consistently remained significantly different from that of placebo. Secondary end points included TNSS, TNNSS, the individual diary symptom scores, and PNIF measurements. Symptoms were recorded for 4 hours after dosing, at 15-minute intervals for the first 2 hours and at 30-minute intervals for the final 2 hours.

Safety assessments recorded for all subjects throughout the study included vital signs (screening and treatment visits) and adverse events (AEs), defined as any physical or clinical change or disease (onset or exacerbation) subjects experienced during the study regardless of its relationship to study drug. AEs were graded as mild, moderate, severe, or life-threatening and rated as unlikely to be, possibly, or probably related to study drug. Serious AEs were those considered life-threatening, requiring hospitalization, resulting in a congenital abnormality or birth defect, significant disability, or death.

Statistical Analyses

Assuming a pooled standard deviation of 4.6, a two-sided *t*-test was used to determine that a sample size of ~ 150 subjects per treatment group would ensure an 80% power to detect a difference of at least 1.5 points in change from baseline in TSS between L/M and placebo (at the $p = 0.05$ significance level). Efficacy and safety analyses were performed for the intent-to-treat population, which included all randomized subjects who had one or more postdose evaluation. At each time point postdose, *t*-tests at the $p = 0.05$ significance level were used to analyze the primary and secondary variables. Onset of action was determined by individual *t*-tests performed for each posttreatment time point and was defined as the first time point at which a consistent statistically significant difference between L/M and placebo was identified. The randomization schedule was generated using the SAS software UNIFORM function (SAS Institute Inc., Cary, NC).

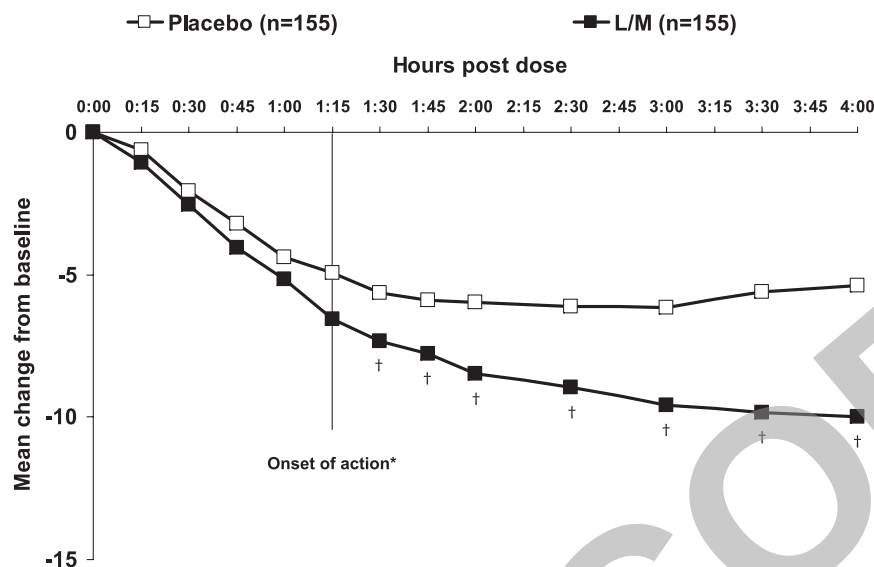


Figure 1. Onset of action of loratadine/montelukast (L/M): mean change from baseline in total symptom score (TSS) over time with L/M versus placebo. The value of * $p = 0.005$ at onset of action; †subsequent differences between L/M and placebo remained statistically significant ($p < 0.01$).

RESULTS

Subjects

A total of 472 subjects gave signed consent and were screened to obtain 310 randomized subjects, with 155 subjects in each treatment group (L/M 10 mg/10 mg and placebo). All randomized subjects completed the study and were included in the efficacy and safety analysis populations. There were no significant differences between treatment groups for subject demographics and other baseline characteristics (Table 1). The mean age of subjects was between 32 and 33 years for both treatment groups, and the mean duration of AR was similar between groups. There was a higher percentage of female subjects in each treatment group and the majority of subjects were white.

