

# Clinical studies of the DP1 antagonist laropiprant in asthma and allergic rhinitis

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**Background:** Prostaglandin D<sub>2</sub> is a proinflammatory mediator believed to be important in asthma and allergic rhinitis (AR). Allelic variants in the prostaglandin D<sub>2</sub> receptor type 1 (DP1) gene (*PTGDR*) have been suggested to be associated with asthma susceptibility.

**Objectives:** We sought to investigate the efficacy of the DP1 antagonist laropiprant (alone or with montelukast) in asthma and seasonal AR and explore whether sequence variations in *PTGDR* are associated with asthma severity.

**Methods:** For asthma, in a double-blind crossover study, 100 patients with persistent asthma were randomized to placebo or laropiprant, 300 mg/d for 3 weeks, followed by addition of montelukast, 10 mg/d for 2 weeks. *PTGDR* promoter haplotypes were categorized as high, medium, or low transcriptional efficiency. The primary efficacy end point was FEV<sub>1</sub>. For AR, in a double-blind parallel-group study, 767 patients sensitized to a regionally prevalent fall allergen with symptomatic fall rhinitis were allocated to laropiprant, 25 mg/d or 100 mg/d; cetirizine, 10mg/d; or placebo for 2 weeks. The primary end point was the Daytime Nasal Symptoms Score.

**Results:** For asthma, no significant differences in FEV<sub>1</sub> or asthma symptoms were noted for laropiprant versus placebo or laropiprant plus montelukast vs montelukast (differences between montelukast and placebo:  $P \leq .001$ ). No clear association was seen between haplotype pair (ie, diplotype) and asthma severity. For AR, although cetirizine (vs placebo) demonstrated an improvement in the Daytime Nasal Symptoms Score ( $P < .001$ ), laropiprant did not.

**Conclusion:** Laropiprant did not demonstrate efficacy in asthmatic patients or patients with AR. Variations in *PTGDR* did not appear related to baseline asthma severity or treatment response (NCT00533208; NCT00783601). (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

**Key words:** Prostaglandin D receptor gene promoter, asthma susceptibility, airway disease, montelukast

## Abbreviations used

|                    |                                                                                          |
|--------------------|------------------------------------------------------------------------------------------|
| AE:                | Adverse experience                                                                       |
| AR:                | Allergic rhinitis                                                                        |
| CRTH2:             | Chemoattractant receptor-homologous molecule on T-helper type 2 cells, also known as DP2 |
| DASS:              | Daytime Asthma Symptoms Score                                                            |
| DNSS:              | Daytime Nasal Symptoms Score                                                             |
| DP1:               | D prostanoid type 1 receptor, also known as PGD <sub>2</sub> type 1 receptor             |
| H haplotype:       | High-transcriptional-efficiency haplotype                                                |
| L haplotype:       | Low-transcriptional-efficiency haplotype                                                 |
| M haplotype:       | Medium-transcriptional-efficiency haplotype                                              |
| NASS:              | Nighttime Asthma Symptoms Score                                                          |
| PEF:               | Peak expiratory flow                                                                     |
| PGD <sub>2</sub> : | Prostaglandin D <sub>2</sub>                                                             |
| <i>PTGDR</i> :     | Prostaglandin D receptor gene                                                            |
| SABA:              | Short-acting $\beta$ -agonist                                                            |

Both asthma and allergic rhinitis (AR) are widespread and often comorbid allergic airway disorders that share a common cause of chronic airway inflammation involving elaboration of several proinflammatory mediators, including prostaglandin D<sub>2</sub> (PGD<sub>2</sub>).<sup>1,2</sup> PGD<sub>2</sub> is believed to exert its biologic effects through interactions with at least 2 G-protein-coupled receptors: D-prostanoid type 1 or PGD<sub>2</sub> receptor type 1 (DP1) and chemoattractant receptor-homologous molecule on T-helper type-2 cells (CRTH2, also known as DP2).<sup>3,4</sup> Mice deficient in DP1 did not develop asthmatic responses in an ovalbumin-induced asthma model.<sup>5,6</sup> In a guinea pig model of allergic airway inflammation, a selective DP1 antagonist, S-5751, reduced antigen-induced nasal blockage, plasma exudation in the conjunctiva, and inflammatory cell infiltration into the upper and lower airways.<sup>7</sup>

The prostaglandin D receptor gene (*PTGDR*) for DP1 has been implicated in the asthma phenotype as a result of studies on linkage and association analyses in human subjects.<sup>8</sup> Oguma et al<sup>9</sup> reported that specific variants in the *PTGDR* promoter are associated with asthma: subjects with at least 1 copy of the promoter haplotype with low *in vitro* transcriptional efficiency for DP1 had a significantly lower risk of asthma than subjects with no copies of this haplotype.

The pharmacokinetics, pharmacodynamics, and safety of a selective and potent DP1 antagonist, laropiprant (previously referred to as MK-0524),<sup>10</sup> have recently been reported.<sup>11</sup> Single doses of 6 to 400 mg were effective in suppressing PGD<sub>2</sub>-induced cyclic adenosine monophosphate accumulation in platelets, demonstrating potent antagonism of DP1. Pretreatment with laropiprant (25 mg or 100 mg daily for 3 days) in healthy subjects

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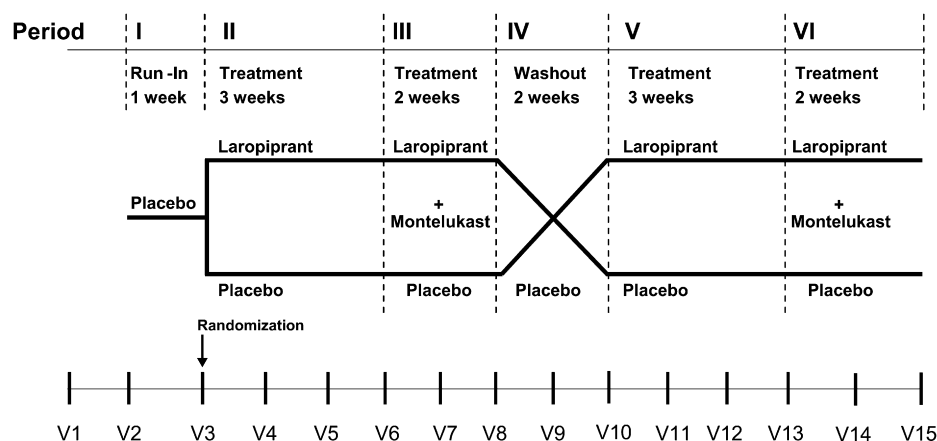


FIG 1. Design of the asthma study showing the 2 treatment sequences. V, Visit (to be performed each week).

inhibited nasal congestion induced by intranasal instillation of PGD<sub>2</sub>; both doses of laropiprant increased the provocative dose of PGD<sub>2</sub> required for a 75% increase in nasal airway resistance by greater than 45-fold compared with placebo.<sup>12</sup> This study showed that laropiprant trough plasma concentrations of greater than 150 nmol/L produced a high degree of DP1 blockade in respiratory tissue.

