# Common Drug Review
## *Clinical Review Report*

**December 2014**

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| **Drug** | Standardized Allergenic Extract, Timothy grass (*Phleum pratense*) (GRASTEK) (sublingual tablet 2,800 BAU) |
| **Indication** | Reducing the signs and symptoms of moderate to severe seasonal Timothy and related grass pollen-induced allergic rhinitis (with or without conjunctivitis) in adults and children 5 years of age and older confirmed by clinically relevant symptoms for at least two pollen seasons and a positive skin prick test and/or a positive titre to *Phleum pratense* specific immunoglobulin E, and who have responded inadequately or are intolerant to conventional pharmacotherapy. |
| **Listing request** | Treatment of patients with Timothy and related grass pollen-induced allergic rhinitis with or without conjunctivitis, in adults and children five years of age and older. |
| **Manufacturer** | Merck Canada Inc. |

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# ABBREVIATIONS

| | |
|---|---|
| **5GPAE** | five-grass pollen allergen extract |
| **AE** | adverse event |
| **ANOVA** | analysis of variance |
| **AR** | allergic rhinitis |
| **ARC** | allergic rhinoconjunctivitis |
| **BAU** | bioequivalent allergy unit |
| **CDR** | Common Drug Review |
| **CI** | confidence interval |
| **CrI** | credible interval |
| **DB** | double-blind |
| **DMS** | daily medication score |
| **DSS** | daily symptom score |
| **FAS** | full analysis set |
| **GPS** | grass pollen season |
| **IgE** | immunoglobulin E |
| **ITT** | intention-to-treat |
| **LDA** | longitudinal data analysis |
| **NR** | not reported |
| **PP** | per-protocol |
| **PPAE** | *Phleum pratense* allergen extract |
| **QoL** | quality of life |
| **RCT** | randomized controlled trial |
| **RQLQ** | Rhinoconjunctivitis Quality of Life Questionnaire |
| **SAE** | serious adverse event |
| **SCIT** | subcutaneous immunotherapy |
| **SD** | standard deviation |
| **SE** | standard error |
| **SLIT** | sublingual immunotherapy |
| **SQ-T** | standardized quality units tablet |
| **SQ-U** | standardized quality units |
| **TCS** | total combined score |
| **VAS** | visual analogue scale |
| **WAO** | World Allergy Organization |
| **WDAE** | withdrawal due to adverse event |

# EXECUTIVE SUMMARY

## Introduction

Allergic rhinitis (AR) is an immunoglobulin E–mediated inflammation of the nasal mucosa triggered by exposure to allergens. AR has been categorized as seasonal or perennial. Generally, seasonal AR is induced by pollen and perennial AR by allergens such as those from animals and dust mites. Symptoms include rhinorrhea (nasal discharge), nasal congestion, nasal itching, and sneezing. AR is often accompanied by allergic conjunctivitis, characterized by itchiness, redness, or irritation of the eye. Current treatment options for AR (with or without conjunctivitis) include avoidance of allergens, pharmacotherapy (including antihistamines, intranasal steroids, decongestants, and others), and specific immunotherapy. Allergen avoidance is not always feasible or practical and pharmacotherapy may not provide adequate relief or be suitable for long-term use. Depending on the route of administration, immunotherapy is categorized as subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). SCIT requires frequent clinic visits, repeated injections, and the risk of systemic reactions including anaphylactic shock. Two SLIT products have been approved by Health Canada, including five-grass pollen allergen extract (5GPAE; brand name Oralair) and now Timothy grass (*Phleum pratense*) standardized allergenic extract (PPAE; brand name Grastek).

PPAE is available as a sublingual tablet of 2,800 bioequivalent allergy units (BAU), equivalent to 75,000 standardized quality units (SQ-U). The Health Canada–recommended dosage is 2,800 BAU sublingually once daily, starting at least eight weeks before the grass pollen season (GPS), and continuing through the entire GPS.

| Indication under review |
| --- |
| Reducing the signs and symptoms of moderate to severe seasonal Timothy and related grass pollen-induced allergic rhinitis (with or without conjunctivitis) in adults and children 5 years of age and older confirmed by clinically relevant symptoms for at least two pollen seasons and a positive skin prick test and/or a positive titre to *Phleum pratense* specific immunoglobulin E; and who have responded inadequately, or are intolerant to conventional pharmacotherapy. |
| **Listing criteria requested by sponsor** |
| Treatment of patients with Timothy and related grass pollen-induced allergic rhinitis with or without conjunctivitis, in adults and children five years of age and older. |

The objective is to conduct a systematic review of the beneficial and harmful effects of PPAE 2,800 BAU, for the treatment of Timothy and related grass pollen–induced AR, with or without conjunctivitis, in adults and children aged five years and older.

## Results and Interpretation

### Included Studies

Eight multi-centre, randomized, parallel-group, double-blind, placebo-controlled studies (GT-02 [N = 855], GT-07 [N = 114], GT-08 [N = 634], GT-12 [N = 253], GT-14 [N = 329], P05238 [N = 439], P05239 [N = 345], and P08067 [N = 1,501]) were included for this systematic review. Six studies (GT-08, GT-12, GT-14, P05238, P05239, and P08067) were phase 3, one study (GT-02) was phase 2/3, and one study (GT-07) was phase 2. Five studies (GT-02, GT-07, GT-08, GT-14, and P05238) involved adult participants, two studies (GT-12, P05239) involved pediatric participants, and one study (P08067)

involved a mixed population of adult and pediatric participants. All studies, except GT-02, randomized patients to one of PPAE 2,800 BAU daily or placebo. In GT-02, participants were randomized to one of six treatment groups based on whether loratadine or placebo were provided as rescue medication; treatment groups included PPAE 2,500 SQ-U + loratadine, PPAE 7,500 SQ-U + loratadine, PPAE 75,000 SQ-U + loratadine, PPAE 75,000 SQ-U + placebo, placebo + loratadine, and placebo + placebo. Results for treatment groups with non-Health Canada doses (2,500 SQ-U and 7,500 SQ-U) are not included in this review. The treatment groups in which loratadine was not provided are specifically designated in the report as PPAE (no L) or placebo (no L). No relevant studies comparing therapy with PPAE versus SCIT or other SLIT products were identified.

Pre-seasonal treatment durations ranged between eight and 16 weeks across studies GT-02, GT-07, GT-12, GT-14, P05238, P05239, and P08067, for total treatment duration of approximately 24 weeks. In study GT-08, the pre-seasonal treatment duration could range from 16 to 35 weeks.

All study protocols (except study GT-02, as noted above) allowed for the use of concomitant rescue medications as required, either for AR or asthma symptoms, in a stepwise manner depending on the persistence and severity of their symptoms.

Outcomes in all studies, except GT-08, were assessed over one GPS. Study GT-08 assessed outcomes in each GPS over five years: seasonal treatment for three years and two non-treatment years. Rhinoconjunctivitis daily symptom score (DSS) and daily medication score (DMS) over the entire GPS were the co-primary outcomes in GT-02, GT-08, and GT-12. DSS over the entire GPS was the primary outcome in GT-14. The total combined score (TCS; DSS plus DMS) over the entire GPS was the primary outcome in P05238, P05239, and P08067. In study GT-07, which specifically enrolled patients with asthma, the primary outcome was the asthma medication score over the entire GPS.

The DSS encompassed six symptoms — four nasal symptoms and two ocular symptoms — and was measured using a four-point rating scale (0 to 3). The maximum total score possible was 18. The DMS was based on the intake of rescue medications. Protocol-specified rescue medications and DMS scoring systems varied across the studies; thus, the maximum possible DMS varied across the trials, being 12 for GT-14; 30 for GT-08; 34 for GT-02 and GT-12; 36 for P05238, P05239, and P08067; and 38 for GT-07. The daily TCS was the sum of daily DSS and DMS

Health-related quality of life was assessed in six studies using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). It uses a seven-point scale (0 = not impaired and 6 = severely impaired) to assess seven domains (sleep impairment, non-nasal symptoms, practical problems, nasal symptoms, eye symptoms, activity limitations, and emotional difficulty). The RQLQ score is the mean of the domain scores, with maximum possible score 6.

**Efficacy**

Adjusted mean DSSs over the entire GPS were reported in all eight studies and were lower for PPAE groups (range 2.18 to 5.69) compared with placebo groups (range 2.80 to 6.06). Between-treatment mean differences ranged between –0.37 and –1.29, being statistically significant in five studies (GT-08, P05238, GT-12, P05239, and P08067) and non-significant in three studies (GT-07, GT-02, and GT-14).

Adjusted mean DMSs over the entire GPS were reported in all eight studies and were lower with PPAE groups (range 0.78 to 2.60) compared with placebo groups (range 1.19 to 3.81). Between-treatment

differences ranged from –0.4 to –1.2, being statistically significant in four studies (GT-02, GT-08, GT-12, and P08067) and non-significant in four studies (GT-07, GT-14, P05238, and P05239).

Adjusted mean TCSs over the entire GPS were reported in six studies and were lower with PPAE (range 3.70 to 6.74) compared with placebo (range 4.86 to 7.53). Between-treatment mean differences ranged from –0.8 to –2.3, being statistically significant in five studies (GT-08, P05238, GT-12, P05239, and P08067) and non-significant in one study (GT-14). The corresponding relative percentage differences in mean TCS ranged between –10% and –34%, being ≥ 20% in four studies (GT-08, P05238, GT-12, and P05239).

DSS, DMS, and TCS were consistently not statistically significantly different between PPAE and placebo in study GT-14. While the manufacturer suggested that flawed reporting or overlapping allergies may explain the lack of statistical significance, an alternate explanation could be a lack of efficacy for PPAE at higher levels of severity, given that DSS, DMS, and TCS were noticeably higher in study GT-14 compared with other included studies.

While many of the included studies reported statistically significant improvements with PPAE compared with placebo, in terms of DSS, DMS, and TCS, these scales have not been validated and the clinical significance of the observed differences is unclear. The World Allergy Organization recommends the use of a combined score to determine efficacy of immunotherapy, suggesting that a ≥ 20% between-treatment difference in the combined score represents a clinically meaningful difference. Although a between-treatment difference in the TCS of ≥ 20% was achieved in a number of trials, the absolute differences in the TCS were small and it was noted that small absolute differences can translate into large percentage differences when TCS scores are relatively low. Whether patients may achieve a ≥ 20% reduction in the TCS at higher levels of symptom severity is unclear.

In addition, there are a number of potential sources of bias, which may affect the validity of the above reported results. Potential unblinding due to the more frequent experience of oral or pharyngeal adverse events in the PPAE group may have influenced patients' assessment of symptoms, quality of life, and need for rescue medication. Knowledge of treatment allocation may also have affected the frequency of diary entries regarding symptoms and medication. The extent of missing data is unclear; however, differential missing data may bias results.

Although the immunotherapy was administered seasonally for several years, only one study examined the effects of PPAE over multiple seasons. Despite findings of continuing efficacy over multiple treatment seasons, the findings are limited by the high (approximately 50%) and differential dropout after the first season.

A key gap in the evidence for PPAE is the absence of randomized controlled trials (RCTs) directly comparing PPAE with SCIT or other SLIT products. The manufacturer provided an indirect comparison suggesting that, in terms of symptom or medication scores, SLIT (both PPAE and 5GPAE combined) did not differ statistically from SCIT, and that PPAE did not differ statistically from 5GPAE. However, there was considerable heterogeneity between trials; thus, the results of the indirect comparison should be interpreted with caution.

**Harms**

In all the included studies, adverse events were higher in the PPAE group compared with the placebo group and were reported as being mild or moderate in severity. The most frequently reported adverse events were those associated with the mouth or throat. The treatment durations were approximately 24 weeks, in most studies; however, longer-term data (seasonal treatment over three years) available from an extension to study GT-08 did not reveal additional safety issues.

Serious adverse events and withdrawals due to adverse events were few and similar in both groups across the trials. Three studies reported one death each in the PPAE groups, but these were not considered to be related to PPAE.

## Pharmacoeconomic Summary

The manufacturer submitted two economic evaluations: a cost-utility analysis (CUA) and a cost minimization analysis (CMA) from a Canadian health care payer's perspective. The CUA was based on inputs mainly from the literature and, to a lesser extent, on a network meta-analysis and observations from the G8 trial. Also, in the CUA, the price used for PPAE was outdated ($3.20 per tablet). It compared PPAE with symptomatic treatment and 5GPAE during a five-year time horizon. The CMA was based mainly on inputs from the network meta-analysis, and it estimated the cost differences between PPAE and perennial and seasonal SCIT, and 5GPAE over a time horizon of three years from a Canadian health care payer's perspective. Costs considered in the CMA included drug acquisition cost, pharmacy fees, physician visits and injection services, pulmonary function test (for SCIT), and lost productivity (from societal perspective). Both analyses targeted patients who suffered from moderate to severe seasonal AR to grass pollen. The manufacturer's submitted price is $3.80 per tablet, or $555 to $897 per year for a GPS of three to six months' duration.

## Results of Manufacturer's Analysis

In the base-case CUA, the manufacturer reported that PPAE had an incremental cost-utility ratio of $36,035 per QALY compared with symptomatic treatment, and an incremental cost-utility ratio of $33,098 per QALY compared with 5GPAE (based on the PPAE price of $3.20 instead of $3.80 per tablet). For the CMA, the manufacturer reported three-year cost savings with PPAE as $1,391 per patient compared with perennial SCIT; $862 per patient compared with seasonal SCIT; and $756 per patient compared with 5GPAE.

## Interpretations and Key Limitations

The Common Drug Review (CDR) noted the following limitations with the CUA:

- The structure of the economic model included health states for allergic asthma, which does not appear to be valid, and did not include health states pertaining to symptom management and resolution.
- The manufacturer assumed differences in post-treatment efficacy between PPAE and 5GPAE; however, the manufacturer's network meta-analysis (included in the submission) showed that 5GPAE was associated with numerically better efficacy (in term of symptoms and medication scores), although it did not reach the statistical significance.
- SCIT was not included as a comparator, despite being included in the network meta-analysis. The results of the network meta-analysis showed that the SCIT has numerically better efficacy than PPAE in term of symptoms and medication scores.
- Prices used in the CUA were outdated. The price used for PPAE was $3.20 per tablet instead of $3.80 (as submitted). Also, the model considered that PPAE would be used for 365 days annually instead of a range of 116 to 236 days annually, depending on pollen season.

With regard to the CMA:

- The manufacturer based its analysis on a pollen season of three months and eight weeks of pre-season treatment. In Canada, the pollen season can range from two to six months. CDR noted that the reported cost savings showed tendency to decrease with longer pollen seasons and longer pre-season treatment; therefore, the base-case analysis from the CMA model underestimated the costs associated with using PPAE for longer treatment duration.

### Results of Common Drug Review Analysis

Given the issues identified with the manufacturer's model and the results of the network meta-analysis, CDR assumed equal post-treatment efficacy of 5GPAE and PPAE. The reanalysis of the CMA, assuming a pollen season that ranged from two to six months long and pre-season treatment with PPAE that ranged from 8 to 16 weeks, showed that total three-year incremental cost of PPAE (per patient) ranged from a cost saving of $1,717 to a cost impact of $245 compared with perennial SCIT, and a cost saving of $97 to a cost impact of $1,864 compared with seasonal SCIT. PPAE was associated with cost savings ranging from $400 to $837 compared with 5GPAE.

Based on current list prices, PPAE could result in produce an incremental cost per patient over three years that ranges from a cost saving of $1,717 to a cost impact of $1,864 compared with SCIT, depending on duration of pre-season treatment with PPAE and the length of pollen season. Cost savings with SCIT are less certain when compared with seasonal SCIT. Compared with 5GPAE, PPAE results in a three-year per-patient cost savings ranging from $400 to $837.