Onset of Action

There was no difference in the baseline TSS between the two treatment groups (Table 1; $p = 0.0561$). The onset of action based on the mean change from baseline in TSS over time for L/M was 1 hour and 15 minutes, at which point L/M had resulted in a 37.1% decrease in TSS compared with 28.0% for placebo (Fig. 1; $p = 0.005$). The TSS for the L/M group continued to decrease from onset through to the end of the 4-hour observation period, whereas decreases in TSS for the placebo group was greatest (35%) between 2.5 and 3 hours postdose, followed by an increase from 3 to 4 hours, the final observation time points.

The reduction in the mean nasal congestion score for L/M was greater than that achieved with placebo (Fig. 2 A). A significant difference between the two groups was first noted at 1 hour and 15 minutes ($p = 0.011$

versus placebo). The decrease in nasal congestion score over baseline at that time point was 28.1% with L/M compared with 18.4% for placebo. At 4 hours postdose, nasal congestion scores had decreased by 42.4% with L/M compared with 15.7% with placebo ($p < 0.001$).

PNIF results were similar and consistent with the findings for subject-assessed nasal congestion scores (Fig. 2 B). Specifically, the mean change from baseline was greater with L/M (23.2% improvement) than with placebo (12.9% improvement) at 1 hour and 15 minutes ($p = 0.007$) and, at the end of the observation period (4 hours postdose), PNIF scores had improved by 29.9% with L/M versus 8.9% with placebo ($p < 0.001$).

The onset of action for the remaining secondary end points was as follows: 1 hour and 15 minutes for TNSS ($p = 0.003$), rhinorrhea ($p = 0.002$), and sneezing ($p = 0.027$); 1 hour and 30 minutes for nasal itching ($p = 0.034$); 1 hour and 45 minutes for TNNSS ($p = 0.017$), eye itching ($p = 0.033$), and itching of the ears/palate ($p = 0.008$); and 2 hours for eye tearing ($p = 0.043$). In each case the benefit of L/M over placebo was maintained from onset until the end of the 4 hours postdose observation period. Significant differences were noted at earlier time points for TNNSS (1 hour and 15 minutes), rhinorrhea (15, 30, and 45 minutes), itching of the ears/palate (15 minutes, 1 hour, and 1 hour and 15 minutes) and PNIF (30 minutes), but these differences were not maintained.

Safety

Overall, L/M was well tolerated. The incidence of treatment-emergent AEs was similar between groups (Table 2): AEs were reported by six subjects in the L/M