In 2 clinical proof-of-concept studies reported here, we tested the hypotheses that treatment with laropiprant improves the signs and symptoms of asthma and seasonal AR, respectively. A dose of laropiprant, 300 mg once daily, was chosen to maximize the ability to show efficacy in the proof-of-concept study in asthmatic subjects; the mean trough plasma concentrations expected with 100 mg/d and 300 mg/d at steady state are 567 nmol/L and approximately 1300 nmol/L, respectively (unpublished data).<sup>12</sup> We also took the opportunity in the asthma efficacy study to perform a pilot study looking for associations of DP1 promoter gene variants with asthma severity; specifically, we hypothesized that asthma severity is lower in patients with at least 1 copy of the *PTGDR* promoter haplotype identified by Oguma et al<sup>9</sup> to be associated with lower asthma susceptibility. Additionally, we assessed whether these *PTGDR* sequence variations influenced the treatment effect of laropiprant.

## METHODS

### Patients

In the asthma study, patients were between 18 and 75 years old, had a clinical history of 1 year or more of persistent asthma, had a prebronchodilator FEV<sub>1</sub> of 50% to 80% of the predicted value, and had an FEV<sub>1</sub> reversibility of 12% or greater after  $\beta$ -agonist. Other inclusion criteria included a weekly Daytime Asthma Symptoms Score (DASS) of 1.4 or greater (see below) and short-acting  $\beta$ -agonist (SABA) use of 1 or more puffs per day. Intranasal corticosteroids at a constant dose were allowed. Inhaled corticosteroids at a constant dose were allowed in up to 50% of patients, and SABAs were allowed as needed.

In the AR study, patients were between 18 and 75 years old, with at least a 2-year documented clinical history of seasonal AR that exacerbated during the fall pollen season, a positive skin test result (wheal diameter  $\geq 3$  mm larger than that elicited by the saline control) to an allergen regionally prevalent during the fall pollen season, and a minimum predefined level of Daytime Nasal Symptoms Score (DNSS; see below).

Each study was approved by the ethical review committees for the study centers. Patients provided written informed consent before treatment, as

well as permission for collection of a whole blood sample (asthma study only).

### Study design

We used a novel design for the asthma study<sup>13</sup> that allowed the simultaneous assessment, in a single study, of laropiprant as a monotherapy and of laropiprant plus montelukast as a combination therapy. This double-blind phase II crossover study (Protocol MK-0524-008) was conducted in 23 centers in the United States between October 2004 and May 2005. After receiving placebo in period I, patients were randomized to laropiprant (300 mg/d) or placebo for 3 weeks in period II, followed by the addition of montelukast, 10 mg/d, for 2 weeks to all patients in period III. After a washout (period IV), patients were crossed over in periods V (placebo or laropiprant) and VI (addition of montelukast) (Fig 1).

The AR study was a double-blind, phase II parallel-group study (Protocol MK-0524-005) conducted in 45 centers in the United States between August and October 2003. After receiving placebo in period I (the run-in phase), patients were randomized to laropiprant, 25 mg/d; laropiprant, 100 mg/d; cetirizine, 10 mg/d (positive control); or placebo for 2 weeks in period II (see Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

In both studies, a computer-generated, randomized, blind schedule allocated subjects to treatment. Compliance rate was assessed (as days that study drug was taken divided by days in the treatment period) by using tablet counts of unused study drug and patient reporting.

### Assessment of asthma severity and efficacy

Baseline severity of asthma was based on percent predicted FEV<sub>1</sub> and DASS (rated on a scale of 0 [least symptomatic] to 6 [most symptomatic]).<sup>14</sup> The primary efficacy end point was the change from baseline in FEV<sub>1</sub> (in liters). DASS and the Nighttime Asthma Symptom Score (NASS), on a scale of 0 (no awakening) to 3 (awake all night),<sup>14</sup> were secondary end points. Other end points were as-needed SABA use (puffs per day), morning and evening peak expiratory flow (PEF), asthma exacerbations (measured as a decrease in morning PEF, increase in SABA use or symptoms, or an asthma attack), asthma attacks (defined as an unscheduled use of a health care resource or treatment with a corticosteroid), oral corticosteroid rescues for worsening asthma, and total peripheral blood eosinophil counts.

### Genetic analyses in the asthma study

Three allelic variants in the *PTGDR* promoter (T-549C, C-441T, and T-197C) were identified; haplotypes were categorized as high transcriptional efficiency (CCC; H haplotype), medium transcriptional efficiency (CCT and TTT; M haplotype), and low transcriptional efficiency (TCT; L haplotype), as previously defined.<sup>9</sup> Haplotype frequency was estimated with the

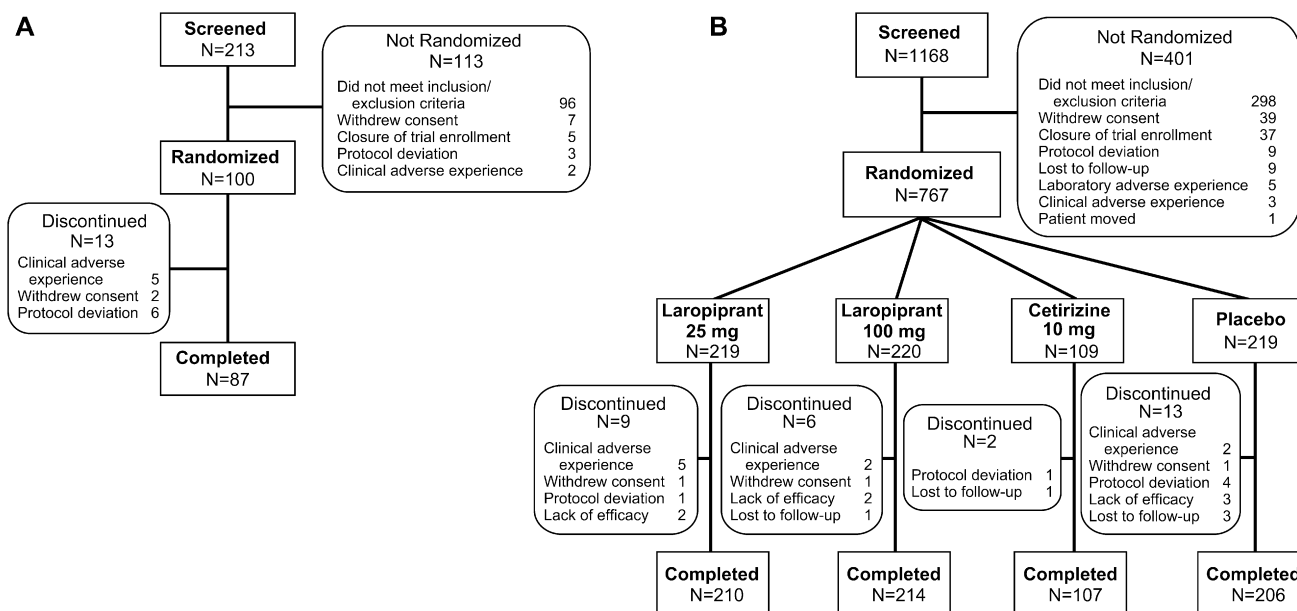


FIG 2. Patient disposition. A, Asthma study. B, AR study.