### Conclusions

Based on a systematic review of eight double-blind RCTs in both children (five years of age or older) and adults (18 to 65 years of age), compared with placebo, seasonal treatment with PPAE 2,800 BAU sublingually once daily resulted in statistically lower symptom scores and rescue medication use over one GPS. The clinical importance of the observed between-treatment differences in symptom and medication scores is uncertain. However, a between-treatment difference of ≥ 20% for a combined symptom plus medication score (considered to be clinically meaningful by the World Allergy Organization) was achieved in five of six studies reporting this outcome. Changes in health-related quality of life, as measured by the RQLQ, were not considered clinically meaningful. Based on one long-term RCT, the beneficial effects of PPAE appear to be sustained over three subsequent years of seasonal treatment, with waning of effect in subsequent untreated years, but the validity of the long-term findings is limited by the large and differential dropout following the first GPS. A manufacturer-provided indirect comparison suggested that SLIT (including PPAE and 5GPAE) is not statistically different from SCIT, and PPAE is not statistically different from 5GPAE, in decreasing AR symptoms and medication scores in patients with grass pollen allergy. However, given a number of limitations with the manufacturer-provided indirect comparison and the lack of RCTs directly comparing these treatments, the comparative efficacy of immunotherapies is uncertain. The most frequently reported adverse events with PPAE were those associated with the mouth or throat. Serious adverse events and withdrawals due to adverse events were few and similar in both groups across the trials.

**TABLE 1: SUMMARY OF RESULTS**

| Outcome | GT-07 | GT-02 | GT-02* | GT-08 | GT-14 | P05238 | GT-12 | P05239 | P08067 |
|---|---|---|---|---|---|---|---|---|---|
| | Adult | Adult | Adult | Adult | Adult | Adult | Pediatric | Pediatric | Mixed |
| **DSS** | | | | | | | | | |
| Difference vs. placebo (95% CI) | –0.78 NR, P = 0.05 | –0.46 (–0.93 to 0.04) | –0.445 (–0.956 to 0.067) | –1.29 (–1.68 to –0.90) | –0.37 (–1.16 to 0.41) | –0.86 (–1.46 to –0.26) | –0.62 (–1.15 to –0.10) | –1.20 (–1.95 to –0.45) | –0.47 (–0.79 to –0.16) |
| % Difference vs. placebo | –25 | –15.74[a] | –13.33[a] | –31 | –6.18 | –18.3 | –22.24 | –25 | –13 |
| **DMS** | | | | | | | | | |
| Difference vs. placebo (95% CI) | –1.21 NR, P = 0.136 | –0.58 (–1.156 to –0.008) | –0.738 (–1.341 to –0.135) | –1.03 (–1.44 to –0.63) | –0.40 (–0.85 to 0.05) | –0.45 (–0.96 to 0.06) | –0.41 (–0.68 to –0.01) | –0.42 (–0.88 to 0.03) | –0.40 (–0.65 to –0.15) |
| % Difference vs. placebo | –32 | –28.45[a] | –29.77[a] | –39 | –27.12 | –26.5 | –34.25 | –31.6 | –31 |
| **TCS** | | | | | | | | | |
| Difference vs. placebo (95% CI) | NR | NR | NR | –2.32 (–2.98 to –1.67) | –0.78 (–1.83 to 0.26) | –1.31 (–2.22 to –0.40) | –1.18 (–2.17 to –0.19) | –1.63 (–2.60 to –0.66) | –0.87 (–1.32 to –0.42) |
| % Difference vs. placebo | NR | NR | NR | –34.2 | –10.4 | –20.5 | –24.2 | –26.1 | –18 |
| **RQLQ score** | | | | | | | | | |
| Difference vs. placebo (95% CI) | NR | –0.208 (–0.384 to –0.033) | –0.229 (–0.424 to –0.035) | –0.37 (–0.50 to –0.23) | –0.08 (–0.32 to 0.16) | –0.27 (–0.48 to –0.05) | NR | –0.32 (–0.60 to –0.03) | –0.15 (–0.26 to –0.03) |
| **AE (treatment emergent)** | | | | | | | | | |
| PPAE, n (%) | 70 (95) | 130 (92.20) | 137 (89.54) | 265 (84) | 121 (74) | 176 (82.6) | 109 (87) | 151 (86.3) | 593 (78.8) |
| Placebo, n (%) | 36 (90) | 100 (73.53) | 115 (76.67) | 205 (64) | 101 (61) | 161 (71.6) | 106 (83) | 131 (77.5) | 508 (68.2) |
| **SAEs** | | | | | | | | | |
| PPAE, n (%) | 0 (0) | 1 (0.71) | 2 (1.31) | 6 (2) | 0 (0) | 2 (0.9) | 2 (2) | 0 (0) | 11 (1.5) |
| Placebo, n (%) | 0 (0) | 0 (0) | 1 (0.67) | 4 (1) | 2 (1) | 5 (2.2 | 2 (2) | 4 (2.4) | 8 (1.1) |
| **WDAEs** | | | | | | | | | |
| PPAE, n (%) | 3 (4) | 8 (5.67) | 7 (4.58) | 16 (5) | 10 (6) | 11 (5) | 4 (3) | 13 (7) | 54 (7.2) |
| Placebo, n (%) | 0 (0) | 1 (0.74) | 2 (1.33) | 8 (3) | 5 (3) | 8 (4) | 2 (2) | 5 (3) | 18 (2.4) |

AE = adverse event; CI = confidence interval; DMS = daily medication score; DSS = daily symptom score; n = number of patients with event; NR = not reported; PPAE = *Phleum pratense* allergen extract; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SAE = serious adverse event; TCS = total combined score; WDAE = withdrawal due to adverse event.

[a]Calculated by Common Drug Review reviewer.

Note: In GT-02, there were six treatment groups. The comparisons relevant for this review are presented here: GT-02* represents the groups in which placebo was provided as step 1 rescue medication, and GT-02 represents groups in which loratadine was provided as step 1 rescue medication.

# 1. INTRODUCTION

## 1.1 Disease Prevalence and Incidence

Allergic rhinitis (AR) is an immunoglobulin E (IgE)–mediated inflammation of the nasal mucosa triggered by exposure to allergens.[1] AR has been categorized as seasonal or perennial. Generally, seasonal AR is induced by pollen and perennial AR by allergens such as those from animals and dust mites. Symptoms include rhinorrhea (nasal discharge), nasal congestion, nasal itching, and sneezing.[1-3] AR is often accompanied with allergic conjunctivitis and is collectively known as allergic rhinoconjunctivitis (ARC). ARC also includes ocular symptoms such as itchiness, redness, or irritation of the eye.[4] Seasonal AR and ARC are commonly referred to as hay fever.[1]

AR is a global health problem and affects a broad spectrum of people (such as various age groups, ethnic backgrounds, and socioeconomic status). The reported prevalence of AR varies from 1% to 40% worldwide and its occurrence is more common in developed countries.[1] Grass pollen is one of the most frequent causes of seasonal AR.[5] In Canada, reports of sensitization toward grass varies in the range of 14% to 30% and specifically for Timothy grass varies between 13% and 29%.[6]

## 1.2 Standards of Therapy

The current treatment options for AR and ARC are avoidance of allergens, pharmacotherapy, and specific immunotherapy.[7-9] Allergen avoidance is not always feasible or practical. Pharmacotherapy includes drugs such as antihistamines, intranasal corticosteroids, oral or nasal decongestants, leukotriene inhibitors, nasal or ocular cromolyn, and other ocular medications (antihistamines, decongestant).[3,7,8,10] Pharmacotherapy is generally well tolerated. However, it may not provide adequate relief in some cases or be suitable for long-term use. In such instances, allergen-specific immunotherapy may be prescribed. Depending on the route of administration, immunotherapy is categorized as subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). Both these modalities use grass pollen allergen extracts for treating grass pollen–induced AR and ARC. SCIT has some limitations. It needs to be administered in a clinical setting, thus requiring substantial use of clinical resources as well as considerable time commitment for the patient; repeated injections could cause discomfort; and there is risk of systemic reactions, including anaphylactic shock.[1] Some of these limitations may be overcome with SLIT. Two SLIT drugs have been approved by Health Canada for treating patients with AR or ARC who have responded inadequately, or are intolerant to conventional pharmacotherapy: five-grass pollen allergen extract (5GPAE; Oralair) and Timothy grass (*Phleum pratense*) standardized allergenic extract (PPAE; Grastek).[11,12]

## 1.3 Drug

PPAE has been referred to by various names, including ALK grass, Grazax, SCH697243, MK-7243, Grass AIT, and Grastek. PPAE is available as a sublingual tablet of 2,800 bioequivalent allergy units (BAU), equivalent to 75,000 standardized quality units (SQ-U). It is indicated for alleviating the symptoms of Timothy and related grass-induced allergic rhinitis with or without conjunctivitis. It is administered daily, starting at least eight weeks prior to the grass pollen season (GPS) and continuing through the entire GPS. It should be prescribed and initiated only by physicians trained in the treatment of respiratory allergic disease.[11]

It is thought that the mechanism of action of PPAE is mediated by a local and systemic immunomodulatory mechanism involving changes in allergen-specific antibodies and T cells leading to long-term development of tolerance.[11]

| Indication under review |
| --- |
| Reducing the signs and symptoms of moderate to severe seasonal Timothy and related grass pollen-induced allergic rhinitis (with or without conjunctivitis) in adults and children 5 years of age and olderconfirmed by clinically relevant symptoms for at least two pollen seasons and a positive skin prick test and/or a positive titre to *Phleum pratense* specific immunoglobulin E, and who have responded inadequately, or are intolerant to conventional pharmacotherapy |
| Listing criteria requested by sponsor |
| Treatment of patients with Timothy and related grass pollen-induced allergic rhinitis with or without conjunctivitis, in adults and children five years of age and older |

The key characteristics of PPAE, 5GPAE, and SCIT approved by Health Canada for grass pollen allergy are presented in Table 2.

**TABLE 2: KEY CHARACTERISTICS OF PPAE, ORALAIR, AND SCIT**

| | Grastek (PPAE)[11] | Oralair (5GPAE)[12] | SCIT (Center-Al Allergenic Extract[a 13] and others) |
|---|---|---|---|
| **Mechanism of Action** | Local and systemic immunomodulatory mechanisms lead to long-term tolerance development | Specific immunotherapy induces immunologic tolerance (defined as a long-lived decrease in allergen-specific T cell responsiveness) | Specific immunotherapy induces immunologic tolerance to the allergens responsible for the symptoms on subsequent exposure |
| **Health Canada–Approved Indication** | Reducing the signs and symptoms of moderate to severe seasonal Timothy and related grass pollen–induced AR (with or without conjunctivitis) in adults and children 5 years of age and older confirmed by clinically relevant symptoms for at least 2 pollen seasons and a positive skin prick test and/or a positive titre to *Phleum pratense* specific IgE, and who have responded inadequately or are intolerant to conventional pharmacotherapy | Treatment of symptoms of moderate to severe seasonal grass pollen AR with or without conjunctivitis in patients 5 to 50 years of age, confirmed by clinically relevant symptoms, a positive cutaneous test and a positive titre of the specific IgE to Poaceae grass pollen, who have suffered from AR with or without conjunctivitis for at least 2 pollen seasons and have not adequately responded to, or tolerated, conventional pharmacotherapy | Diagnosis and treatment (hyposensitization therapy) of patients who experience allergic symptoms due to exposure to grass pollen and who exhibit Type I skin sensitivity when tested for those specific allergens |
| **Route of Administration** | Sublingual | | Subcutaneous |
| **Recommended Dose** | Treatment should be initiated at least 8 weeks before the grass pollen season and maintain dosing throughout the season. 2,800 BAU sublingually once daily | Treatment should be initiated about 4 months before the expected onset of the pollen season and maintained throughout the pollen season. 300 IR sublingually once daily (treatment should be discontinued if no improvement is noted after 3 seasons) | Treatment is generally initiated at 1/10 of the required dose, and may be increased by 0.05 mL each time until 0.5 mL is reached. Treatment intervals: maintained at once every 2 weeks to once a month (average minimum course of treatment: 2 or 3 years) |
| **Serious Side Effects or Safety Issues** | In clinical trials, compared with placebo, Grastek-treated patients were associated with more epinephrine use. Serious systemic allergic reaction generally occurred with the first dose. Rare cases of serious systemic allergic reactions including anaphylactic reactions have been reported in post-marketing experience | Serious adverse events such as hypersensitivity, diarrhea, and angioneurotic edema have occurred in clinical trials. No events of anaphylactic reactions were reported in clinical trials but were observed post marketing | Anaphylaxis and deaths were reported, although rare. Children younger than 5 years of age on extract immunotherapy may have an increased risk of a severe reaction |

| | Grastek (PPAE)[11] | Oralair (5GPAE)[12] | SCIT (Center-Al Allergenic Extract[a 13] and others) |
|---|---|---|---|
| **Other** | First dose should be administered at the physician's office; the patient must be monitored for 30 minutes. Subsequent doses may be taken at home. For pediatric patients, administration should be under adult supervision | First tablet must be taken at the physician's office; the patient must be monitored for at least 30 minutes. For pediatric patients, administration must be under adult supervision for at least 30 minutes | Patients should be observed for at least 30 minutes after injection. The physician must be prepared to treat anaphylaxis should it occur and have the necessary drugs and equipment on hand to do so |

5GPAE = five-grass pollen allergen extract (standardized allergenic extracts of *Anthoxanthum odoratum* [sweet vernal grass]; *Dactylis glomerata* [cocksfoot]; *Lolium perenne* [rye grass]; *Phleum pratense* (Timothy grass), and *Poa pratensis* [meadow grass or Kentucky blue grass]);
AR = allergic rhinitis; BAU = bioequivalent allergy unit; IgE = immunoglobulin E; IR = index of reactivity; PPAE = *Phleum pratense* (Timothy grass) standardized allergenic extract; SCIT = subcutaneous immunotherapy.
[a]Standardized allergenic extract of grass pollens from Timothy, orchard, June, red top, sweet vernal, meadow fescue, perennial rye, or a mixture of four or five standard grass pollens.

# 2. OBJECTIVES AND METHODS

## 2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of PPAE 2800 BAU, for the treatment of Timothy and related grass pollen–induced AR, with or without conjunctivitis, in adults and children aged five years and older.

## 2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 3.

**TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW**

| | |
|---|---|
| **Patient Population** | Adults and children aged five years and older with moderate to severe seasonal Timothy and related grass pollen–induced allergic rhinitis with or without conjunctivitis, which has been confirmed by clinically relevant symptoms for at least two pollen seasons and a positive skin prick test and/or a positive titre to *Phleum pratense* specific IgE, and who have responded inadequately or are intolerant to conventional pharmacotherapy |
| **Intervention** | PPAE, sublingual tablet (2,800 BAU) daily |
| **Comparators**[a] | - Other immunotherapies, including subcutaneous and sublingual<br>- Placebo |
| **Outcomes** | ***Key efficacy outcomes:***<br>- Symptom relief (e.g., of rhinitis and conjunctivitis) assessed by a validated measure<br>- Health-related quality of life (assessed by validated measuring tools, generic or disease-specific)<br>***Other efficacy outcomes:***<br>- Rescue medication use (e.g., antihistamine, corticosteroids, decongestants, leukotriene receptor antagonists, anti-allergy eye drops)<br>***Harms outcomes:***<br>AEs, SAEs (including systemic allergic reaction and asthma attack), mortality, WDAEs |
| **Study Design** | Published and unpublished DB RCTs |

AE = adverse events; BAU = bioequivalent allergy unit; DB = double-blind; IgE = immunoglobulin; PPAE = *Phleum pratense* allergen extract; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.
[a]Approved and marketed for use in Canada.

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 through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. The main search concepts were Grastek (standardized allergenic extract, Timothy grass [*Phleum pratense*]).