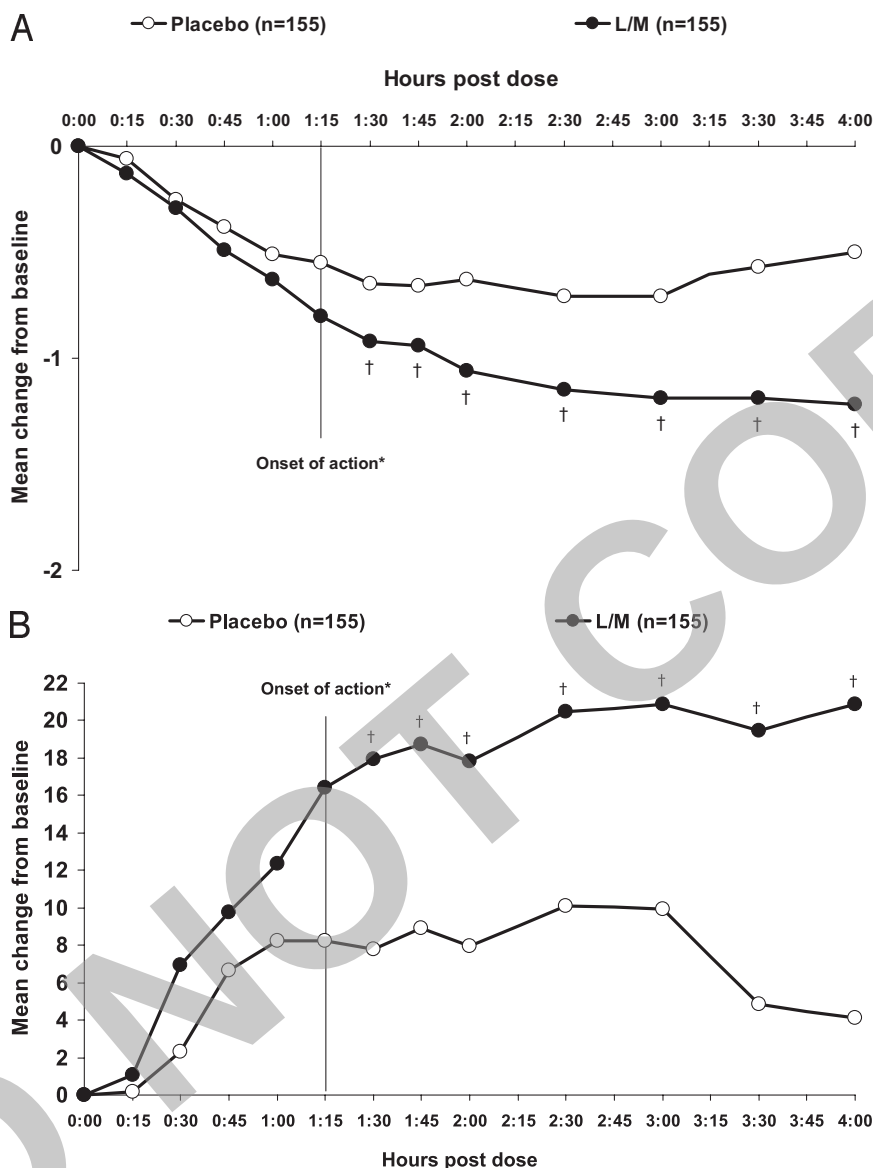


Figure 2. (A) Mean change from baseline in nasal congestion score over time of loratadine/montelukast (L/M) versus placebo; The value of $*p = 0.011$ for nasal congestion score at onset of action; †subsequent differences between L/M and placebo remained statistically significant ($p \leq 0.01$). (B) Mean change from baseline in peak nasal inspiratory flow (PNIF) over time of L/M versus placebo; $*p = 0.007$ for PNIF at onset of action; †subsequent differences between L/M and placebo remained statistically significant ($p < 0.01$).

group (4%) versus nine subjects in the placebo group (6%). The most commonly reported AE was headache (three subjects in each group). Other common AEs included epistaxis and pharyngitis, reported by subjects in the placebo group, and dizziness, reported by subjects in the L/M group. The majority of treatment-emergent AEs were considered unlikely to be related to study drug.

No subjects discontinued the study, and there were no deaths or life-threatening AEs during the study. Two AEs reported during the 4-hour treatment period were considered severe: one subject in the L/M group experienced a migraine and one subject in the placebo

group experienced a severe headache. Both severe AEs were considered to be unlikely related to study drug.

DISCUSSION

In this study, the onset of action of L/M 10 mg/10 mg for TSS in subjects with SAR was 1 hour and 15 minutes and provided relief of a broad range of symptoms, including nasal congestion, a symptom not generally thought to be improved by H_1 -receptor antagonists. Significant improvement in PNIF, an objective measure of nasal airway patency, also occurred at 1 hour and 15 minutes, supporting the subject-assessed

Table 2 Total treatment-emergent adverse effects (AE) experienced during the study

	L/M (n = 155) No. (%)	Placebo (n = 155) No. (%)
Any AE	6 (4)	9 (6)
Headache	3 (2)	3 (2)
Dizziness	2 (1)	0
Somnolence	0	1 (<1)
Epistaxis	0	2 (1)
Pharyngitis	0	2 (1)
Urticaria	0	1 (<1)
Migraine	1 (<1)	0

nasal congestion results and TSS results. It has been reported that the sensation of nasal airflow is related to feelings of discomfort—not necessarily the actual degree of nasal congestion/obstruction—and therefore can vary from patient to patient.^{15–17} PNIF provides an objective and reproducible measure of nasal congestion that supplements the subjective measure of patient-assessed symptoms and thus can be particularly useful for investigating the early/acute impact of medications on nasal patency.^{14,15,17}