Expectation-Maximization algorithm.<sup>15</sup> Analyses were also performed by imputed haplotype pair (ie, by diplotype; H/M, H/L, M/M, and M/L).

### Assessments in the AR study

The primary end point, DNSS, assessed daily nasal congestion, rhinorrhea, nasal itching, and sneezing (each rated on a 4-point scale of 0 = none to 3 = severe symptoms). Secondary end points included daytime eye symptoms (tearing, itchy, red, puffy eyes), nighttime symptoms (nasal congestion on awakening, difficulty sleeping, and nighttime awakenings), daytime nasal congestion, and nasal congestion on awakening. These end points have been described in previous studies.<sup>16,17</sup>

### Safety

Safety measurements in both studies included clinical and laboratory monitoring, electrocardiograms, and pulmonary function tests (asthma study only).

### Statistical analysis

In the asthma study, baseline efficacy values for all patients were established in period I (the run-in phase). The primary efficacy analysis on the average change from baseline in FEV<sub>1</sub>, measured once weekly during the last 2 weeks of each active treatment period, used an ANOVA model appropriate for a 2-period crossover design. Secondary efficacy variables used the same model. A sample size of 72 patients had 80% power ( $\alpha = .05$ , 2-sided) to detect a difference of 0.114 L in change from baseline in FEV<sub>1</sub> between treatment groups.

An F test for independence was used to assess associations between diplotypes and baseline efficacy end points. Genetic effects on efficacy were assessed by using a regression model of within-patient treatment difference with diplotypes as covariates. These genetic analyses were exploratory because the study was not designed *a priori* to enroll specified numbers of patients based on diplotype or haplotype status, and no multiplicity adjustments were made.

In the AR study, average changes from baseline over the 2 weeks of treatment in the efficacy parameters were estimated by using an analysis of covariance model with treatment and study site as factors, and baseline values of the dependent variable as a covariate. A sample size of 160 patients in each of the laropirant dose groups and 160 patients in the placebo group had 80% power to detect a treatment difference of 0.16 in the primary end point of DNSS (using a 2-sided test with  $\alpha = .05$ ).

## RESULTS

### Asthma study

**Patients.** Two hundred thirteen patients were screened; 100 patients were randomized to treatment (Fig 2, A). DNA for genetic analysis was available from 171 patients (71 nonrandomized and 100 randomized patients). Demographics and baseline characteristics for these 171 patients are shown in Table I. The mean compliance rate for each of the treatments (placebo, laropirant, montelukast, and laropirant plus montelukast) was greater than 98%.

**Efficacy.** No significant differences were seen in the change from baseline in FEV<sub>1</sub> (in liters) and DASS for laropirant versus placebo and for laropirant plus montelukast versus montelukast (Table II). However, mean differences in change from baseline in FEV<sub>1</sub> and DASS for montelukast versus placebo, montelukast versus laropirant, laropirant plus montelukast versus placebo, and laropirant plus montelukast versus laropirant were all significant ( $P \leq .001$ ). There was no period effect on FEV<sub>1</sub>.

Similarly, no significant treatment differences were observed for laropirant versus placebo and for laropirant plus montelukast versus montelukast for the end points of morning PEF, evening PEF, total daily SABA use, NASS, percentage of days with asthma exacerbations, percentage of patients with an asthma attack, and peripheral blood eosinophil counts (data not shown). On the other hand, montelukast, in comparison with placebo, significantly improved the end points of morning PEF, evening PEF, total daily SABA use, NASS, and the percentage of days with asthma exacerbations (data not shown).

**Genetic profile and haplotype construction.** Allele and genotype frequencies of the *PTGDR* promoter are shown in Table E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org). These frequencies were similar between the randomized and nonrandomized patients (data not shown). Haplotype and diplotype frequencies were similar between the randomized and nonrandomized patients (Table III) and were also similar to those reported previously.<sup>9</sup> Because the majority of patients were white,

**TABLE I.** Demographics and select baseline characteristics in the asthma study\*

| Baseline characteristics                                        | Screened patients with available DNA data† (n = 171) | Randomized patients                         |                                             |
|-----------------------------------------------------------------|------------------------------------------------------|---------------------------------------------|---------------------------------------------|
|                                                                 |                                                      | Laropirant crossed over to placebo (n = 53) | Placebo crossed over to laropirant (n = 47) |
| Age (y), mean ± SD (range)                                      | 37.9 ± 12.8 (18-74)                                  | 39.8 ± 13.6 (19-74)                         | 34.9 ± 10.5 (18-60)                         |
| Sex, no. (%)                                                    |                                                      |                                             |                                             |
| Female                                                          | 106/170 (62.4)                                       | 32 (60.4)                                   | 25 (53.2)                                   |
| Race, no. (%)                                                   |                                                      |                                             |                                             |
| White                                                           | 134/170 (78.8)                                       | 40 (75.5)                                   | 37 (78.7)                                   |
| Other                                                           | 36/170 (21.2)                                        | 13 (24.5)                                   | 10 (21.3)                                   |
| Baseline FEV <sub>1</sub> (L), mean ± SD (range)                | 2.46 ± 0.64 (1.2-4.4)                                | 2.34 ± 0.59 (1.2-3.9)                       | 2.56 ± 0.64 (1.4-3.8)                       |
| Baseline percent predicted FEV <sub>1</sub> , mean ± SD (range) | 70.8 ± 11.9 (33.3-105.2)                             | 67.4 ± 10.8 (41.3-90.7)                     | 69.6 ± 10.3 (47.9-85.0)                     |
| Daytime asthma symptom scores, mean ± SD (range)                | 2.42 ± 0.83 (0.56-4.61)                              | 2.37 ± 0.73 (0.75-3.88)                     | 2.67 ± 0.94 (1.00-4.83)                     |
| No. reporting a history of AR (%)                               | 162/169 (95.9)                                       | 50 (94.3)                                   | 45 (95.7)                                   |
| No. using an inhaled corticosteroid (%)                         | 37/117 (31.6)                                        | 20 (37.7)                                   | 11 (23.4)                                   |

\*Assessed at the prestudy visit (visit 1).