No filters were applied to limit retrieval by 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 February 7, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on June 18, 2014. 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): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), and Clinical Trials. 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 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 and Table 5.

# 3. RESULTS

## 3.1 Findings from the Literature

A total of eight studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and Table 5 and described in Section 3.2. Included Studies.

A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES

**FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES**

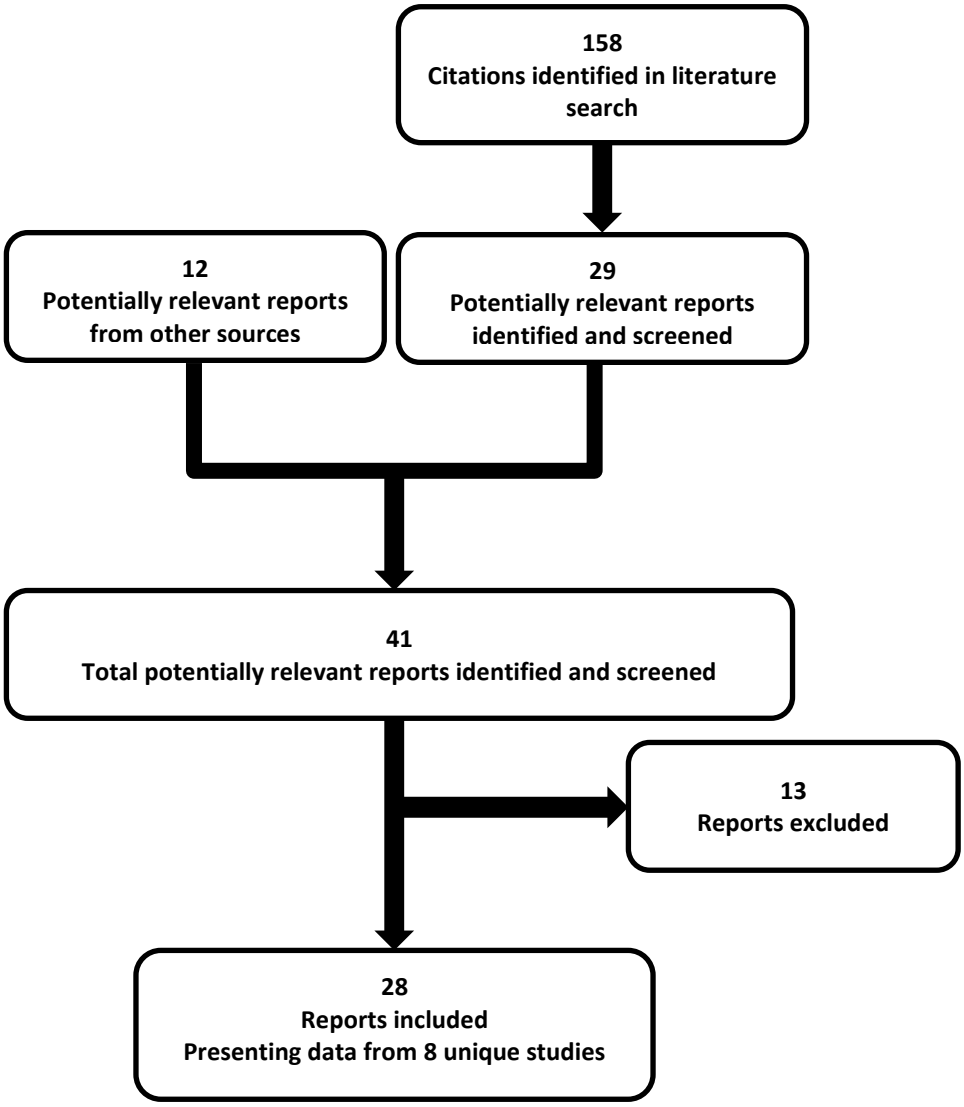


**TABLE 4: DETAILS OF INCLUDED STUDIES (ADULTS)**

| | | GT-07 | GT-02 | GT-08 | GT-14 | P05238 |
|---|---|---|---|---|---|---|
| DESIGNS & POPULATIONS | **Study Design** | DB RCT, phase 2 | DB RCT, phase 2/3 | DB RCT, phase 3 | DB RCT, multi-centre, phase 3 | DB RCT, phase 3 |
| | **Locations** | Europe | Canada and Europe | Europe | US | Canada and US |
| | **Randomized (N)** | 114 | 855 | 634 | 329 | 439 |
| | **Inclusion Criteria** | Adults aged 18 to 65 years with significant symptoms for seasonal grass pollen AR, for ≥ 2 years, a positive SPT, and positive specific IgE to *Phleum pratense*. (In GT-07, participants were required to have mild to moderate asthma.) | | | | |
| | **Exclusion Criteria** | Clinical history of significant symptomatic seasonal AR and/or asthma due to tree or weed pollen during tx period.<br>Clinical history of significant active perennial AR and/or asthma due to allergens exposed to regularly.<br>Clinical history of severe asthma.<br>$FEV_1$ < 70% of PV | Clinical history of significant symptomatic seasonal AR due to tree or weed pollen during planned tx period.<br>Clinical history of significant active perennial AR due to allergens exposed to regularly.<br>Clinical history of significant asthma outside GPS.<br>$FEV_1$ < 70% of PV | Clinical history of symptomatic seasonal AR and/or asthma due to tree or weed pollen either adjacent to or overlapping the GPS.<br>Clinical history of active perennial AR and/or asthma due to allergens exposed to regularly.<br>$FEV_1$ < 70% of PV | Clinical history of symptomatic seasonal AR and/or asthma due to another allergen during or overlapping the GPS.<br>Clinical history of symptomatic perennial AR and/or asthma due to allergens exposed to regularly.<br>Clinical history of severe asthma.<br>$FEV_1$ < 70% of PV | Clinical history of symptomatic seasonal AR and/or asthma due to another allergen during or overlapping the GPS.<br>Clinical history of symptomatic perennial AR and/or asthma due to allergens exposed to regularly.<br>Clinical history of severe asthma.<br>$FEV_1$ < 70% of PV |
| DRUGS | **Intervention** | PPAE: (75,000 SQ-T) SL once daily | PPAE: (2,500; 25,000; or 75,000 SQ-U)[a] SL once daily | PPAE: ALK grass (75,000 SQ-T) tablet SL once daily | PPAE: (75,000 SQ-T) tablet SL once daily | PPAE: (2800 BAU) tablet SL once daily |
| | **Comparator(s)** | Matching placebo | Matching placebo[a] | Matching placebo | Matching placebo | Matching placebo |
| DURATION | **Phase** | | | | | |
| | **Double-Blind** | 10 to 14 weeks prior to GPS and during GPS | 8 weeks prior to GPS and during GPS | 16 to 35 weeks prior to GPS and during GPS. DB treatment continued for 2 additional years | 8 to 16 weeks prior to GPS and during GPS | 16 weeks prior to GPS and during GPS |
| | **Follow-up** | 1 week after final visit (i.e., end of season or treatment visit) | 1 week after end of treatment | 2 years after end of treatment | Up to end of season visit; i.e., ~1 week after GPS has ended | Up to end of season visit; i.e., ~1 week after GPS has ended |

| | | GT-07 | GT-02 | GT-08 | GT-14 | P05238 |
|---|---|---|---|---|---|---|
| OUTCOMES | **Primary End Point** | AMS over entire GPS | Co-primary: DSS, DMS over entire GPS | Co-primary: DSS, DMS over entire GPS | DSS over entire GPS | TCS over entire GPS |
| | **Other End Points** | DSS, DMS over entire GPS; AE | DSS, DMS over entire GPS DSS, DMS in peak GPS; QoL over entire GPS. AE | DSS, DMS over peak GPS; QoL over entire GPS. AE | DMS over entire GPS, DSS, DMS over peak GPS, QoL over entire GPS. AE | DSS, DMS over entire GPS; TCS, DSS, DMS over peak GPS; QoL over entire GPS. AE |
| NOTES | **Publications** | Dahl et al.[14] | Durham et al., [15] Rak et al.[4] | Dahl et al., [16,17] Durham,[18] Durham et al., [19-21] Durham and Riis, [22] Frolund et al.[23] | Murphy et al.[24] | Nelson et al.[25] |

AE = adverse event; AMS = asthma medication score; AR = allergic rhinitis; BAU = bioequivalent allergy unit; DB = double-blind; DMS = daily medication score; DSS = rhinoconjunctivitis daily symptom score; $FEV_1$ = forced expiratory volume in 1 second; GPS = grass pollen season; IgE = immunoglobulin E; L = loratadine; PPAE = *Phleum pratense* allergen extract; PV = predictive value; QoL = quality of life; RCT = randomized controlled trial; SL = sublingual; SPT = skin prick test; SQ-T = standardized quality units tablet; SQ-U = standardized quality unit; TCS = total combined score: DSS + DMS; tx = treatment.
Note: For PPAE dosing, 75,000 SQ-T ≡ 2,800 BAU.
[a]Study GT-02 had six treatment groups based on whether loratadine rescue medication allowed at step 1 (single-blind) was provided as loratadine or placebo. The six treatment groups included 1) Placebo+L; 2) 2,500SQ+L; 3) 25,000SQ+L; 4) 75,000SQ+L; 5) Placebo+Placebo; 6) 75,000SQ+Placebo, where L = loratadine (if needed, given at step 1).
Note: 10 clinical study reports,[26-30,34-38] 1 Common Drug Review submission,[39] and the Health Canada reviewer's report[40] were included, in addition to the publications listed in Table 4 and Table 5.
Source: Clinical study reports.[26-30]

**TABLE 5: DETAILS OF INCLUDED STUDIES (CHILDREN OR MIXED POPULATION)**

| | | GT-12 | P05239 | P08067 |
|---|---|---|---|---|
| DESIGNS & POPULATIONS | **Study Design** | DB RCT, multi-centre, phase 3 | DB RCT, multi-centre, phase 3 | DB RCT, multi-centre, phase 3 |
| | **Locations** | Europe (Germany) | Canada and US | Canada and US |
| | **Randomized (N)** | 253 | 345 | 1,501 |
| | **Inclusion Criteria** | Children aged 5 to 16 years, with grass pollen–induced AR, received pharmacotherapy for their disease during the previous GPS, with positive SPT and positive specific IgE to *Phleum pratense* | Children aged 5 to < 18 years, with grass pollen–induced AR (with or without asthma), received pharmacotherapy for their disease during the previous GPS, with positive SPT and positive specific IgE to *Phleum pratense* | Patients aged 5 to 65 years, with grass pollen–induced AR (with or without asthma), received pharmacotherapy for their disease during the previous GPS, with positive SPT and positive specific IgE to *Phleum pratense* |
| | **Exclusion Criteria** | Clinical history of symptomatic seasonal AR and/or asthma due to another allergen during or overlapping the GPS.<br>Clinical history of symptomatic perennial AR and/or asthma due to allergens exposed to regularly.<br>Clinical history of severe asthma; $FEV_1$ < 80% of expected value with tx | Clinical history of symptomatic seasonal AR and/or asthma due to another allergen during or overlapping the GPS.<br>Clinical history of symptomatic perennial AR and/or asthma due to allergens exposed to regularly.<br>Clinical history of severe asthma; $FEV_1$ < 70% of predicted value with tx | Clinical history of symptomatic seasonal AR and/or asthma due to another allergen during or overlapping the GPS.<br>Clinical history of symptomatic perennial AR and/or asthma due to allergens exposed to regularly.<br>Clinical history of severe asthma; $FEV_1$ < 70% of expected value with tx |
| DRUGS | **Intervention** | PPAE: (2,800 BAU) SL once daily | PPAE: (2,800 BAU) SL once daily | PPAE: (2,800 BAU) SL once daily |
| | **Comparator(s)** | Matching placebo | Matching placebo | Matching placebo |
| | Double-blind | 16 weeks prior to and during GPS | 16 weeks prior to and during GPS | At least 12 weeks prior to and during GPS |
| | Follow-up | 1 week after end of season visit | 1 week after end of season visit | 1 week after end of season visit |
| OUTCOM | **Primary End Point** | Co-primary: DSS, DMS over entire GPS | TCS over entire GPS | TCS over entire GPS |
| | **Other End Points** | DSS, DMS over peak GPS; TCS over entire and peak GPS. AE | DSS, DMS over entire GPS; DSS, DMS, TCS over peak GPS; QoL over entire GPS. AE | DSS, DMS over entire and peak GPS; TCS over peak GPS; QoL over peak GPS. AE |
| NOTES | **Publications**[a] | Bufe et al.[31] | Blaiss et al.[32] | Maloney et al.[33] |

AE = adverse event; AR = allergic rhinitis; BAU = Bioequivalent Allergy Unit; DB = double-blind; DMS = rhinoconjunctivitis medication score; DSS = rhinoconjunctivitis daily symptom score; $FEV_1$ = forced expiratory volume in 1 second; GPS = grass pollen season; IgE = immunoglobulin E; PPAE = *Phleum pratense* allergen extract; QoL = quality of life; RCT = randomized controlled trial; SL = sublingual; SPT = skin prick test; TCS = total combined score: DSS + DMS; tx = treatment.

Note: 10 clinical study reports,[26-30,34-38] 1 Common Drug Review submission,[39] and the Health Canada reviewer's report[40] were included, in addition to the publications listed in Table 4 and Table 5.

Source: Clinical study reports.[34-36]

## 3.2 Included Studies

### 3.2.1 Description of Studies

Eight multi-centre, randomized, parallel-group, double-blind, placebo-controlled studies (GT-02,[26] GT-07,[27] GT-08,[28] GT-12,[34] GT-14,[29] P05238,[30] P05239,[35] and P08067[36]) met the inclusion criteria for this systematic review. The studies compared the efficacy and safety of PPAE versus placebo in patients with AR with or without conjunctivitis. Six studies (GT-08, GT-12, GT-14, P05238, P05239, and P08067) were phase 3 and considered as pivotal studies, one study (GT-02) was phase 2/3, and one study (GT-07) was phase 2. Five studies (GT-02, GT-07, GT-08, GT-14, and P05238) involved adult patients, two studies (GT-12, P05239) involved pediatric patients, and one study (P08067) involved a mixed population of adult and pediatric patients.

### 3.2.2 Populations

**a) Inclusion and Exclusion Criteria**

The main inclusion criteria were significant symptoms for seasonal grass pollen AR, for two or more pollen seasons, confirmed by a positive skin prick test to *Phleum pratense* and a positive *Phleum pratense* specific IgE test. The age limit for adults was up to 65 years and for the pediatric population no less than five years. In GT-07, participants were required to have mild or moderate asthma. The main exclusion criteria were clinical history of symptomatic seasonal AR and/or asthma due to tree or weed pollen, either adjacent to or overlapping the GPS or clinical history of active perennial AR and/or asthma due to allergens exposed to regularly.

**b) Baseline Characteristics**

Baseline characteristics were generally well balanced across treatment groups in the studies on adults (Table 6) and in studies on pediatric or mixed populations (Table 7). The mean ages varied between 34 and 36 years in the adult studies and between 10 and 13 years in the pediatric studies. The majority of the studies had a higher percentage of males compared with females, except studies GT-14, P05238, and P08067, where the male/ female ratios were approximately equal. The proportion of males in study GT-07 was somewhat imbalanced across the two treatment groups; 72% versus 60% in the PPAE and placebo groups, respectively. The majority of the population studied was Caucasian, ranging from 81% to 99%. The mean number of years with grass pollen allergies varied between 16 and 21 years in the adult studies and between three and seven years in the pediatric studies. The proportion of patients with asthma was reported in six studies, ranging between 21% and 28% in four studies (GT-14, P05238, P05239, and P08067), 41% in GT-12, and 100% in GT-07. The proportion of participants with severe grass pollen allergy was reported in three studies: 33% in GT-07, 56% in GT-08, and 27% in GT-12. However, it was unclear how the level of severity was determined.

**TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS (ADULTS)**

| | GT-07 | | GT-02 | | | | GT-08 | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 74 | Placebo N = 40 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) [a] N = 153 | Placebo (no L) [a] N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 213 | Placebo N = 225 |
| **Age (Years)** | | | | | | | | | | | | |
| **Mean (SD)** | 36.5 (10.6) | 34.1 (9.9) | 36.5 (9.3) | 33.4 (9.2) | 36.1 (10.9) | 36.0 (10.5) | 33.8 (9.6) | 34.5 (10.0) | 35.9 (11.7) | 35.9 (11.7) | 35.9 (11.1) | 35.9 (9.8) |
| **Range** | 18 to 64 | 20 to 60 | 19 to 62 | 18 to 61 | 18 to 66 | 18 to 64 | 21 to 53 | 20 to 54 | 18 to 65 | 18 to 62 | 18 to 63 | 18 to 61 |
| **Sex (%)** | | | | | | | | | | | | |
| **Male** | 72 | 60 | 60 | 65 | 62.1 | 59.3 | 57 | 61 | 46 | 47 | 51 | 50 |
| **Female** | 28 | 40 | 40 | 35 | 37.9 | 40.7 | 43 | 39 | 54 | 53 | 49 | 50 |
| **Ethnic Origin, N (%)** | | | | | | | | | | | | |
| **Caucasian** | 73 (98.6) | 39 (97.5) | 135 (95.7) | 129 (94.9) | 136 (88.9) | 133 (88.7) | 299 (95) | 308 ( 97) | 134 (82) | 134 (81) | 182 (85) | 187 (83) |
| **Other** | 1 (1.4) | 1 (2.5) | 6 (4.2)[b] | 7 (5.1)[b] | 17 (11.1)[b] | 17 (11.3)[b] | 17 (5)[b] | 10 (3)[b] | 29(18)[b] | 32 (19)[b] | 31 (15) | 38 (17) |
| **Grass Pollen Allergy Severity, N (%)** | | | | | | | | | | | | |
| **Mild** | 2 (2.7) | 3 (7.5) | NR | NR | NR | NR | 0 | 0 | NR | NR | NR | NR |
| **Moderate** | 48 (64.9) | 23 (57.5) | NR | NR | NR | NR | 137 (43) | 144 (45) | NR | NR | NR | NR |
| **Severe** | 24 (32.4) | 14 (35.0) | NR | NR | NR | NR | 179 (57) | 174 (55) | NR | NR | NR | NR |
| **Grass Pollen Allergy (Years)** | | | | | | | | | | | | |
| **Mean (SD)** | 19.6 (9.81) | 19.4 (12.5) | 19.2 (12.1) | 18.2 (10.9) | 20.5 (12.9) | 22.6 (12.9) | 15.9 (9.8) | 15.7 (10.4) | 21.4 (12.9) | 20.5 (12.0) | 21.28 (11.64) | 20.67 (11.53) |
| **History of Asthma** | | | | | | | | | | | | |
| **Yes (%)** | 100 | 100 | NR | NR | NR | NR | NR | NR | 28 | 26 | 21 | 26 |

L = loratadine; NR = not reported; PPAE = *Phleum pratense* allergen extract; SD = standard deviation.
[a]Patients randomized to receive rescue medication of placebo instead of loratadine at step 1.
[b]Calculated by Common Drug Review reviewer.
Source: Clinical study report.[26-30]

**TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS (PEDIATRIC OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 175 | Placebo N = 169 | PPAE N = 752 | Placebo N = 749 |
| **Age (Years)** | | | | | | |
| **Mean (SD)** | 10.1 (2.9) | 10.1 (3.1) | 12.1 (3.0) | 12.6 (3.0) | 32.9 (14.5) | 33.5 (14.5) |
| **Range** | 5 to 16 | 5 to 16 | 6 to 17 | 5 to 18 | 5 to 65 | 5 to 65 |
| **Sex (%)** | | | | | | |
| **Male** | 66 | 65 | 67 | 62 | 49 | 56 |
| **Female** | 34 | 35 | 33 | 38 | 51 | 44 |
| **Ethnic Origin, N (%)** | | | | | | |
| **Caucasian** | 123 (98) | 123 (97) | 153 (87) | 149 (88) | 613 (82) | 641 (86) |
| **Other** | 3 (2) | 4 (3) | 22 (13) | 20 (12) | 138 (18) | 108 (14) |
| **Grass Pollen Allergy Severity, N (%)** | | | | | | |
| **Mild** | 9 (7) | 9 (7) | NR | NR | NR | NR |
| **Moderate** | 78 (62) | 88 (69) | NR | NR | NR | NR |
| **Severe** | 39 (31) | 30 (24) | NR | NR | NR | NR |
| **Grass Pollen Allergy (Years)** | | | | | | |
| **Mean (SD)** | 3.5 (2.6) | 3.4 (2.4) | 6.31 (3.41) | 6.72 (3.76) | 17.33 (12.44) | 18.11 (13.22) |
| **History of Asthma** | | | | | | |
| **Yes (%)** | 42 | 39 | 26 | 26 | 24.2 | 24.8 |

NR = not reported; PPAE = *Phleum pratense* allergen extract; SD = standard deviation.
Source: Clinical study report.[34-36]

### 3.2.3 Interventions

In all studies, participants were randomized to receive either PPAE (2800 BAU; equivalent to 75,000 SQ-U) or matching placebo. In GT-08, GT-12, GT-14, P05238, P05239, and P08067, patients were randomized in a 1:1 ratio, and in GT-07, patients were randomized in a 2:1 ratio. In all the above seven studies, if symptoms were not controlled, participants were allowed to take rescue medications as required based on the study protocol as described below.

In GT-02, participants were randomized to six treatment groups based on whether loratadine rescue medication allowed at step 1 was provided as loratadine or placebo. The six treatment groups included PPAE 2,500 SQ-U + loratadine, PPAE 7,500 SQ-U + loratadine, PPAE 75,000 SQ-U + loratadine, PPAE 75,000 SQ-U + placebo, placebo + loratadine, and placebo + placebo. Results for treatment groups with non-Health Canada doses (2,500 SQ-U and 7,500 SQ-U) are not included in this review. The treatment groups in which loratadine was not provided are specifically designated in the report as PPAE (no L) or placebo (no L) or this particular comparison of the GT-02 study is indicated as GT-02*.

In all studies, treatment started prior to the GPS and continued for the entire season. Pre-seasonal treatment durations ranged between 8 and 16 weeks across studies GT-02, GT-07, GT-12, GT-14, P05238, P05239, and P08067, for total treatment duration of approximately 24 weeks. In study GT-08, the pre-seasonal treatment duration could range from 16 to 35 weeks.

GT-08 was originally designed to assess efficacy and safety of PPAE compared with placebo for one GPS (in 2005), and later the study was amended to extend the treatment for two more years (2006, 2007)

and to continue follow-up for an additional two years (2008, 2009) without treatment. Results of these extension studies are summarized in APPENDIX 6: SUMMARY OF GT-08 EXTENSION STUDIES.

All study protocols allowed for the use of concomitant rescue medications as required, either for AR or asthma symptoms, in a stepwise manner depending on the persistence and severity of their symptoms (Table 8). Of note, in study GT-02, receipt of loratadine was contingent upon randomization.

**TABLE 8: RESCUE MEDICATIONS ALLOWED PER PROTOCOL**

| Medication | Adults | | | | | Pediatrics | | Mixed |
|---|---|---|---|---|---|---|---|---|
| | GT-07 | GT-02 | GT-08 | GT-14 | P05238 | GT-12 | P05239 | P08067 |
| **Allergy Rescue Medication** | | | | | | | | |
| Loratadine tablet or syrup | y | y | | | y | y | y | y |
| Desloratadine tablet | | | y | y | | | | |
| Olopatadine eye drops | | | y | y | y | | y | y |
| Levocabastine eye drops | y | | y | | | y | | |
| Mometasone nasal spray | | | | | y | | y | y |
| Budesonide nasal spray | y | y | y | | | y | | |
| Prednisone or prednisolone tablet | y | y | y | | y | y | y | y |
| **Asthma Rescue Medication** | | | | | | | | |
| Albuterol or salbutamol | Y | Y | Y | Y | Y | Y | Y | Y |
| Fluticasone propionate | Y | Y | Y | Y | Y | Y | Y | Y |
| Prednisone or prednisolone tablet | Y | Y | Y | | Y | Y | Y | Y |

Y = medication was allowed.
Source: Common Drug Review submission,[39] clinical study report.[36]

### 3.2.4 Outcomes

Rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) over the entire GPS were the co-primary outcomes in GT-02, GT-08, and GT-12. DSS over the entire GPS was the primary outcome in GT-14. The total combined score (TCS; DSS plus DMS) over the entire GPS was the primary outcome in P05238, P05239, and P08067. In study GT-07, which specifically enrolled patients with asthma, the primary outcome was the asthma medication score (AMS) over the entire GPS. Secondary outcomes of interest included DSS, DMS, and TCS over the peak GPS, health-related quality of life, and adverse events.

The entire GPS was defined as the first day of three consecutive recorded days with a grass pollen count of ≥ 10 grains/$m^3$ to the last day of the last occurrence of three consecutive recorded days with a grass pollen count of ≥ 10 grains/$m^3$, inclusive of both days. The peak GPS was defined as the 15 consecutive recorded days within the GPS with the highest moving average grass pollen count.

**a) Daily Symptom Score**

The DSS encompassed six symptoms: four nasal symptoms (runny nose, blocked nose, sneezing, and itchy nose) and two ocular symptoms (gritty feeling, or red or itchy eyes, and watery eyes) and was measured using a four-point rating scale (0 to 3) as described in Table 9. The maximum total score possible was 18. Participants were instructed to record symptoms in an electronic diary, once daily in the evening before bedtime, and electronic diary records were reviewed with the participant, at each visit. The average DSS was calculated based on all available data during the GPS.

**TABLE 9: DAILY SYMPTOM SCORING**

| Symptom Severity | Description | Score |
|---|---|---|
| **Absent** | No sign or symptom evident | 0 |
| **Mild** | Sign or symptom clearly present, but minimal awareness; easily tolerated | 1 |
| **Moderate** | Definite awareness of sign or symptom, which is bothersome but tolerable | 2 |
| **Severe** | Sign or symptom that is hard to tolerate, may cause interference with activities of daily living and/or sleeping | 3 |

Source: Common Drug Review submission.[39]

**DMS**

As noted above, if symptoms were not controlled with the investigational medication, study protocols allowed for the use of rescue medication in a stepwise manner. For a description of the particular rescue medications employed in each study, see APPENDIX 4: DETAILED OUTCOME DATA, Table 14 to Table 21. Step 1 and step 2 medications were provided to participants at the pre-GPS visit. The participants were instructed to record rescue medication usage in an electronic diary.

Step 1 medications were not to be taken until the investigator had confirmed that the GPS had started and that the participant had adequate level of symptoms (symptom score ≥ 4) warranting rescue medication use. If eye symptoms persisted, the participant could use additional eye drops.

Step 2: If symptoms were not controlled with step 1 medication, the participant needed to call the investigator or trial site for confirmation of adequate symptoms (symptom score ≥ 4) in order to take additional step 2 medication.

Step 3: If symptoms were not controlled with step 1 plus step 2 medication (symptom score ≥ 4 persistently), the participant was to call the site for an unscheduled visit for confirmation of symptoms (symptom score ≥ 4). Upon confirmation, and if the investigator considered appropriate, the participant was provided with step 3 medication at the time of the visit and a further seven-day supply to be taken in addition to step 1 and step 2 medications.

Once symptoms improved, participants were to reduce or stop use of rescue medication. In case of repeat supply of rescue medication and/or escalation to step 3 medication, a visit to the trial site was required (unscheduled or next scheduled).

Protocol-specified rescue medications and DMS scoring systems varied across the studies. Details of the rhinoconjunctivitis DMS scoring systems are presented in APPENDIX 4: DETAILED OUTCOME DATA, Table 14 to Table 21). Given differences in the rescue medication protocols, the maximum possible DMS

varied across the trials. The maximum possible DMS for the individual studies were 12 for GT-14; 30 for GT-08; 34 for GT-02 and GT-12; 36 for P05238, P05239, and P08067; and 38 for GT-07. Scoring scales were not seen by the participants. The total DMS was the sum of the daily scores for each medication step. The average DMS was calculated based on all available data during the GPS and was the total DMS divided by the number of days for which data were available.

**Total Combined Score**
The daily TCS was the sum of daily DSS and DMS. The average TCS during the entire GPS was the sum of the daily TCS during the GPS, divided by the number of days for which data were available.

**Well Day**
Well day was defined as a day without intake of rescue medication and a rhinoconjunctivitis DSS ≤ 2. Percentage well days were calculated from the daily diary data during the GPS.

**Visual Analogue Scale**
Participants recorded daily in their diary the overall severity of their rhinoconjunctivitis symptoms throughout the GPS, by answering the question "How has your hay fever been today?" and indicating a point on the visual analogue scale (VAS; a scale ranging from 0 to 100, with 0 = no symptoms and 100 = severe symptoms).

**a) Rhinoconjunctivitis Quality of Life Questionnaire**
The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) with standardized activities (RQLQ(S)) was used for adults, the Pediatric RQLQ (RQLQ[P]) was used for children (six to 12 years of age), and the Adolescent RQLQ (RQLQ[A]) was used for adolescents (12 years old to younger than 18 years) for assessment of quality of life. The RQLQ is a validated instrument. It uses a seven-point scale (0 = not impaired and 6 = severely impaired). The instrument encompasses seven domains (sleep impairment, non-nasal symptoms, practical problems, nasal symptoms, eye symptoms, activity limitations, and emotional difficulty). The RQLQ(P) focuses on five domains (nose symptoms, eye symptoms, practical problems, activity limitation, and other symptoms). The RQLQ(A) focuses on six domains (nose symptoms, eye symptoms, practical problems, activity limitation, non-hay fever symptoms, and emotional function). RQLQ scores were recorded weekly throughout GPS. The participants reflected on the previous seven days and indicated a score for each item in each domain. RQLQ score was calculated as mean of the domain scores; the maximum possible score was 6. The RQLQ total score was calculated as the average of the weekly assessments.

### 3.2.5 Statistical Analysis
In GT-07 (a phase 2 study enrolling patients with mild to moderate asthma), analysis of safety as well as efficacy was planned to be descriptive, and no formal sample size calculation was conducted. Sample size calculations were described in the other studies. In designing the studies, power calculation was based on a two-sided t-test and a 5% significance level. In GT-02, the sample size calculated had sufficient power to detect a between-treatment difference of 20% in the DSS. In GT-08, the sample size calculated had 95% power to detect a between-treatment difference of 25% in the DSS. In GT-14, the sample size calculated had 90% power to detect a between-treatment difference in the DSS of 24%. In P05238 and P05239, the sample size calculated had 88% power to detect a between-treatment difference in TCS of 23%. In GT-12, the sample size calculated had 90% power to detect a between-treatment difference in the DSS of 21%. In P08067, the sample size calculated had a > 99% power to detect a between-treatment difference in TCS of 23%.

Analyses of the key efficacy end points were performed using analysis of variance (ANOVA) and adjusting for different error variation for each treatment group. The analysis model was adjusted for additional factors, such as site or region effect and asthma status. The least square mean and two-sided 95% confidence interval (CI) and *P* values were estimated for the between-treatment differences. Also, the relative percentage reduction with respect to placebo was calculated as 100 x (PPAE – placebo)/placebo using the least square means for the PPAE group and the placebo group.

When normality assumptions were not satisfied, analysis was based on appropriately transformed data (e.g., square root and log transformation) or non-parametric analysis such as the Wilcoxon rank sum test and Hodges–Lehmann analysis was conducted.