Traditional outpatient RCTs are commonly accepted as the standard for investigating AR treatment efficacy and tolerability.⁴ For SAR, these outpatient studies are intended to be conducted over several weeks during peak pollen periods when individuals experience seasonal allergy symptoms (*i.e.*, spring and autumn). To be meaningful, parallel-group studies designed to compare treatments under “real-life” conditions must recruit a large number of subjects from multiple centers to ensure that they are adequately powered to detect between-treatment differences.⁵ Participants continue with normal daily activities and record symptoms, often morning and evening reflective symptom scores, or complete objective testing at home increasing the risk of recall bias in the study results. Because of factors such as fluctuating pollen levels within and between-study sites, weather, and participant lifestyle as well as the lack of control over subject adherence to study protocols, traditional RCTs are not sufficiently sensitive to accurately determine medication pharmacodynamic properties such as onset of action.⁵

The EEU is a validated allergen challenge model that provides the necessary environmental controls and study participant supervision required for the precise determination of the pharmacodynamic properties of antiallergic medications, including onset of action.^{4,5–7} In the EEU, trial participants are exposed to a quantifiable and uniform concentration of allergen, and factors that have the potential to confound results, such as

humidity, temperature, airflow, and subject compliance, are highly controlled.^{5–7} The level of precision in data collection in these types of trials can mean that fewer subjects need to be enrolled to detect treatment differences.⁵ The EEU model is enhanced by using a priming phase to awaken subject reactivity to the allergen under study to ensure subjects have adequate symptoms on the treatment day. Overall, data from allergen challenge chamber studies complement those obtained in traditional outpatient studies and can aid physicians in making therapeutic decisions for their AR patients.⁴

In the context of similarly designed investigations of L/M, this study supports the finding that L/M provides consistent relief of AR symptoms after allergen challenge. In another double-blind, randomized, parallel-group trial conducted in the EEU, L/M 10 mg/10 mg was compared with phenylephrine 10 mg and placebo in 379 subjects with SAR exposed to ragweed pollen for 8 hours postdosing.^{12,18} The primary end point was the efficacy in relief of nasal congestion expressed as the average change from baseline over the first 6 hours of the postdose evaluation period. That study showed that L/M was more effective than phenylephrine and placebo for the relief of nasal congestion, as well as for TSS and PNIF ($p \leq 0.024$).¹⁸ In contrast, there were no differences between phenylephrine and placebo for any of these measures.¹⁸ Although these results are based on a 6-hour evaluation period, they are similar to those observed in the present study, in which nasal congestion scores, TSS, and PNIF scores were all significantly improved with L/M compared with placebo.

A second, similarly designed crossover study conducted by Horak *et al.* in the Vienna Challenge Chamber involving 74 subjects with AR to grass pollen also evaluated onset of action of L/M.¹² Consistent with the results from the present study, Horak *et al.* showed that the onset of action for L/M was 1 hour and 45 minutes and that the onset of action for nasal congestion was 2 hours. In the Horak study, rhinomanometry and nasal secretions, not PNIF were used as objective measures of nasal patency and were positively correlated with the subject-assessed nasal congestion scores.¹²

This study has shown L/M to be an effective therapy for the treatment of the symptoms of AR, including the difficult to treat and bothersome symptom of nasal congestion. The onset of action for the primary efficacy end point, TSS, was 1 hour and 15 minutes, showing that L/M provided relatively quick relief for the full range of AR symptoms. Notably, L/M also provided an associated significant increase in PNIF, an objective measure of nasal airflow. L/M was well tolerated with an incidence of AEs similar to that of placebo.

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