†Seventy-one nonrandomized and 100 randomized patients: Data for these 100 randomized patients are shown in the last 2 columns. The data were not available for all patients, and therefore the actual numbers of patients with data are shown in the denominator.

**TABLE II.** Average FEV<sub>1</sub> and DASS over the final 2 weeks of each treatment period and changes from baseline by treatment group in the asthma study

|                             | No. | FEV <sub>1</sub> during treatment (L), mean ± SD | Change from baseline (L), mean ± SD |
|-----------------------------|-----|--------------------------------------------------|-------------------------------------|
| Placebo                     | 95  | 2.53 ± 0.71                                      | 0.07 ± 0.30                         |
| Laropirant                  | 98  | 2.50 ± 0.70                                      | 0.07 ± 0.32                         |
| Montelukast                 | 90  | 2.60 ± 0.68                                      | 0.16 ± 0.32                         |
| Laropirant plus montelukast | 92  | 2.62 ± 0.70                                      | 0.15 ± 0.34                         |

|                             | No. | DASS during treatment (mean ± SD) | Change from baseline (mean ± SD) |
|-----------------------------|-----|-----------------------------------|----------------------------------|
| Placebo                     | 94  | 2.32 ± 0.86                       | − 0.19 ± 0.70                    |
| Laropirant                  | 97  | 2.32 ± 0.82                       | − 0.18 ± 0.69                    |
| Montelukast                 | 90  | 2.02 ± 0.85                       | − 0.47 ± 0.80                    |
| Laropirant plus Montelukast | 92  | 2.03 ± 0.89                       | − 0.45 ± 0.84                    |

$P > .5$  for mean differences in changes from baseline for laropirant versus placebo and laropirant plus montelukast versus montelukast.  $P \leq .001$  for mean differences in changes from baseline for montelukast versus placebo, montelukast versus laropirant, laropirant plus montelukast versus placebo, and laropirant plus montelukast versus laropirant.

with small sample sizes for other races, the 3 DP1 promoter variants were not summarized by race. Because of the small sample sizes for randomized patients with H/H (n = 1) and L/L (n = 3) diplotypes, the H/H patient was combined into the H/M diplotype group and the L/L patients were combined into the M/L diplotype group for further analysis by diplotype.

**Baseline data analyzed by diplotype.** A wide variance in asthma severity at baseline was seen across patients: the percent predicted FEV<sub>1</sub> (mean ± SD) was 70.8% ± 11.9% (range, 33.3% to 105.2%), ranging from mild to moderate to severe, and the DASS was 2.42 ± 0.83 (range, 0.56–4.61), ranging from symptoms almost none of the time to most of the time. Potential associations between baseline measures of asthma and diplotypes are summarized in Table E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org). These analyses assessed whether the L haplotype was associated with lower baseline asthma severity and the H haplotype with higher baseline asthma severity. In general, no meaningful associations were seen between diplotypes and measures of asthma severity at baseline. Specifically, patients with the H/M or H/L diplotype (ie, bearing the high-efficiency transcription haplotype) had the highest baseline measures of FEV<sub>1</sub> (ie, the converse of the hypothesized relationship), whereas patients with the M/M diplotype had the highest levels of both morning and evening PEF and the lowest total use of daily SABAs (see Table E2).

The relative levels of DASSs across the 4 diplotype groups also failed to show a clear association of the L haplotype with lower asthma severity or the H haplotype with higher severity (see Table E2). For instance, patients with the M/M diplotype had the lowest DASSs at baseline compared with the others; this finding is inconsistent with the hypothesized relationship between diplotype and severity. Furthermore, although the DASS showed a statistically significant difference among *PTGDR* diplotypes at baseline for the screened patients (n = 166,  $P = .009$ ; see Table E2) and for the nonrandomized patients (n = 67,  $P = .021$ ), no significant difference was seen for the randomized patients (n = 99,  $P = .115$ ). Interpreting this result for DASS is further complicated by the fact that these  $P$  values (like all the  $P$  values in Tables E2-E6 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)) were not adjusted for statistical multiplicity because of the exploratory nature of the analyses.

**Efficacy data analyzed by diplotype.** The differences in mean change from baseline in FEV<sub>1</sub> for laropirant versus placebo in the 4 diplotype groups, both within and between diplotypes, are shown in Table E3. No significant increase in FEV<sub>1</sub> for laropirant versus placebo was seen in any of the diplotypes, and no significant difference in treatment effect between the diplotypes was seen ( $P = .575$  for a treatment-by-diplotype interaction). Similarly, no significant increase in mean change from baseline in FEV<sub>1</sub> for laropirant plus

**TABLE III.** Haplotype and diplotype distribution at the promoter region of DP1

| Promoter haplotype                                        | Transcriptional efficiency* | Patients                                            |                      |                        |
|-----------------------------------------------------------|-----------------------------|-----------------------------------------------------|----------------------|------------------------|
|                                                           |                             | Screened patients with available DNA data (n = 171) | Randomized (n = 100) | Nonrandomized (n = 71) |
| TCT                                                       | L                           | 22%                                                 | 22%                  | 23%                    |
| CCT                                                       | M                           | 35%                                                 | 33%                  | 37%                    |
| TTT                                                       | M                           | 27%                                                 | 31%                  | 23%                    |
| CCC                                                       | H                           | 16%                                                 | 16%                  | 17%                    |
| <b>Promoter diplotype (by transcriptional efficiency)</b> |                             |                                                     |                      |                        |
| L/L                                                       |                             | 4%                                                  | 3%                   | 4%                     |
| M/L                                                       |                             | 29%                                                 | 30%                  | 27%                    |
| M/M                                                       |                             | 37%                                                 | 37%                  | 38%                    |
| H/L                                                       |                             | 8%                                                  | 7%                   | 10%                    |
| H/M                                                       |                             | 20%                                                 | 22%                  | 18%                    |
| H/H                                                       |                             | 2%                                                  | 1%                   | 3%                     |

\*Transcriptional efficiency (H, high; M, medium; L, low) *in vitro*, defined as described by Oguma et al.<sup>9</sup>

montelukast versus montelukast was seen in 3 (H/M, H/L, and M/M) of the 4 diplotypes (data not shown).

There were no significant differences in DASSs in the 4 diplotype groups for laropiprant versus placebo (see Table E4) or laropiprant plus montelukast versus montelukast (data not shown). Treatment effects between diplotypes were also not significant. In a similar analysis with the other end points, there were no significant improvements in treatment effects for laropiprant versus placebo or laropiprant plus montelukast versus montelukast in the diplotypes (data not shown).