Health Canada did not consider ANOVA to be an appropriate analysis method for repeated measurement of primary and secondary points and requested that the manufacturer provide results using statistical methods appropriate for longitudinal data analysis (LDA). The manufacturer conducted post hoc LDA. The LDA model included treatment group, asthma status, and site as covariates. Results from LDA are available for GT-08, GT-14, P05238, P05239, and P08067.

Missing data were handled in a similar way in most studies. There was no imputation of missing data for DSS and TCS. For DMS, the missing data were imputed as 0 if the DSS was non-missing on the same day; otherwise, DMS was not imputed. This assumption was considered reasonable, as a patient who filled in DSS but did not fill in DMS is likely not to have taken any rescue medication. The primary analysis was supplemented with sensitivity analyses using missing data imputed by various imputation techniques such as last observation carried forward and worst-case scenario. Last observation carried forward was used in GT-12, P05238, and P05239. Worst-case scenario was used in P05238, P05239, and P08067. In GT-02, missing data were imputed for patients with at least one daily score recorded using predicted values from an imputational model. In the case of RQLQ data, no imputation of missing data was carried out.

As there were multiple end points, methods to control for multiplicity were used. Multiplicity was controlled for by using either a gatekeeping step-down testing procedure in which the hypotheses were tested according to a pre-specified hierarchal ordering (in GT-02, GT-12, and P08067), or by adjusting for *P* values based on the Benjamini–Hochberg method (in P05238 and P05239).

**a) Analysis Populations**

The full analysis set (FAS) was used for the primary efficacy analysis. In addition, analyses employing the per-protocol (PP) population were conducted. Safety analyses were conducted using the FAS for all studies.

In studies GT-07, GT-02, GT-08, GT-14, and GT-12, FAS was defined as all randomized patients following the intention-to-treat (ITT) principle. In studies P05238 and P05239, FAS was defined as all patients randomized with at least one post-treatment diary datum following the ITT principle. In study P08067, FAS was defined as all randomized patients who received at least one dose of study treatment and had at least one post-treatment efficacy measurement.

In studies GT-07 and GT-02, the PP population was defined as all patients randomized and exposed to at least one dose of trial medication as well as having completed the trial and with no major protocol deviations. In studies GT-08, GT-14, P05238, P05239, and P08067, the PP population was defined as all

patients with no major protocol deviations. In study GT-12, PP was defined as all patients in FAS and who did not have any major protocol deviation.

## 3.3 Patient Disposition

Patient disposition for each included study is presented in Table 10 and Table 11. The number of patients randomized ranged between 253 and 1,501 in the six phase 3 studies (GT-08, GT-14, P05238, GT-12, P05239, and P08067) and was 114 in the phase 2 study (GT-07). The number of patients randomized to the four relevant groups of the phase 2/3 study (GT-02) was 580. The proportion of patients discontinuing the study ranged between 6% and 20% in the studies. The proportion of patients discontinuing the study was similar in both the PPAE and placebo groups in GT-02, GT-07, GT-08, GT-14, P05238, and P05239. In GT-12 and P08067, there was greater discontinuation in the PPAE group compared with the placebo group (10% versus 6%, and 20% versus 13%, respectively). Generally, discontinuation due to adverse events was greater in the PPAE group compared with the placebo group.

**TABLE 10: PATIENT DISPOSITION (ADULTS)**

| | GT-07 | | GT-02 | | | | GT-08 | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE | Placebo | PPAE | Placebo | PPAE (no L)[a] | Placebo (no L)[a] | PPAE | Placebo | PPAE | Placebo | PPAE | Placebo |
| Screened, N | 130 | | 1,008 | | | | 888 | | 405 | | 531 | |
| Randomized, N | 74 | 40 | 141 | 136 | 153 | 150 | 316 | 318 | 163 | 166 | 213 | 225 |
| Discontinued, N (%) | 8 (10.8) | 4 (10.0) | 12 (8.5) | 10 (7.4) | 15 (9.8) | 11 (7.3) | 42 (13) | 46 (14) | 27 (17) | 26 (16) | 38 (18) | 33 (15) |
| Adverse events | 3 (4.1) | 0 | 7 (5.0) | 1 (0.7) | 7 (4.6) | 2 (1.3) | 16 (5) | 8 (3) | 10 (6) | 5 (3) | 11 (5) | 8 (4) |
| Lost to follow-up | 2 (2.7) | 1 (2.5) | 0 (0) | 2 (1.5) | 3 (2) | 2 (1.3) | 5 (2) | 7 (2) | 2 (1) | 5 (3) | 5 (2) | 4 (2) |
| Withdrawal of consent | NR | NR | 1 (0.7) | 0 (0) | 1 (0.7) | 2 (1.3) | 9 (3) | 4 (1) | 8 (5) | 7 (4) | 9 (4) | 8 (4) |
| Lack of efficacy | NR | NR | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (< 1) | 0 | NR | NR | NR | NR |
| Other[b] | 3 (4.1) | 3 (7.5) | 4 (2.8) | 7 (5.1) | 4 (2.6) | 5 (3.3) | 11 (3) | 10 (3) | 7 (4.3) | 9 (5.4) | 13 (6.1) | 13 (5.7) |
| FAS or ITT, N (%) | 74 (100) | 40 (100) | 141 (100) | 136 (100) | 153 (100) | 150 (100) | 316 (100) | 318 (100) | 163 (100) | 166 (100) | 213 (100) | 225 (10) |
| PP, N (%) | 61 (82.4) | 32 (80.0) | 124 (87.9) | 122 (89.7) | 127 (83.0) | 128 (85.3) | NR | NR | 121 (74) | 119 (72) | 164 (77) | 188 (84) |
| Safety, N (%) | 74 (100) | 40 (100) | 141 (100) | 136 (100) | 153 (100) | 150 (100) | 316 (100) | 318 (100) | 163 (100) | 166 (100) | 213 (100) | 225 (100) |

FAS = full analysis set; ITT = intention-to-treat; L = loratadine; PP = per-protocol; PPAE = *Phleum pratense* allergen extract.
[a]Patients randomized to receive rescue medication of placebo instead of loratadine at step 1.
[b]Calculated by Common Drug Review reviewer.
Source: Clinical study reports.[26-30]

**TABLE 11: PATIENT DISPOSITION (CHILDREN OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE | Placebo | PPAE | Placebo | PPAE | Placebo |
| **Screened, N** | 307 | | 378 | | 1,501 | |
| **Randomized, N** | 126 | 127 | 175 | 169 | **752** | 749 |
| **Discontinued, N (%)** | 12 (10) | 7 (6) | 33 (19) | 29 (17) | 149 (20) | 97 (13) |
| **Discontinuation reason, N (%)** | | | | | | |
| **Adverse events** | 4 (3) | 2 (2) | 13 (7) | 5 (3) | 54 (7) | 19 (3) |
| **Lost to follow-up** | 2 (2) | 0(0) | 4 (2) | 0 (0) | 16 (2) | 16 (2) |
| **Withdrawal of consent** | 0 (0) | 1 (< 1) | 10 (6) | 8 (5) | 52 (7) | 39 (5) |
| **Lack of efficacy, or treatment failure** | NR | NR | 0 | 1 (1) | NR | NR |
| **Other**[a] | 6 (4.8) | 4 (3.1) | 6 (3.4) | 15 (8.9) | 27 (3.6) | 23 (3.1) |
| **FAS or ITT, N (%)** | 126 (100) | 127 (100) | 173 | 167 | 744 (99) | 744 (99) |
| **PP, N (%)** | 91 (72) | 100 (79) | 135 (77) | 124 (73) | 684 (91) | 683 (91) |
| **Safety, N (%)** | 126 (100) | 127 (100) | 175 (100)[a] | 169 (100)[a] | 753 (100)[a] | 745 (99)[a] |

FAS = full analysis set; ITT = intention-to-treat; NR = not reported; PP = per-protocol set; PPAE = *Phleum pratense* allergen extract.
[a]Calculated by Common Drug Review reviewer.
Source: Clinical study reports.[26-30]

## 3.4 Exposure to Study Treatments

In all studies, patients were exposed to the study treatment prior to and during the GPS. Compliance was assessed by tablet counts and expressed as percentage of the expected intake.

Exposure to study treatment was similar in the PPAE and placebo groups in all the studies. Across the various studies, the mean exposure ranged between 125 and 189 days. Compliance was similar in the PPAE and placebo groups. The percentage compliance in PPAE and placebo groups was, respectively, 94% and 95% in GT-02; 91% and 95% in GT-12; and 101% and 101% in GT-14. The percentages of patients who were 60% to ≤ 120% compliant in the PPAE and placebo groups were, respectively, 92% and 93% in P05238; 91% and 83% in P05239; and 96% and 98% in P08067.

## 3.5 Critical Appraisal

### 3.5.1 Internal Validity

All eight studies were randomized, double-blinded, multi-centre trials. The methods of randomization, allocation concealment, and blinding were considered appropriate. Computer-generated randomization was used and the codes were kept strictly confidential.

Study discontinuation rates were similar for active treatment and placebo groups in most studies except in GT-12 and P08067, where discontinuation rates were higher in the active treatment groups. Differential study discontinuation across treatment groups may bias results; however, given the magnitude of the between-treatment differences in study discontinuation observed in these two trials, this was not a major concern.

The more frequent occurrence of adverse events in the PPAE groups compared with the placebo groups may have compromised blinding, and may be expected to bias the assessment of comparative efficacy, especially given the subjective nature of the primary outcomes.

Except for the RQLQ tool used for evaluating quality of life, efficacy outcome measures used in the studies (DSS, DMS, and TCS) have not been validated. No rationale was provided for the scores assigned to specific rescue medications in the calculation of the DMS. Thus, the validity of the DMS and the TCS (which is the sum of DSS plus DMS) seems particularly uncertain, as does the minimal clinically important difference. The World Allergy Organization (WAO) recommends the use of a combined symptom and medication score to determine efficacy of immunotherapy, suggesting that a ≥ 20% between-treatment difference in the combined score represents a clinically meaningful difference.[41] However, it should be noted that when scale scores are low, small absolute between-treatment differences, when expressed as a percentage, could appear large.

Although it was mentioned that ITT analysis was conducted, the number of participants included in the analysis was consistently lower than the number randomized. The reason for this is unclear and the missing data could potentially introduce bias.

### 3.5.2 External Validity

The majority of the patient populations in the studies were Caucasian. This may not reflect the patient population generally seen in clinical practice, but there is no reason to believe that the treatment effect of immunotherapy is dependent on ethnicity, and this was also corroborated by the clinical expert on this review.

The age range of patients in the included studies was between five and 65 years; hence, the efficacy and safety of PPAE in patients beyond this age range is uncertain.

Of the six pivotal studies (GT-08, GT-12, GT-14, P05238, P05239, and P08067), three studies (P05238, P05239, and P08067) were conducted in Canada and the US, one study (GT-14) was conducted in the US, and two studies (GT-08 and GT-12) were conducted in Europe. Results were comparable. One study (GT-07) required inclusion of participants with mild or moderate asthma; thus, results may not be generalizable to the general AR population.

In this review, all the included studies were placebo controlled. No relevant, head-to-head studies with active controls were identified. Hence, there is a lack of high-quality evidence regarding the relative effects of PPAE therapy compared with SCIT or other SLIT products.

## 3.6 Efficacy

In all the studies, PPAE was compared with placebo and both groups received step 1 medication as needed. In GT-02, there were two additional comparator groups in which step 1 medication, loratadine, was not allowed. These two groups are referred to as PPAE (no L) and placebo (no L) in this review.

### 3.6.1 Symptom Relief

#### a) Daily Symptom Score

The range of the rhinoconjunctivitis DSS ranges from 0 to 18, with higher scores indicating higher symptom severity. Adjusted mean rhinoconjunctivitis DSSs over the entire GPS were reported in all eight studies and were lower for PPAE groups (range 2.18 to 5.69) compared with placebo groups (range 2.80 to 6.06); see Figure 2, Table 22, and Table 23. DSSs were noticeably higher in study GT-14, compared with other studies. Between-treatment mean differences ranged between –0.37 and –1.29, being statistically significant in five studies (GT-08, P05238, GT-12, P05239, and P08067) and non-significant in three studies (GT-07, GT-02, and GT-14). The corresponding relative percentage differences in mean DSS ranged between –6.18% and –31%, being ≥ 20% lower for PPAE compared with placebo in three studies (GT-08, P05239, and GT-12). In study GT-02, between-treatment mean differences were similar regardless of whether loratadine or placebo was used for rescue. However, median DSSs were lower in the treatment groups that received loratadine.

Adjusted mean DSSs over the peak GPS were reported in seven studies and were lower in PPAE groups (range 2.84 to 5.99) compared with placebo groups (range 3.79 to 6.49); see APPENDIX 4: DETAILED OUTCOME DATA, Table 24 and Table 25. Between-treatment mean differences ranged between –0.34 and –1.39, being statistically significant in six studies (GT-02, GT-08, P05238, GT-12, P05239, and P08067) and non-significant in one study (GT-14). In GT-02, the between-treatment mean difference was not statistically significant for PPAE (no L) versus placebo (no L). The corresponding relative percentage difference in mean DSS ranged between –8% and –28%, being ≥ 20% lower for PPAE compared with placebo in four studies (GT-08, P05238, GT-12, and P05239).

Between-treatment differences in DSS were greater when measured over the peak GPS compared with the entire GPS in six studies (GT-08, GT-14, P05238, GT-12, P05239, and P08067), and in one study (GT-02) they were similar for PPAE versus placebo and lower for PPAE (no L) versus placebo (no L).

**b) Daily Medication Score**

The possible range of rhinoconjunctivitis DMSs differed between trials due to differences in allowed rescue medications and scoring systems. Adjusted mean rhinoconjunctivitis DMSs over the entire GPS were reported in all eight studies and were lower with the PPAE groups (range 0.78 to 2.60) compared with the placebo groups (range 1.19 to 3.81); see Figure 3, Table 26, and Table 27. DMSs were lower in studies enrolling children compared with studies enrolling adults. DMSs were highest in study GT-07, which exclusively enrolled patients with asthma. Between-treatment differences ranged from –0.4 to –1.2, being statistically significant in four studies (GT-02, GT-08, GT-12, and P08067) and non-significant in four studies (GT-07, GT-14, P05238, and P05239). In study GT-02, the between-treatment mean difference was not statistically significant for the comparison of PPAE (no L) versus placebo (no L). The corresponding relative percentage differences in mean DMS ranged between –27% and –39%.

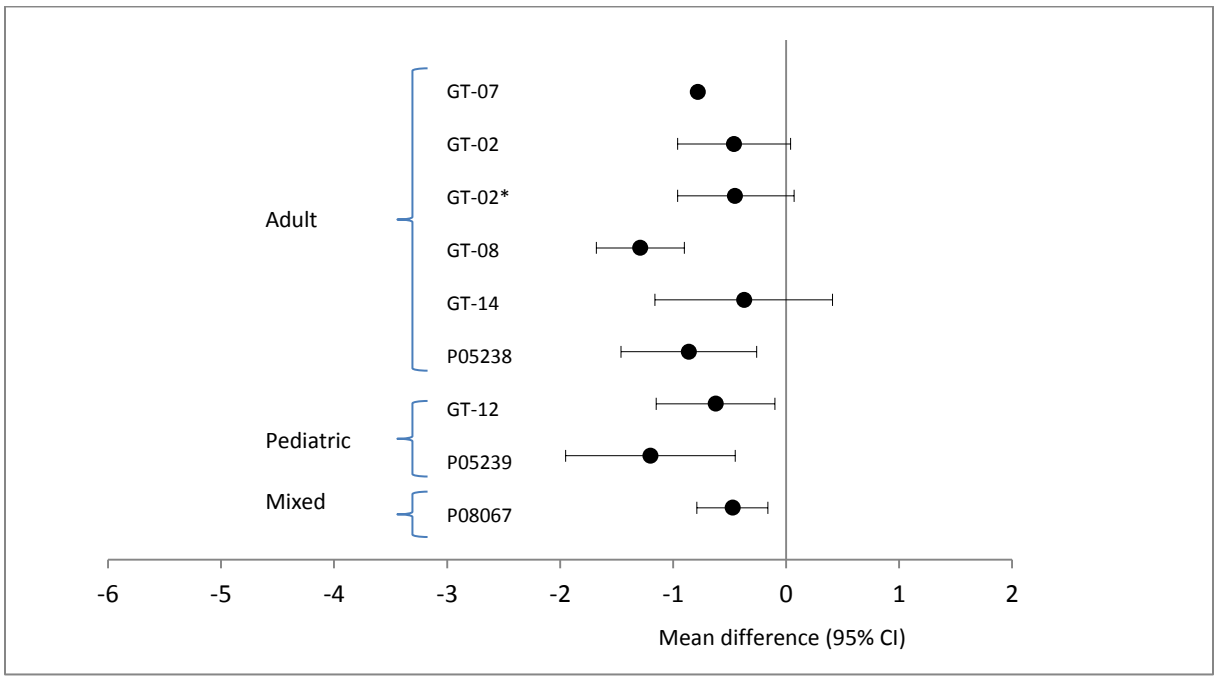
Adjusted mean DMSs over the peak GPS were reported in seven studies and were lower with PPAE (range 0.92 to 2.28) compared with placebo (range 1.55 to 3.46); see Table 28 and Table 29. Again, DMSs were lower in studies enrolling children compared with studies enrolling adults. Between-treatment mean differences ranged between –0.40 and –1.34, being statistically significant in four studies (GT-08, GT-12, P05239, and P08067) and non-significant in three studies (GT-02, GT-14, and P05238). In study GT-02, the between-treatment mean difference was statistically significant only for the comparison of PPAE versus placebo where loratadine rescue medication was received. The corresponding percentage differences ranged between –19% and –41%, being ≥ 20% in six studies (GT-08, GT-14, P05238, GT-12, P05239, and P08067). The between-treatment differences in DMS were greater when measured over the peak GPS compared with entire GPS in four studies (GT-08, GT-12, P05239, and P08067), similar in two studies (GT-14, and P05238), and conflicting in GT-02, based on receipt of loratadine as rescue medication.

**c) Total Combined Score**

Adjusted mean rhinoconjunctivitis TCSs during the entire GPS were reported in six studies and were lower with PPAE (range 3.70 to 6.74) compared with placebo (range 4.86 to 7.53); see Figure 4, Table 30, and Table 31. Between-treatment mean differences ranged from –0.8 to –2.3, being statistically significant in five studies (GT-08, P05238, GT-12, P05239, and P08067) and non-significant in one study (GT-14). The corresponding relative percentage differences in mean TCS ranged between –10% and –34%, being ≥ 20% in four studies (GT-08, P05238, GT-12, and P05239).

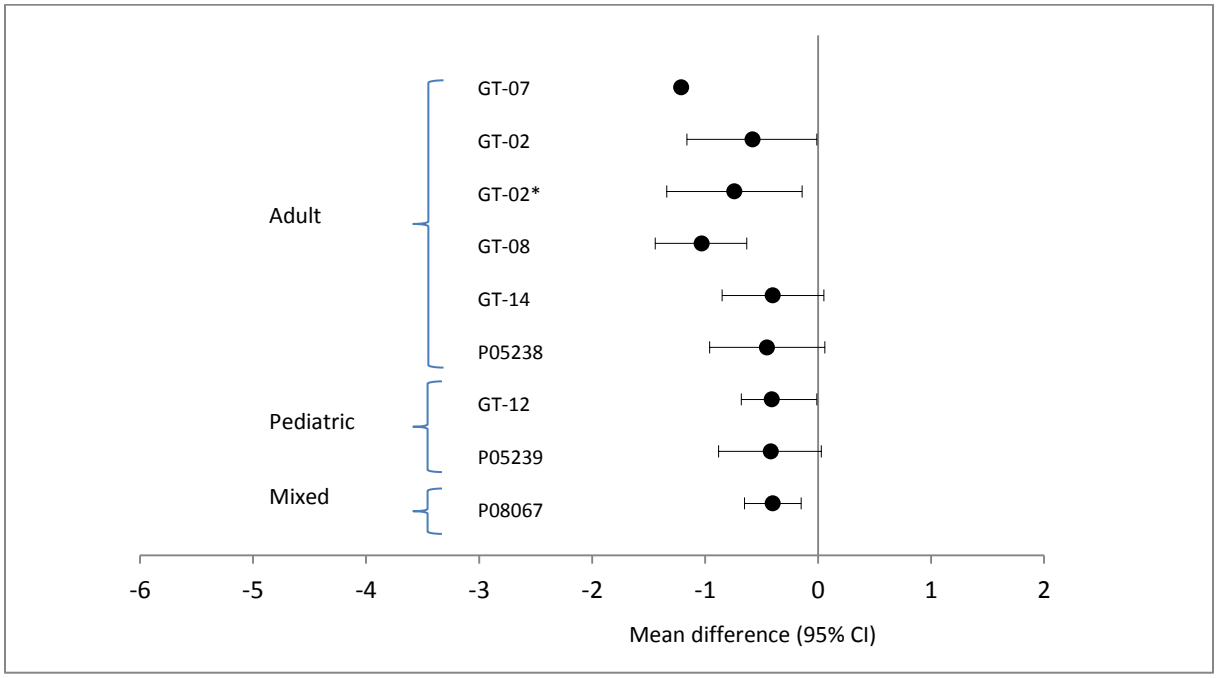
Adjusted mean TCSs over the peak GPS were reported in four studies and were lower with PPAE (range 4.20 to 7.13) compared with placebo (range 5.35 to 8.05) (Figure 4, Table 32, and Table 33). Between-treatment mean differences ranged between –0.91 and –2.12, being statistically significant in three studies (P05238, P05239, and P08067) and non-significant in one study (GT-14). The corresponding relative percentage differences in mean TCS ranged between –11% and –31%, being ≥ 20% in three studies (P05238, P05239, and P08067). The between-treatment differences in TCSs were greater when measured over the peak GPS compared with entire GPS in all four studies.

**FIGURE 2: DSS; PPAE VERSUS PLACEBO OVER ENTIRE GPS**



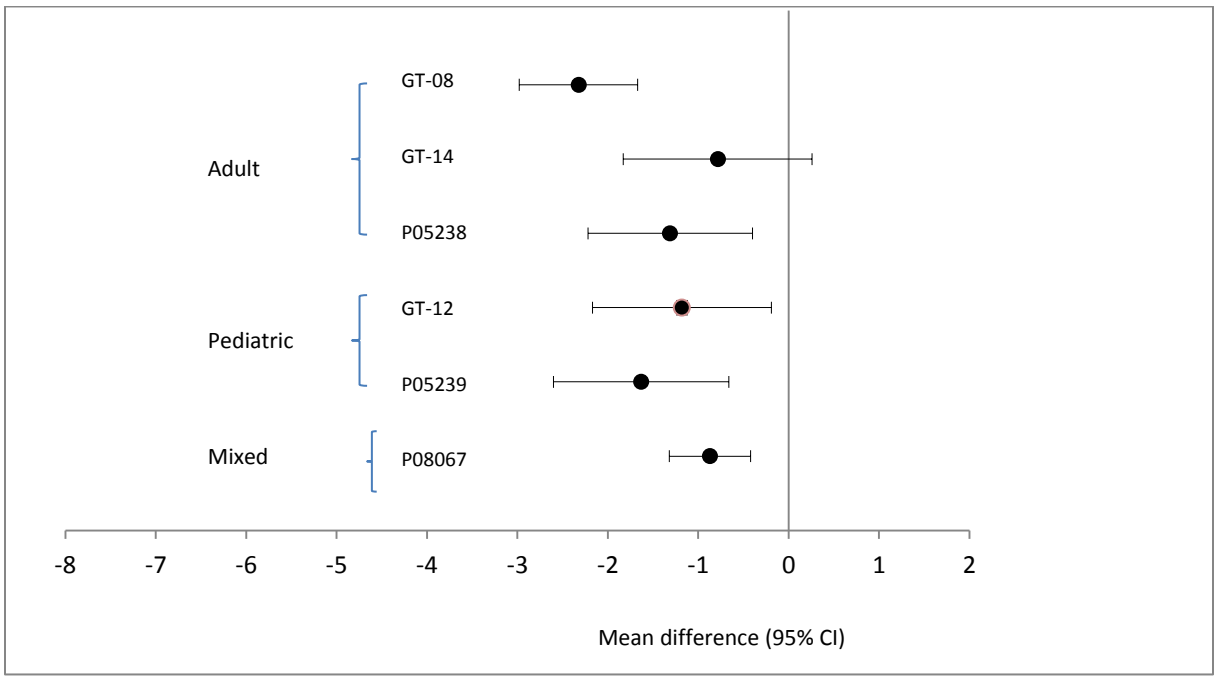

CI = confidence interval; DSS = daily symptom score; GPS = grass pollen season; L = loratadine; PPAE = *Phleum pratense* allergen extract.
Note: For GT-02*, the comparator groups are PPAE (no L) versus placebo (no L). For GT-07, 95% CI was not available.

**FIGURE 3: DMS; PPAE VERSUS PLACEBO OVER ENTIRE GPS**




CI = confidence interval; DMS = daily medication score; GPS = grass pollen season; L = loratadine; PPAE = *Phleum pratense* allergen extract.
Note: For GT-02*, the comparator groups were PPAE (no L) versus placebo (no L). For GT-07, 95% CI was not available.

**FIGURE 4: TCS; PPAE VERSUS PLACEBO OVER ENTIRE GPS**




CI = confidence interval; GPS = grass pollen season; PPAE = *Phleum pratense* allergen extract; TCS = total combined score.

Results obtained with post hoc longitudinal data analyses were comparable with the results obtained using ANOVA for DSS, DMS, and TCS (APPENDIX 4: DETAILED OUTCOME DATA, Table 40).

**d) Well Days**

The adjusted mean percentage of well days was reported in six studies and was higher in PPAE groups (range 27.44 to 52.27) compared with placebo groups (26.03 to 44.43) (Table 34 and Table 35). The between-treatment differences ranged from 1.4% to 12.4%. Percentage of well days was statistically significantly higher for PPAE groups compared with placebo in three studies (GT-08, GT-12, and P05239), whereas there were no statistically significant between-treatment differences in two studies (GT-14, and P05238). In GT-02, the percentage of well days was statistically significantly higher for the PPAE group compared with placebo, whereas there was no statistically significant between-treatment difference for PPAE (no L) versus placebo (no L).

**e) Visual Analogue Scale**

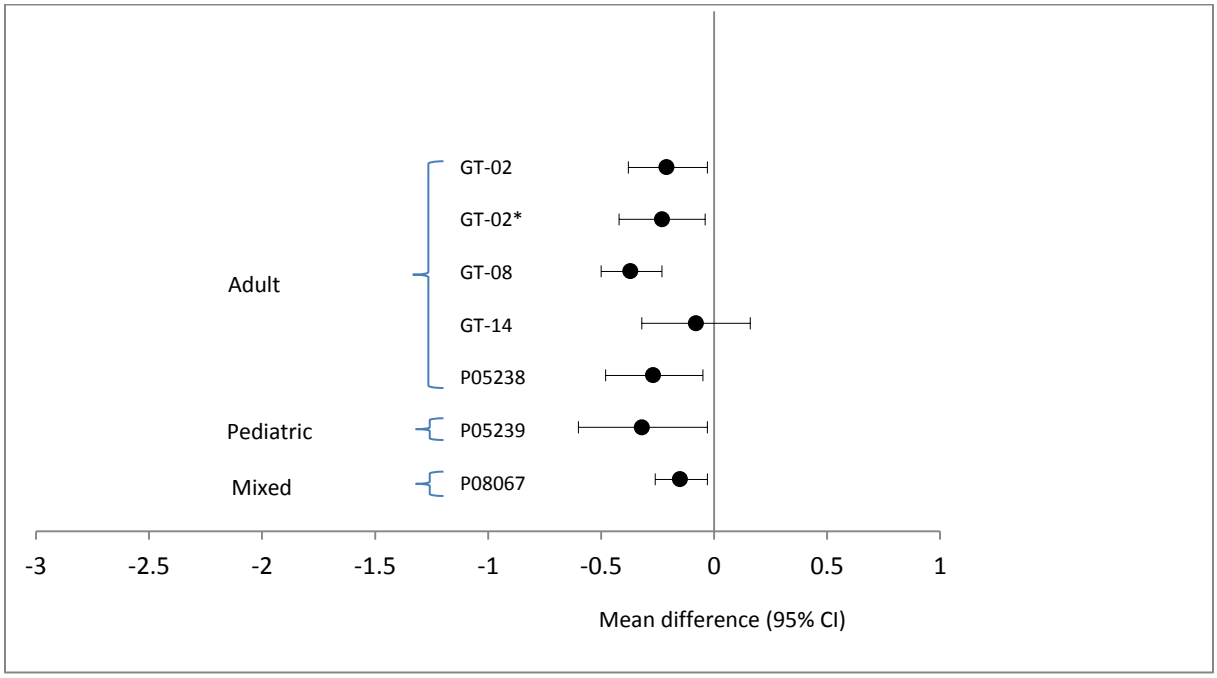
The adjusted mean VAS scores for symptoms were reported in six studies and were lower with PPAE (range 11.03 to 32.23) compared with placebo (13.82 to 35.85); lower scores indicate lesser symptoms (Table 36 and Table 37). The between-treatment mean differences ranged between –2.3 and –6.7, being statistically significant in three studies (GT-08, P05238, and P05239) and non-significant in two studies (GT-14 and GT-12). In GT-02, the between-treatment mean difference was statistically significant for PPAE (no L) versus placebo (no L) and statistically non-significant for PPAE versus placebo.

### 3.6.2 Quality of Life

Health-related quality of life was assessed using RQLQ where lower scores indicated better health-related quality of life. RQLQ results were reported for six studies and adjusted mean scores were lower

with PPAE (range 0.84 to 1.45) compared with placebo (range 1.05 to 1.77); see Figure 5, Table 38, and Table 39. The between-treatment mean differences in RQLQ scores ranged between –0.08 and –0.37, being statistically significant in five studies (GT-02, GT-08, P05238, P05239, and P08067) and non-significant in one study (GT-14).

**FIGURE 5: RQLQ SCORE OVER ENTIRE GRASS POLLEN SEASON**




CI = confidence interval; L = loratadine; PPAE = *Phleum pratense* allergen extract; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.
Note: For GT-02*, the comparator groups were PPAE (no L) versus placebo (no L).

## 3.7 Harms

Only those harms identified in the review protocol (Section 2.2.1 Protocol) and common adverse events are reported below. Additional details are available in APPENDIX 4: DETAILED OUTCOME DATA (Table 41 and Table 42).

### 3.7.1 Adverse Events

In all eight studies, the percentage of patients reporting adverse events was higher in the PPAE group compared with the placebo group (Table 12 and Table 13). Adverse events were reported as being mild or moderate in severity. Commonly reported adverse events with PPAE included ear pruritus, eye pruritus, mouth edema, oral pruritus, throat irritation and nasopharyngitis. The percentage of patients reporting oral pruritus varied between 18% and 55% and frequency of throat irritation varied between 9% and 37%.

### 3.7.2 Serious Adverse Events

Across all studies, the frequency of serious adverse events was low (≤ 2%) with no notable between-treatment differences.

### 3.7.3 Withdrawals due to Adverse Events

Withdrawals due to adverse events varied across studies, with a range of 0% to 7% across all study groups; the frequency was generally higher in the PPAE groups.