Similar pharmacogenetic interactions were also examined for montelukast versus placebo; there were no significant differences between DP1 diplotypes for FEV<sub>1</sub> (see Table E5), DASS (see Table E6), or any of the other efficacy end points when comparing montelukast and placebo (data not shown).

**Safety.** Laropiprant was generally well tolerated, with a safety profile generally comparable with that of placebo. The number of patients with 1 or more clinical adverse experiences (AEs) while receiving placebo, laropiprant, montelukast, and laropiprant plus montelukast were as follows: 21 (22.1%) of 95, 33 (33.7%) of 98, 23 (25.3%) of 91, and 23 (24.7%) of 93, respectively. Five patients discontinued because of AEs: 1 while receiving placebo (upper abdominal pain) and 4 while receiving laropiprant (1 for dyspepsia, 2 for asthma exacerbations, and 1 for angioneurotic edema). No serious AEs were reported. Laboratory AEs occurred infrequently during the study. No clinically important safety issues were identified for laropiprant alone or in combination with montelukast.

## AR study

**Patients.** Of 1168 patients screened, 767 were randomly allocated to the 4 treatment groups (Fig 2, B). A majority of the patients were female (64%), with a mean age ( $\pm$  SD) of 37.7 ( $\pm$  11.7) years. Most patients were white (80.4%), followed by black (9.1%). See Table E7 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org) for demographics for randomized patients by treatment group. The mean compliance rate for each of the treatments was greater than 98%. One patient allocated to placebo was randomized in error and never received the study drug; this patient was excluded from efficacy and safety analyses.

**Efficacy.** No significant differences were seen between either dose of laropiprant and placebo in the primary end point of DNSS; however, cetirizine demonstrated a significant improvement

(difference vs placebo of  $-0.25$  [ $P < .001$ ]). Although daytime nasal congestion and nasal congestion on awakening were not improved with any of the active treatments, daytime eye symptoms and nighttime symptoms were significantly improved with cetirizine (respective differences vs placebo of  $-0.15$  score [ $P = .008$ ] and  $-0.13$  score [ $P = .010$ ]). See Table E8 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org) for treatment-period average symptom scores and changes from baseline by treatment group.

**Safety.** Laropiprant was generally well tolerated, with a safety profile generally comparable with that of placebo. The number of patients with 1 or more clinical AEs in the placebo; laropiprant, 25 mg; laropiprant, 100 mg; and cetirizine treatment groups were as follows: 39 (17.9%) of 218, 51 (23.3%) of 219, 54 (24.5%) of 220, and 33 (30.3%) of 109, respectively. Seven patients discontinued because of AEs: 5 in the laropiprant 25-mg treatment group (asthma exacerbation, dyspepsia, back pain, urinary tract infection, and upper respiratory tract infection) and 2 in the laropiprant 100-mg treatment group (renal colic and upper abdominal pain). Two serious AEs were reported: asthma exacerbation in a patient receiving laropiprant, 25 mg (resulted in discontinuation), and nephrolithiasis in a patient receiving laropiprant, 100 mg; neither of these serious AEs was determined to be drug related. Laboratory AEs were infrequent and similar among treatment groups.

## DISCUSSION

We hypothesized in these studies that the blockade of the PGD<sub>2</sub> receptor, DP1, with a potent antagonist would ameliorate asthma and seasonal AR. A second hypothesis was that the combination of 2 receptor antagonists acting on 2 different inflammatory pathways in asthma would have additive clinical effects. Hence, the asthma study also examined whether the combination of montelukast, a leukotriene receptor antagonist that is an established asthma controller,<sup>18</sup> and laropiprant would show an additive improvement in treatment effects.

On both the primary (FEV<sub>1</sub>) and secondary (symptoms) efficacy end points of asthma, no consistent improvements were noted for laropiprant versus placebo. Also, no consistent improvements in FEV<sub>1</sub> or asthma symptoms were noted for laropiprant plus montelukast versus montelukast. It is not known whether longer exposure to treatment, the use of asthma end points other than the several tested, or both would have allowed a demonstration

of efficacy by laropiprant, but it appears unlikely that longer treatment would yield an effect that is clinically important because clinically relevant effects of inhaled corticosteroids are generally seen by 2 weeks.<sup>19</sup> The clear demonstration of efficacy by montelukast alone, serving as a positive control, shows that the study design and conduct were broadly appropriate, with sufficient power to demonstrate the efficacy of laropiprant along the same magnitude seen with montelukast.

Oguma et al<sup>9</sup> identified certain haplotypes from *PTGDR* promoter variations that differed in their *in vitro* transcriptional efficiency. We explored in this study whether the effects of DP1 antagonism varied based on such haplotype definitions. Our pilot results showed no meaningful treatment effect of laropiprant (vs placebo) or laropiprant plus montelukast (vs montelukast) on FEV<sub>1</sub> or asthma symptoms when the population was analyzed based on *PTGDR* promoter diplotype.

In their US study, Oguma et al<sup>9</sup> showed that the presence of at least 1 copy of the low-transcriptional-efficiency haplotype (L haplotype) was associated with a lower risk of asthma in both the white and black populations. This result, however, was not seen in studies of a Spanish white population,<sup>20</sup> a Chinese population,<sup>21</sup> or Mexican, Puerto Rican, and African-American populations,<sup>22</sup> nor was it suggested in our US study. Other nonethnic differences among these studies, such as inclusion and exclusion criteria, might also have contributed to the differing results. In the present study, the small sample size for nonwhite subjects limited meaningful comparison between races.

This study also offered us the opportunity to explore the implications of Oguma et al<sup>9</sup> and the suggestions of Morita and Nagai<sup>23</sup> that asthma severity would be lower in patients with at least 1 copy of the L haplotype and, conversely, higher with the H haplotype. Our asthma study included patients whose asthma severity ranged from mild to moderate to severe. However, our results fail to support the postulated relationship between *PTGDR* promoter diplotypes and asthma severity. In particular, asthma was not less severe in patients with diplotypes associated with low transcriptional efficiency. Instead, the numerically highest lung function at baseline was seen in patients with at least 1 copy of the H haplotype, whereas patients with the M/M diplotype had the lowest daytime asthma symptoms at baseline. However, the inability to show a relationship between *PTGDR* promoter variants and asthma severity might not negate the suggestion that certain variants confer an increased susceptibility to asthma; this is a question not addressed by the current asthma study because all patients, by definition, had persistent asthma.