**TABLE 12: HARMS (ADULTS)**

| | GT-07 | | GT-02 | | | | GT-08 | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 74 | Placebo N = 40 | PPAE N = 141 | Placebo N = 136 | PPAE (no L)[a] N = 153 | Placebo (no L)[a] N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 213 | Placebo N = 225 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **AE** | 70 (95) | 36 (90) | 130 (92.20) | 100 (73.53) | 137 (89.54) | 115 (76.67) | 265 (84) | 205 (64) | 121 (74) | 101 (61) | 176 (82.6) | 161 (71.6) |
| **Ear Pruritus** | 14 (19) | 0 | 11 (7.80) | 0 (0) | 25 (16.34) | 6 (4.00) | 38 (12) | 3 (1) | 16 (10) | 1 (< 1) | 42 (19.7) | 3 (1.3) |
| **Eye Pruritus** | 5 (7) | 1 (3) | 6 (4.26) | 5 (3.68) | 7 (4.58) | 7 (4.67) | 11 (3) | 7 (2) | 5 (3) | 1 (< 1) | 11 (5.2) | 8 (3.6) |
| **Edema Mouth** | 9 (12) | 1 (3) | 22 (15.60) | 0 (0) | 17 (11.11) | 1 (0.67) | 58 (18) | 2 (1) | 9 (6) | - | 17 (8.0) | 1 (0.4) |
| **Oral Pruritus** | 39 (53) | 2 (5) | 78 (55.32) | 15 (11.03) | 75 (49.02 | 18 (12.00) | 145 (46) | 13 (4) | 29 (18) | 1 (< 1) | 75 (35.2) | 7 (3.1) |
| **Throat Irritation** | 25 (34) | 3 (8) | 33 (23.40) | 2 (1.47) | 44 (28.76) | 5 (3.33) | 30 (9) | 3 (1) | 24 (15) | 4 (2) | 63 (29.6) | 11 (4.9) |
| **Nasopharyngitis** | 27 (36) | 10 (25) | 23 (16.31) | 25 (18.38) | 25 (16.34) | 25 (16.67) | 47 (15) | 60 (19) | 23 (14) | 24 (14) | 17 (8.0) | 29 (12.9) |
| **Upper Respiratory Tract Infection** | NR | NR | 2 (1.42) | 2 (1.47) | 6 ( 3.92) | 8 (5.33) | 13 (4) | 7 (2) | 17 (10) | 15 (9) | 38 (17.8) | 25 (11.1) |
| **SAE** | 0 | 0 | 1 (0.71) | 0 (0) | 2 ( 1.31) | 1 (0.67) | 6 (2) | 4 (1) | 0 | 2 (1) | 2 (0.9) | 5 (2.2) |
| **WDAE** | 3 (4) | 0 | 8 (5.67) | 1 (0.74) | 7 ( 4.58) | 2 (1.33) | 16 (5) | 8 (3) | 10 (6) | 5 (3) | 11 (5) | 8 (4) |

AE = adverse events; L = loratadine; NR = not reported; PPAE = *Phleum pratense* allergen extract; SAE = serious adverse events; WDAE = withdrawal due to adverse events.
[a]Patients randomized to receive rescue medication of placebo instead of loratadine at step 1.
Source: Clinical study reports.[26-30]

**TABLE 13: HARMS (CHILDREN OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 175 | Placebo N = 169 | PPAE N = 753 | Placebo N = 745 |
| | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| **AE** | 109 (87) | 106 (83) | 151 (86.3) | 131 (77.5) | 593 (78.8) | 508 (68.2) |
| **Ear Pruritus** | 5 (4) | 0 (0) | 21 (12.0) | 1 (0.6) | 92 (12.2) | 12 (1.6) |
| **Eye Pruritus** | 5 (4) | 5 (4) | 15 (8.6) | 4 (2.4) | 25 (3.3) | 26 (3.5) |
| **Oedema Mouth** | 3 (2) | 0 (0) | 19 (10.9) | 1 (0.6) | 98 (13.0) | 9 (1.2) |
| **Oral Pruritus** | 40 (32) | 3 (2) | 68 (38.9) | 6 (3.6) | 139 (18.5) | 21 (2.8) |
| **Throat Irritation** | 13 (10) | 2 (2) | 65 (37.1) | 5 (3.0) | 181 (24.0) | 29 (3.9) |
| **Nasopharyngitis** | 19 (15) | 6 (5) | 26 (14.9) | 32 (18.9) | 103 (13.7) | 122 (16.4) |
| **Upper respiratory tract infection** | 12 (10) | 11 (9) | 21 (12.0) | 22 (13.0) | 78 (10.4) | 86 (11.5) |
| **SAE** | 2 (2) | 2 (2) | 0 | 4 (2.4)[a] | 11 (1.5) | 8 (1.1) |
| **WDAE** | 4 ( 3) | 2 ( 2) | 13 (7)[b] | 5 (3)[b] | 54 (7.2) | 18 (2.4) |

AE = adverse event; PPAE = *Phleum pratense* allergen extract; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a]Includes one patient not randomized to any group (P05239 had an observation period before randomization).
[b]Calculated by Common Drug Review reviewer.
Source: Clinical study reports.[34-36]

### 3.7.4 Mortality

There were no deaths reported in studies GT-07, GT-02, GT-14, GT-12, and P05239. In studies GT-08, P05238, and P08067, one death was reported in each study, as described below, but none were considered by the manufacturer to be treatment related.

In study GT-08 (first year), a 31-year-old male participant in the PPAE treatment group was diagnosed with subarachnoid haematoma/ subarachnoid haemorrhage and later died. In study P05238, a 28-year-old male patient in the PPAE group suffered a multiple drug overdose. In study P08067, a 42-year-old male patient who had been treated with PPAE completed the study and had reported no adverse events during the study. He later died. He had been off the study drug for a month. The cause of death was reported as unknown.

### 3.7.5 Notable Harms

In studies P05238, P05239, and P08067, it was mentioned that no participants experienced anaphylactic shock, and in studies GT-02, GT-07, GT-08, GT-12, and GT-14, there was no specific mention of anaphylactic shock.

No incidence of anaphylaxis was reported in GT-02, GT-07, GT-08, and GT-12.

In study P05238, one participant in the PPAE group received epinephrine due to an adverse event that occurred following the first administration of the study drug, and one placebo-treated patient used epinephrine in response to an anxiety attack, which the manufacturer stated was not an indicated (or medically appropriate) use for this medication.

In study GT-14, five participants in the study drug group had anaphylactic reactions that were reported as probably being study drug related. One was considered of moderate severity and the remaining four were considered mild. Three participants were treated with epinephrine. All participants recovered from the event. No anaphylactic reaction was reported for the placebo group.

In study P05239, three participants received epinephrine. In one participant, it was given for an allergic reaction following the first administration of the PPAE under the supervision of the investigator. In the other two cases, one participant in the PPAE group had viral pharyngitis and one participant in the placebo group had asthma exacerbation. The manufacturer determined that the two participants in the PPAE group requiring epinephrine had a systemic event or reaction that was probably related to the study drug. The events were considered mild or moderate.

In study P08067, two patients in the PPAE group experienced moderate systemic allergic reactions but epinephrine was not administered for treating the events. Of these two participants, one was assessed as having an anaphylactic reaction, and for the other there was no mention of anaphylactic reaction. Two patients received epinephrine for local application site reactions considered by the manufacturer to be related to the study drug.

During the treatment period, the recording of “asthma” as an adverse event was infrequent (≤ 2%) in six studies (GT-02, GT-08, GT-14, P05238, P05239, and P08067) and were not noticeably different between the PPAE and placebo groups. In two studies (GT-07 and GT-12), which had enrolled a substantial proportion of patients with asthma (100% in GT-07 and 40% in GT-12), the incidences of asthma during the treatment period were 11% versus 10%, and 6% versus 9% in the PPAE and placebo groups, respectively. Details are available in APPENDIX 4: DETAILED OUTCOME DATA, Table 41 and Table 42.

# 4. DISCUSSION

## 4.1 Summary of Available Evidence

Eight multi-centre, randomized, parallel-group, double-blinded, placebo-controlled studies met the inclusion criteria for this systematic review. The studies compared the efficacy and safety of PPAE with placebo in patients with AR, with or without conjunctivitis. Six studies (GT-08, GT-12, GT-14, P05238, P05239, and P08067) were phase 3 and considered pivotal studies, one study (GT-02) was phase 2/3, and one study (GT-07) was phase 2. Five studies (GT-02, GT-07, GT-08, GT-14, and P05238) involved adult patients, two studies (GT-12 and P05239) involved pediatric patients and one study (P08067) involved a mixed population of adult and pediatric patients. Except for GT-02, all other studies compared PPAE 2,800 BAU (equivalent to 75,000 SQ-U) with placebo, with oral antihistamines being allowed as rescue medication in all groups as needed. In GT-02, participants were randomized to six treatment groups, with various doses of PPAE, in which the use of oral antihistamine (loratadine) as a rescue treatment was controlled based on randomization. Only results for treatment groups employing the Health Canada–recommended doses of PPAE or placebo (with or without loratadine as rescue treatment) are included in this report.

In all studies, the treatment with PPAE was started several weeks prior to the GPS and continued for the entire GPS. Total treatment duration was approximately 24 weeks in studies GT-02, GT-07, GT-12, GT-14, P05238, P05239, and P08067. The product monograph for PPAE states that PPAE should be initiated at least eight weeks before the GPS, and the clinical expert consulted for this review considered that clinicians would likely prescribe only eight weeks of pre-seasonal treatment. However, the majority of studies had pre-seasonal treatment durations between 8 and 16 weeks, with the exception of study GT-08, which allowed a pre-seasonal treatment duration between 16 and 35 weeks. The reason for the wide range in the pre-seasonal duration, and how the duration of the pre-seasonal treatment was determined for individual patients, in study GT-08 was unclear.

Outcomes in all studies, except GT-08, were assessed over one GPS. Study GT-08 assessed outcomes in each GPS over five years; seasonal treatment for three years and two non-treatment years. Thus, evidence for repeated courses of treatment, such as would be used in clinical practice, comes from only one RCT.

An important limitation of the evidence is the lack of RCTs comparing PPAE with other SLIT or SCIT products.

## 4.2 Interpretation of Results

### 4.2.1 Efficacy

Given that GT-07 was a phase 2 study specific to patients with asthma, and GT-02 was a phase 2/3 dose-finding study, this discussion focuses mainly on the results of the six phase 3 studies (GT-08, GT-14, GT-12, P05238, P05239 and P08067). In five (GT-08, P05238, GT-12, P05239, and P08067) of the six phase 3 studies, there was a statistically significant between-treatment difference in DSS and TCS over the entire GPS, favouring PPAE over placebo. The WAO recommends the use of a combined score (symptoms plus rescue medication use) to assess the efficacy of immunotherapy in AR, suggesting that a ≥ 20% between-treatment difference in the combined score represents a clinically meaningful difference.[41] The between-treatment difference in TCS was above 20% in four studies (GT-08, P05238, GT-12, and P05239) and 18% in study P08067. However, while a between-treatment difference in the TCS of ≥ 20% was achieved in a number of trials, the absolute differences in the TCS were small, and it was noted that small absolute differences can translate into large percentage differences when TCS

scores are relatively low. Whether patients may achieve a ≥ 20% reduction in the TCS at higher levels of symptom severity is unclear.

In GT-14, the between-treatment differences in DSS, DMS, and TCS did not reach statistical significance. According to the manufacturer, in this study, 64% of the patients reported allergic rhinoconjunctivitis symptoms weeks before the start of GPS and had only a slight increase in symptoms at the start of GPS and no further increase in symptoms during the GPS. Considering this, the manufacturer suspected that the interpretation or entries of symptom scoring were flawed or patients were affected by overlapping allergies or other factors that interfered with the demonstration of statistically significant treatment effect. However, it should be noted that reported DSS, DMS, and TCS were higher in GT-14 than the other included trials. Thus, an alternative explanation for the lack of statistically significant differences between PPAE and placebo in study GT-14 may be lesser efficacy of PPAE in patients with greater symptom severity.

RQLQ was reported in five (GT-08, GT-14, P05238, P05239, and P08067) of the six phase 3 studies. Improvement in RQLQ scores with PPAE compared with placebo was statistically significant in four studies (GT-08, P05238, P05239, and P08067) and not significant in one study (GT-14). However, in these four studies with statistically significant results, the absolute values of differences ranged between 0.08 and 0.37, which are less than 0.5, which is considered to be a minimally important difference.

Thus, while many of the trials reported statistically significant improvements with PPAE compared with placebo, in terms of DSS, DMS, and TCS, there are a number of limitations with the available evidence. The symptom and medication scales have not been validated and the clinical significance of the observed differences is unclear. In addition, patients were required to record their symptoms and rescue medication use in daily diary entries. The degree to which patients adhered to diary reporting is unclear. Given the approach to data analyses, patients need only have one recorded DSS or DMS to be included in the analyses. The amount of missing data for individual patients is unclear; however, it was noted that the number of patients included in the analyses was consistently less than those randomized. Missing data, either at the observation level or the patient level, may have biased the results. In addition, the DSS and RQLQ are subjective measures. Given that there may be potential for blinding being compromised, due to the high frequency of adverse events in the PPAE groups, the assessment of the symptom severity and quality of life, and the frequency with which patients recorded these, may have differed between treatment groups, affecting the validity of results.

The clinical expert consulted for this review confirmed that immunotherapy is administered seasonally for several years. Only one trial of PPAE (GT-08) assessed the benefits and harms of PPAE over multiple years. The extent of reduction in DSS, DMS, and TCS with PPAE in comparison with placebo further increased in year two and then declined closer to year one values in year three, and subsequently declined in years four and five, when treatment was no longer administered. Similar findings were observed for RQLQ scores. Immunotherapy is believed to go beyond just treating the symptoms associated with AR by modifying the disease itself, so that after treatment for three to five years, the effect persists without treatment. However, the results from GT-08 suggest a waning of the benefit achieved with treatment. In addition, caution should be exercised in the interpretation of these results, given the loss of approximately 50% of the originally randomized patients by years two to five, which was not equally distributed between treatment groups.

A key gap in the evidence for PPAE is the absence of RCTs directly comparing PPAE with other SLIT or SCIT. CDR previously reviewed 5GPAE, another SLIT product. Evidence for 5GPAE included four double-blind, placebo-controlled RCTs (three in adults and one in children); one study in adults assessed the effect of treatment with 5GPAE over multiple grass pollen seasons. The 5GPAE and PPAE studies were similarly designed, employing unvalidated symptom scales, and the RQLQ. In general, reported effect sizes for symptom scores for 5GPAE compared with placebo[42-45] were slightly greater than those reported for PPAE versus placebo. The rescue medication scales used in the 5GPAE studies were different from those used in the PPAE studies, and so the combined scores were also different; thus, it is difficult to assess the similarity of findings between PPAE and 5GPAE studies.

An indirect comparison (IDC) was provided by the manufacturer of PPAE (Merck), employing a network meta-analysis (NMA) using Bayesian techniques. (APPENDIX 7: CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS BETWEEN SUBLINGUAL IMMUNOTHERAPY TABLETS AND SUBCUTANEOUS IMMUNOTHERAPY, Table 48.) The results suggest that there were no statistically significant differences between SLIT-T and SCIT in reducing AR symptom and medication scores for the treatment of grass pollen allergy. In addition, a subgroup analysis indicated that within the SLIT-T group, PPAE was not statistically significantly different from 5GPAE in reducing symptom and medication scores. The point estimates of efficacy results from the NMA provided by Merck Canada Inc. (in its Grastek submission to CDR) and those reported from an IDC sponsored by the manufacturer of 5GPAE (Paladin, Inc.)[2] were similar and numerically favoured 5GPAE over PPAE; however, the difference was not statistically significant in the NMA conducted by Merck. Differences between the IDCs may be partially explained by the differences in the adopted statistical techniques and number of studies included. Finally, given that there was considerable heterogeneity across the individual studies included in the IDCs, the results need to be interpreted with caution.