In interpreting our results, it must be kept in mind that this pilot genetic analysis was not designed *a priori* to enroll specified numbers of patients based on diplotype or haplotype status, and the overall sample size of 171 patients was too small for significant genetic analysis of a widespread, multiracial, population-based disease such as asthma. For the genetic analyses, this study is likely underpowered to draw a clear conclusion that there is a lack of association between particular diplotypes or haplotypes (eg, the H haplotype, present in the lowest proportion of both the general and asthmatic populations<sup>9</sup>) and measures of asthma (including baseline characteristics). Also, there are statistical multiplicity issues associated with testing the large number of baseline characteristics we examined, adding to the difficulty of drawing clear conclusions from these results. For instance, the significant association of baseline daytime asthma symptoms with the diplotypes observed in screened patients was not observed in

randomized patients, and the effect sizes observed were inconsistent with the hypothesized relationship between the L-bearing diplotype (vs H) and asthma severity. Nevertheless, even by pattern or trend, these pilot data are not consistent with the hypothesis of an association between *PTGDR* promoter variants and asthma severity. Additionally, an effect on symptoms, bronchoconstriction, or both would have been anticipated if DP1 did have a direct and important role in allergic airway disease.

As with the results from the asthma study, symptoms of AR were not ameliorated by blocking the action of PGD<sub>2</sub> through antagonism at DP1. Laropiprant did not improve the primary end point, which measured the burden of nasal symptoms, and did not improve other symptoms, such as eye and nighttime symptoms. The efficacy of the antihistamine cetirizine in the primary end point and in some of the secondary end points, despite low pollen counts at approximately 30% of the study centers (caused by Hurricane Isabel), is a strong indication that the design and conduct of the study did not have an adverse effect on the results with laropiprant. The relative roles of DP1 and CRTH2 in patients with AR remain unclear. For instance, although both receptors are expressed in the nasal mucosa of patients with AR<sup>24</sup> and by eosinophils infiltrating the mucosa in patients with nasal polypsis,<sup>25</sup> only CRTH2 levels correlated with the level of eosinophil infiltration into the upper airway.<sup>24</sup> Recent reviews of data from animal and clinical studies<sup>3,4</sup> have assigned complementary roles to the PGD<sub>2</sub> receptors in allergic airway disease. Along these lines, our results, although not demonstrating a clinically meaningful function for DP1 in the pathogenesis of asthma or seasonal AR, do not exclude a role for the CRTH2 receptor in either disease state.

In conclusion, laropiprant, at the doses used, was generally well tolerated, with a safety profile generally comparable with that of placebo. These studies, which we believe are the first to report the clinical results of DP1 antagonism in asthma and AR, did not demonstrate efficacy of a potent DP1 antagonist on lung function and asthma symptoms or on nasal and other AR symptoms. Furthermore, the study did not demonstrate an association between baseline asthma severity and *PTGDR* promoter variants that previously had been associated with asthma susceptibility. Taken together, these results suggest that DP1 antagonism is not an important mechanism to pursue for new asthma or AR therapies.

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**Clinical implications:** This clinical study highlights the limitations of targeting DP1 for airway disease therapy and discusses whether allelic variants in the *PTGDR* gene are associated with asthma severity.

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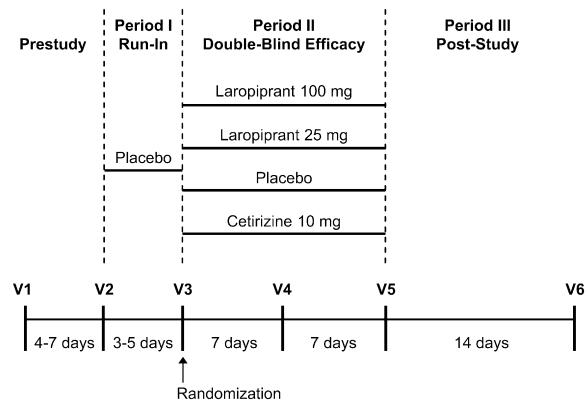


**FIG E1.** Design of AR study. V, Visit.

**TABLE E1.** Allelic and genotype frequencies at the promoter region of DP1 in screened patients\*

| SNP    | Allele frequency (%) |      | Genotype frequency (%) |      |      | HWD    | P value† |
|--------|----------------------|------|------------------------|------|------|--------|----------|
|        | C                    | T    | C/C                    | C/T  | T/T  |        |          |
| T-197C | 16.1                 | 83.9 | 1.7                    | 28.7 | 69.6 | −0.008 | .420     |
| C-441T | 72.5                 | 27.5 | 53.2                   | 38.6 | 8.2  | 0.006  | .678     |
| T-549C | 50.6                 | 49.4 | 26.9                   | 47.4 | 25.7 | 0.013  | .492     |

SNP, Single nucleotide polymorphism; HWD, Hardy-Weinberg disequilibrium coefficient.

\*All patients with available DNA data (n = 171).

†P value of the  $\chi^2$  test of Hardy-Weinberg equilibrium.

**TABLE E2.** Association between baseline characteristic and diplotype in screened patients with available DNA data (n = 171)\*

| Diplotype†                             | No. | Mean ± SD     | Range      | P value‡ |
|----------------------------------------|-----|---------------|------------|----------|
| FEV <sub>1</sub> (L)                   |     |               |            |          |
| H/M                                    | 38  | 2.53 ± 0.6    | 1.23-3.81  | .639     |
| H/L                                    | 14  | 2.60 ± 0.6    | 1.63-3.97  |          |
| M/M                                    | 64  | 2.43 ± 0.5    | 1.44-3.71  |          |
| M/L                                    | 55  | 2.41 ± 0.7    | 1.16-4.38  |          |
| All                                    | 171 | 2.46 ± 0.6    | 1.16-4.38  |          |
| Percent predicted FEV <sub>1</sub> (%) |     |               |            |          |
| H/M                                    | 38  | 73.4 ± 10.3   | 49.5-92.8  | .154     |
| H/L                                    | 13  | 75.4 ± 11.9   | 52.7-95.3  |          |
| M/M                                    | 64  | 69.8 ± 12.0   | 36.6-105.2 |          |
| M/L                                    | 55  | 69.2 ± 12.6   | 33.3-97.9  |          |
| All                                    | 170 | 70.8 ± 11.9   | 33.3-105.2 |          |
| DASS                                   |     |               |            |          |
| H/M                                    | 37  | 2.66 ± 0.81   | 1.29-4.15  | .009     |
| H/L                                    | 13  | 2.56 ± 1.04   | 1.16-4.61  |          |
| M/M                                    | 62  | 2.15 ± 0.77   | 0.56-4.11  |          |
| M/L                                    | 54  | 2.54 ± 0.80   | 0.79-4.25  |          |
| All                                    | 166 | 2.42 ± 0.83   | 0.56-4.61  |          |
| NASS                                   |     |               |            |          |
| H/M                                    | 37  | 0.52 ± 0.49   | 0.00-1.53  | .546     |
| H/L                                    | 13  | 0.47 ± 0.53   | 0.00-1.33  |          |
| M/M                                    | 63  | 0.55 ± 0.50   | 0.00-2.00  |          |
| M/L                                    | 53  | 0.65 ± 0.56   | 0.00-2.00  |          |
| All                                    | 166 | 0.57 ± 0.52   | 0.00-2.00  |          |
| Morning PEF (L/min)                    |     |               |            |          |
| H/M                                    | 37  | 404 ± 67.0    | 273-579    | .833     |
| H/L                                    | 14  | 404 ± 94.4    | 311-579    |          |
| M/M                                    | 62  | 416 ± 76.6    | 280-689    |          |
| M/L                                    | 54  | 405 ± 78.0    | 263-570    |          |
| All                                    | 167 | 408 ± 76.2    | 263-689    |          |
| Eosinophil count (10 <sup>3</sup> /μL) |     |               |            |          |
| H/M                                    | 35  | 0.28 ± 0.19   | 0.10-0.90  | .772     |
| H/L                                    | 12  | 0.28 ± 0.15   | 0.10-0.50  |          |
| M/M                                    | 62  | 0.32 ± 0.24   | 0.10-1.40  |          |
| M/L                                    | 55  | 0.31 ± 0.19   | 0.00-0.80  |          |
| All                                    | 164 | 0.31 ± 0.21   | 0.00-1.40  |          |
| Evening PEF (L/min)                    |     |               |            |          |
| H/M                                    | 37  | 419.7 ± 76.5  | 281-599    | .981     |
| H/L                                    | 13  | 424.7 ± 104.6 | 291-594    |          |
| M/M                                    | 63  | 426.7 ± 78.9  | 283-700    |          |
| M/L                                    | 54  | 422.8 ± 82.3  | 262-604    |          |
| All                                    | 167 | 423.7 ± 81.0  | 262-700    |          |
| Total daily β-agonist use (puffs)      |     |               |            |          |
| H/M                                    | 37  | 3.6 ± 2.5     | 0.0-12.7   | .706     |
| H/L                                    | 13  | 3.8 ± 1.7     | 1.0-6.6    |          |
| M/M                                    | 62  | 3.2 ± 1.7     | 0.0-9.5    |          |
| M/L                                    | 53  | 3.6 ± 2.1     | 0.0-9.7    |          |
| All                                    | 165 | 3.5 ± 2.0     | 0.0-12.7   |          |

Transcriptional efficiency: *H*, high; *M*, medium; *L*, low.

\*Seventy-seven percent of patients were white; data were not summarized by race because of small sample sizes for persons of other races.

†Because of small sample sizes for patients with H/H (n = 1) and L/L (n = 3) diplotypes, the H/H patient was combined into the H/M diplotype group and the L/L patients were combined into the M/L diplotype group.

‡P value of the F test for independence of baseline characteristics and genotype.

**TABLE E3.** Differences within and between diplotypes for laropiprant versus placebo in change from baseline in FEV<sub>1</sub> (liters) averaged over the last 2 weeks of each treatment period (asthma study)

| Laropiprant vs placebo                                                |                |                                   |
|-----------------------------------------------------------------------|----------------|-----------------------------------|
| Difference in FEV <sub>1</sub> within diplotype                       |                |                                   |
| Diplotype                                                             | No.            | Mean* $\pm$ SD (95% CI)           |
| H/M                                                                   | 21             | 0.01 $\pm$ 0.22 (−0.09 to 0.10)   |
| H/L                                                                   | 6              | −0.11 $\pm$ 0.13 (−0.21 to −0.01) |
| M/M                                                                   | 34             | −0.01 $\pm$ 0.25 (−0.10 to 0.07)  |
| M/L                                                                   | 32             | 0.04 $\pm$ 0.27 (−0.06 to 0.13)   |
| Total                                                                 | 93             | 0.00 $\pm$ 0.24 (−0.05 to 0.05)   |
| Difference in treatment effect in FEV <sub>1</sub> between diplotypes |                |                                   |
| Diplotype                                                             | Estimated mean | P value                           |
| H/M vs M/L + M/M                                                      | −0.00          | .959                              |
| M/L vs H/M + M/M                                                      | 0.04           | .489                              |
| Overall genetic effect                                                |                | .575                              |

Transcriptional efficiency: *H*, high; *M*, medium; *L*, low.

\*A positive change denotes a larger increase from baseline in the laropiprant group compared with the placebo group.

**TABLE E4.** Differences within and between diplotypes for laropiprant versus placebo in change from baseline in DASS averaged over the last 2 weeks of each treatment period (asthma study)

| Laropiprant vs placebo                                    |                |                                        |
|-----------------------------------------------------------|----------------|----------------------------------------|
| Difference in DASS within diplotype                       |                |                                        |
| Diplotype                                                 | No.            | Mean* $\pm$ SD (95% CI)                |
| H/M                                                       | 21             | $-0.14 \pm 0.46$ ( $-0.33$ to $0.06$ ) |
| H/L                                                       | 6              | $-0.35 \pm 0.63$ ( $-0.85$ to $0.15$ ) |
| M/M                                                       | 34             | $0.11 \pm 0.60$ ( $-0.09$ to $0.31$ )  |
| M/L                                                       | 31             | $0.10 \pm 0.83$ ( $-0.19$ to $0.39$ )  |
| Total                                                     | 92             | $0.02 \pm 0.67$ ( $-0.12$ to $0.16$ )  |
| Difference in treatment effect in DASS between diplotypes |                |                                        |
| Diplotype                                                 | Estimated mean | P value                                |
| H/M vs M/L + M/M                                          | $-0.24$        | .153                                   |
| M/L vs H/M + M/M                                          | $0.11$         | .452                                   |
| Overall genetic effect                                    |                | .262                                   |

Transcriptional efficiency: *H*, high; *M*, medium; *L*, low.

\*A negative change denotes an improvement from baseline in the laropiprant group compared with the placebo group.

**TABLE E5.** Differences within and between diplotypes for montelukast versus placebo in change from baseline in FEV<sub>1</sub> (liters) averaged over the last 2 weeks of each treatment period (asthma study)

| Montelukast vs placebo                                                |                |                             |
|-----------------------------------------------------------------------|----------------|-----------------------------|
| Difference in FEV <sub>1</sub> within diplotype                       |                |                             |
| Diplotype                                                             | No.            | Mean* ± SD (95% CI)         |
| H/M                                                                   | 21             | 0.12 ± 0.29 (−0.00 to 0.25) |
| H/L                                                                   | 5              | 0.11 ± 0.24 (−0.11 to 0.32) |
| M/M                                                                   | 34             | 0.07 ± 0.17 (0.01 to 0.12)  |
| M/L                                                                   | 30             | 0.11 ± 0.24 (0.02 to 0.19)  |
| Total                                                                 | 90             | 0.10 ± 0.23 (0.05 to 0.14)  |
| Difference in treatment effect in FEV <sub>1</sub> between diplotypes |                |                             |
| Diplotype                                                             | Estimated mean | P value                     |
| H/M vs M/L + M/M                                                      | 0.04           | .521                        |
| M/L vs H/M + M/M                                                      | 0.01           | .841                        |
| Overall genetic effect                                                |                | .821                        |

Transcriptional efficiency: *H*, high; *M*, medium; *L*, low.

\*A positive change denotes a larger increase from baseline in the montelukast group compared with the placebo group.

**TABLE E6.** Differences within and between diplotypes for montelukast versus placebo in change from baseline in DASS averaged over the last 2 weeks of each treatment period (asthma study)

| Montelukast vs placebo                                    |                |                                         |
|-----------------------------------------------------------|----------------|-----------------------------------------|
| Difference in DASS within diplotype                       |                |                                         |
| Diplotype                                                 | No.            | Mean* $\pm$ SD (95% CI)                 |
| H/M                                                       | 21             | $-0.25 \pm 0.55$ ( $-0.48$ to $-0.02$ ) |
| H/L                                                       | 5              | $-0.46 \pm 0.69$ ( $-1.07$ to $0.15$ )  |
| M/M                                                       | 34             | $-0.28 \pm 0.57$ ( $-0.47$ to $-0.09$ ) |
| M/L                                                       | 30             | $-0.23 \pm 0.54$ ( $-0.42$ to $-0.04$ ) |
| Total                                                     | 90             | $-0.27 \pm 0.55$ ( $-0.38$ to $-0.15$ ) |
| Difference in treatment effect in DASS between diplotypes |                |                                         |
| Diplotype                                                 | Estimated mean | P value                                 |
| H/M vs M/L + M/M                                          | 0.01           | .965                                    |
| M/L vs H/M + M/M                                          | 0.04           | .774                                    |
| Overall genetic effect                                    |                | .855                                    |

Transcriptional efficiency: *H*, high; *M*, medium; *L*, low.

\*A negative change denotes an improvement from baseline in the montelukast group compared with the placebo group.

**TABLE E7.** Demographics for randomized patients by treatment group in the AR study\*

|                                | Laropiprant, 25 mg (n = 219) | Laropiprant, 100 mg (n = 220) | Cetirizine, 10 mg (n = 109) | Placebo (n = 219)        |
|--------------------------------|------------------------------|-------------------------------|-----------------------------|--------------------------|
| Age (y), mean $\pm$ SD (range) | 37.6 $\pm$ 12.05 (18-74)     | 38.1 $\pm$ 11.75 (18-75)      | 38.0 $\pm$ 11.05 (18-72)    | 37.2 $\pm$ 11.76 (18-68) |
| Sex, no. (%)                   |                              |                               |                             |                          |
| Female                         | 139 (63.5)                   | 146 (66.4)                    | 68 (62.4)                   | 137 (62.6)               |
| Race, no. (%)                  |                              |                               |                             |                          |
| White                          | 181 (82.6)                   | 174 (79.1)                    | 84 (77.1)                   | 178 (81.3)               |
| Other                          | 38 (17.4)                    | 46 (20.9)                     | 25 (22.9)                   | 41 (18.7)                |

\*Assessed at the prestudy visit (visit 1).

**TABLE E8.** Average symptom scores over 2 weeks of treatment and changes from baseline by treatment group in the AR study

|                                  | Score during treatment (mean $\pm$ SD) | Change from baseline (mean $\pm$ SD) |
|----------------------------------|----------------------------------------|--------------------------------------|
| DNSS                             |                                        |                                      |
| Laropiprant, 25 mg               | 1.91 $\pm$ 0.58                        | −0.26 $\pm$ 0.45                     |
| Laropiprant, 100 mg              | 1.90 $\pm$ 0.61                        | −0.30 $\pm$ 0.50                     |
| Cetirizine, 10 mg                | 1.68 $\pm$ 0.62                        | −0.48 $\pm$ 0.62                     |
| Placebo                          | 1.94 $\pm$ 0.63                        | −0.24 $\pm$ 0.53                     |
| Daytime Nasal Congestion Score   |                                        |                                      |
| Laropiprant, 25 mg               | 2.16 $\pm$ 0.60                        | −0.22 $\pm$ 0.53                     |
| Laropiprant, 100 mg              | 2.07 $\pm$ 0.70                        | −0.33 $\pm$ 0.53                     |
| Cetirizine, 10 mg                | 2.12 $\pm$ 0.68                        | −0.38 $\pm$ 0.70                     |
| Placebo                          | 2.18 $\pm$ 0.63                        | −0.25 $\pm$ 0.60                     |
| Daytime Eye Symptoms Score       |                                        |                                      |
| Laropiprant, 25 mg               | 1.42 $\pm$ 0.72                        | −0.23 $\pm$ 0.46                     |
| Laropiprant, 100 mg              | 1.49 $\pm$ 0.77                        | −0.25 $\pm$ 0.50                     |
| Cetirizine, 10 mg                | 1.16 $\pm$ 0.76                        | −0.33 $\pm$ 0.54                     |
| Placebo                          | 1.49 $\pm$ 0.78                        | −0.23 $\pm$ 0.51                     |
| Nighttime Symptoms Score         |                                        |                                      |
| Laropiprant, 25 mg               | 1.46 $\pm$ 0.64                        | −0.18 $\pm$ 0.44                     |
| Laropiprant, 100 mg              | 1.46 $\pm$ 0.66                        | −0.24 $\pm$ 0.44                     |
| Cetirizine, 10 mg                | 1.31 $\pm$ 0.58                        | −0.33 $\pm$ 0.50                     |
| Placebo                          | 1.46 $\pm$ 0.66                        | −0.21 $\pm$ 0.47                     |
| Nighttime Nasal Congestion Score |                                        |                                      |
| Laropiprant, 25 mg               | 2.18 $\pm$ 0.63                        | −0.21 $\pm$ 0.54                     |
| Laropiprant, 100 mg              | 2.15 $\pm$ 0.68                        | −0.25 $\pm$ 0.53                     |
| Cetirizine, 10 mg                | 2.19 $\pm$ 0.67                        | −0.29 $\pm$ 0.63                     |
| Placebo                          | 2.21 $\pm$ 0.65                        | −0.24 $\pm$ 0.54                     |

Number of patients evaluated: laropiprant, 25 mg (n = 217); laropiprant, 100 mg (n = 219); cetirizine, 10 mg (n = 109); and placebo (n = 215).  $P \leq .05$  for mean differences in changes from baseline for cetirizine versus placebo for DNSS, Daytime Eye Symptoms Score, and Nighttime Symptoms Score.