The rationale for the use of SLIT tablets over SCIT is the convenient route of administration and fewer physician office visits. However, SLIT needs to be administered daily over several months, and as with any self-administered medication, there exists a possibility of poor adherence. In the included studies, the compliance rate was generally good, so the impact of poor compliance on treatment effect is not known.

### 4.2.2 Harms

In all the included studies, adverse events were higher in the PPAE group compared with the placebo group and were reported as being mild or moderate in severity. The most frequently reported adverse events were those associated with the mouth or throat. The treatment durations were approximately 24 weeks, in most studies, but longer-term data (seasonal treatment over three years) available from an extension to study GT-08 did not reveal additional safety issues.

Serious adverse events and withdrawals due to adverse events were few and similar in both groups across the trials. Three studies reported one death each in the PPAE groups, but these were not considered to be related to PPAE.

# 5. CONCLUSIONS

Based on a systematic review of eight double-blind RCTs in both children (≥ 5 years) and adults (18 to 65 years), compared with placebo, seasonal treatment with PPAE 2,800 BAU sublingually once daily resulted in statistically lower symptom scores and rescue medication use over one GPS. The clinical importance of the observed between-treatment differences in symptom and medication scores is uncertain. However, a between-treatment difference of ≥ 20% for a combined symptom plus medication score (considered to be clinically meaningful by the WAO) was achieved in five of six studies reporting this outcome. Changes in health-related quality of life, as measured by the RQLQ, were not considered clinically meaningful. Based on one long-term RCT, the beneficial effects of PPAE appear to be sustained over three subsequent years of seasonal treatment, with waning of effect in subsequent untreated years; however, the validity of the long-term findings are limited by the large and differential dropout following the first GPS. A manufacturer-provided IDC suggested that SLIT (including PPAE and 5GPAE) is not statistically different from SCIT, and PPAE is not statistically different from 5GPAE, in decreasing AR symptom and medication scores in patients with grass pollen allergy. However, given a number of limitations with the manufacturer-provided IDC and the lack of RCTs directly comparing these treatments, the comparative efficacy of immunotherapies is uncertain. The most frequently reported adverse events with PPAE were those associated with the mouth or throat. Serious adverse events and withdrawals due to adverse events were few and similar in both groups across the trials.

# APPENDIX 1: PATIENT INPUT SUMMARY

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

## 1. Brief Description of Patient Group(s) Supplying Input

The Asthma Society of Canada (ASC) is a national charitable volunteer-supported organization that is committed to enhancing the quality of life and health for people with asthma and associated allergies, through education and research. It was founded 39 years ago and offers evidence-based and age-appropriate asthma and allergy education, as well as disease management programs to consumers and health care professionals.

The ASC established the National Asthma Patient Alliance, a grassroots patient group of the ASC, in 2007; the group has an outreach to more than 5,000 patients with allergy and asthma. It is overseen by an Executive Committee made up of volunteers from across Canada and aims to increase patient awareness about how to achieve optimal asthma control and to address communication and advocacy needs for patients who have these diseases.

***The ASC receives approximately 20% of its revenue from research-based pharmaceutical companies. In 2013, funds were received from GlaxoSmithKline, Novartis, AstraZeneca, Roche Canada, Boehringer-Ingelheim International, and Rx&D. In 2012, the ASC received a grant of $18,000 from Merck Canada to host a patient conference. No funds were expected in 2013 from Merck Canada. No conflict of interest was declared in the preparation of the submission.***

## 2. Condition and Current Therapy-Related Information

Information for this submission was attained through an online survey regarding respiratory allergies sent to National Asthma Patient Alliance members across Canada in September 2013 (161 responses received) and a focus group of allergy patients (seven) held in Toronto (September 2013). Additionally, a concurrent study of severe asthma patients was conducted in August and September 2013, using one-on-one interviews with 24 patients and an extensive online survey of patients; it yielded both qualitative and quantitative information relevant to this submission. Of those surveyed or interviewed, 82% were diagnosed with allergies to grass pollen and other seasonal allergies; 79% had this confirmed with positive skin prick test and/or specific immunoglobulin E test to grass pollen; 23% were diagnosed with a specific allergy to Timothy grass, 23% have not been, and 54% were unsure.

Of the surveyed patients, 69% reported a diagnosis of allergy-induced asthma, and their principal concern is living with the daily or weekly threat of severe asthma exacerbations that may be triggered by seasonal allergy. Commonly reported symptoms by these patients include shortness of breath, wheezing, itchy throat, sinus congestion, poor or disrupted sleep and resultant fatigue, nasal passage inflammation, loss of sense of taste and smell, tightness in the chest, itchy eyes, skin rashes, hives, sneezing, persistent cough, and depression. Respiratory allergies adversely affected ability to work, leisure activities, physical activities, emotional well-being, ability to travel, ability to socialize, independence, financial situation, and relationships with family and friends.

The disease has a significant impact on caregivers as well. Their daily routines, such as taking time off work to support the patient (25%), had to be changed. Coping with treatment-related adverse events negatively affected 50% of caregivers. In addition, 46% of the patients indicated that the financial burden of the disease and corresponding treatment was shared by their caregiver in an adverse way.

Patients identified the following as important in the management of their condition: a reduction in asthma attacks, sinusitis, and rhinitis; better sleep; easier breathing, including less wheezing and coughing; and less sneezing and chest congestion.

Although allergen avoidance is used to manage grass allergies, complete avoidance is rarely possible. Current pharmacological therapies for patients with allergic rhinitis include prescription oral antihistamines, intranasal corticosteroids and antihistamine eye drops, as well as over-the-counter (OTC) products. Allergy shots, multiple injections of grass pollen allergens administered in a physician's office, are the current standard of care in Canada for people with seasonal allergic rhinitis that is specifically related to grass pollens. The survey found that 11% of patients received allergy shots, 16% used prescribed antihistamines, 55% used prescribed nasal sprays, 61% used OTC antihistamines, 25% used OTC decongestants, 23% used OTC nasal sprays, and 96% also used prescribed asthma medication (inhaled corticosteroids, leukotriene receptor antagonists, short-acting relievers, long-acting beta-receptor antagonists, and combination medications). While 44% of the patients claimed to have their asthma under control, 76% reported ongoing asthma symptoms, and 42% had a significant asthma exacerbation in the last year. Patients identified a desire for the reduction of the following side effects: blocked nasal passages, asthma attacks, cough, fatigue, mood swings, and headache.

## 3. Related Information About the Drug Being Reviewed

Patients' expectations for the sublingual tablet for treatment of Timothy grass allergy include allergic symptom relief (such as reducing runny nose; persistent coughing; itchy eyes, nose, or throat; or watery eyes), reducing the number and severity of asthma attacks, improving sleep and reducing fatigue, and less dependency upon rescue medications for breathing problems. Although 70% of the surveyed patients were interested in requesting this new drug from their physician, 56% expressed concern that it would be available only through allergists or other specialists, who are often perceived as difficult to find, to trust, and to access in a timely manner. Of those currently receiving allergy shots (only 11% of survey group), 78% said that they would appreciate an oral treatment to take at home. Some patients expressed a need for the development of a full range of oral prescription medications for all respiratory allergies — e.g., pet dander, dust mites, mold, birch, cedar, other tree pollens — but with no additional financial burden for the patients.

The surveyed patients had no experience with Grastek or with any other sublingual treatment for grass allergy of any kind.

# APPENDIX 2: LITERATURE SEARCH STRATEGY

| **OVERVIEW** | |
|---|---|
| Interface: | Ovid |
| Databases: | Embase 1974 to present<br>MEDLINE Daily and MEDLINE 1946 to present<br>MEDLINE In-Process & Other Non-Indexed Citations<br>**Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | February 7, 2014 |
| Alerts: | Weekly search updates until June 18, 2014 |
| Study Types: | No search filters were applied |
| Limits: | No date or language limits were used<br>Human filter was applied<br>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 |
| 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 |
| 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 | Publication type |
| .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 | |
|---|---|
| **#** | **Searches** |
| 1 | 927830-54-4.rn,nm. or (Grazax or Grastek or "MK-7243").ti,ot,ab,sh,rn,hw,nm. |
| 2 | (Phleum/ or (phleum or timothy grass or timothy grasses or "Phl p 6" or "Phl p 2").ti,ot,ab,sh,rn,hw,nm.) and (exp pollen/ or allergens/ or exp hypersensitivity/ or (pollen or allergen* or allergy or allergies or allergic or hypersensitiv* or male gametophyte*).ti,ot,ab,sh,rn,hw,nm.) |
| 3 | exp Administration, oral/ or (sublingual* or sub-lingual* or oral or orally or buccal or "under the tongue").ti,ot,ab,sh,rn,hw,nm. |
| 4 | Immunotherapy/ or exp Desensitization, Immunologic/ or (immunotherap* or immuno-therap* or immune therap* or immunolog* or immunoglobulin therap* or desensiti*).ti,ot,ab,sh,rn,hw,nm. |
| 5 | 2 and 3 and 4 |
| 6 | Sublingual Immunotherapy/ |
| 7 | 2 and 6 |
| 8 | exp Anti-allergic agents/ or (anti-allergics or anti-allergic agent* or anti-allergic drug* or antiallergy agent* or antiallergy drug* or antiallergic agent* or antiallergic drug*).ti,ot,ab,sh,rn,hw,nm. |
| 9 | 2 and 8 |
| 10 | 1 or 5 or 7 or 9 |
| 11 | 10 use pmez |
| 12 | *Grass pollen vaccine/ or (Grazax or Grastek or "MK-7243").ti,ab. |
| 13 | (*Phleum pratense/ or (phleum or timothy grass or timothy grasses or "Phl p 6" or "Phl p 2").ti,ab.) and (exp *pollen/ or exp *allergen/ or *pollen allergy/ or *allergy/ or exp *hypersensitivity/ or (pollen or allergen* or allergy or allergies or allergic or hypersensitiv* or male gametophyte*).ti,ab.) |
| 14 | exp buccal drug administration/ or (sublingual* or sub-lingual* or oral or orally or buccal or "under the tongue").ti,ab. |
| 15 | exp *Immunotherapy/ or *desensitization/ or *systematic desensitization/ or (immunotherap* or immuno-therap* or immune therap* or immunolog* or immunoglobulin therap* or desensiti*).ti,ab. |
| 16 | 13 and 14 and 15 |
| 17 | sublingual immunotherapy/ |
| 18 | 13 and 17 |
| 19 | exp *Antiallergic agent/ or (anti-allergics or anti-allergic agent* or anti-allergic drug* or antiallergy agent* or antiallergy drug* or antiallergic agent* or antiallergic drug*).ti,ab. |
| 20 | 13 and 19 |
| 21 | 12 or 16 or 18 or 20 |
| 22 | 21 not conference abstract.pt. |
| 23 | 22 use oemezd |
| 24 | 11 or 23 |
| 25 | exp animals/ |
| 26 | exp animal experimentation/ or exp animal experiment/ |
| 27 | exp models animal/ |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **#** | **Searches** |
| 28 | nonhuman/ |
| 29 | exp vertebrate/ or exp vertebrates/ |
| 30 | animal.po. |
| 31 | or/25-30 |
| 32 | exp humans/ |
| 33 | exp human experimentation/ or exp human experiment/ |
| 34 | human.po. |
| 35 | or/32-34 |
| 36 | 31 not 35 |
| 37 | 24 not 36 |
| 38 | remove duplicates from 37 |

| OTHER DATABASES | |
|---|---|
| PubMed | Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used. |
| Trial registries (Clinicaltrials.gov and others) | Grastek, Grazax, |

### Grey Literature

| | |
|---|---|
| Dates for Search: | January 2014 to February 2014 |
| Keywords: | Grastek, Grazax, *Phleum pratense*, Timothy grass |
| Limits: | No date or language limits were used |

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
- Drug Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Clinical Trials

# APPENDIX 3: EXCLUDED STUDIES

| Reference | Reason for Exclusion |
|---|---|
| Alesina et al.[46] | Intervention |
| Panizo et al.[47]<br>Reich et al.[48]<br>Valvorita et al.[49]<br>Valvorita[50] | Outcome |
| Caledron et al.[51]<br>Ibanez et al.[52]<br>Malling et al.[53]<br>TePas et al.[54] | Study design |
| Divekar et al.[55]<br>Durham[56]<br>Senna et al.[57]<br>Holt et al.[58] | Review, letter, or comment |

# APPENDIX 4: DETAILED OUTCOME DATA

**TABLE 14: RHINOCONJUNCTIVITIS MEDICATION SCORING SYSTEM FOR GT-07**

| Step in Rescue Medication Pathway | Medication | Score/Dose | Maximum Score |
|---|---|---|---|
| **1** | Loratadine 10 mg QD | 6 | 6 |
| **1** | Levocabastine eye drops (0.5 mg/mL; 1 drop in each eye BID) | 2 | 8 |
| **2** | Budesonide nasal spray (up to 32 mcg; 2 puffs per nostril BID) | 1 per puff | 8 |
| **3** | Prednisone (up to 50 mg QD) | 1.6/5 mg | 16 |
| | Maximum possible daily rhinoconjunctivitis medication score | | 38 |

BID = twice daily; QD = once daily.

**TABLE 15: RHINOCONJUNCTIVITIS MEDICATION SCORING SYSTEM FOR GT-02**

| Step in Rescue Medication Pathway | Medication | Score/Dose | Maximum Score |
|---|---|---|---|
| **1** | Loratadine 10 mg QD | 6 | 6 |
| **1** | Levocabastine eye drops (0.5 mg/ml 1 drop in each eye BID) | 2 | 4 |
| **2** | Budesonide nasal spray (32 mcg 2 puffs twice daily) | 4 | 8 |
| **3** | Prednisone 50 mg QD | 16 | 16 |
| | Maximum possible daily rhinoconjunctivitis medication score | | 34 |

BID = twice daily; QD = once daily.

**TABLE 16: RHINOCONJUNCTIVITIS MEDICATION SCORING SYSTEM FOR GT-08**

| Step in Rescue Medication Pathway | Medication | Score/Dose | Maximum Score |
|---|---|---|---|
| **1** | Desloratadine — 5 mg/1 tablet QD | 6 | 6 |
| **2** | Budesonide nasal spray — 32 mcg/puff up to 2 puffs per nostril BID | 1 per puff | 8 |
| **3** | Prednisone — 5 mg/tablet up to 10 tablets (50 mg) QD | 1.6 per tablet | 16 |
| | Maximum possible daily rhinoconjunctivitis medication score | | 30 |

BID = twice daily; QD = once daily.

**TABLE 17: RHINOCONJUNCTIVITIS MEDICATION SCORING SYSTEM FOR GT-14**

| Step in Rescue Medication Pathway | Medication | Score/Dose | Maximum Score |
|---|---|---|---|
| **1** | Desloratadine — 5 mg/1 tablet QD | 6 | 6 |
| **2** | Olopatadine eye drops – 1.0 mg/mL /1 drop in each eye, up to BID | 1.5 | 6 |
| | Maximum possible daily rhinoconjunctivitis medication score | | 12 |

BID = twice daily; QD = once daily.

**TABLE 18: RHINOCONJUNCTIVITIS MEDICATION SCORING SYSTEM FOR P05238**

| Step in Rescue Medication Pathway | Medication | Score/Dose | Maximum Score |
|---|---|---|---|
| **1** | Loratadine 10 mg — 1 tablet QD | 6 | 6 |
| **1b** | Olopatadine hydrochloride 0.1% ophthalmic solution — 1 drop in the affected eye BID | 1.5 per drop | 6 |
| **2** | Mometasone furoate monohydrate nasal spray 50 mcg — 2 sprays in each nostril QD | 2 per spray | 8 |
| **3** | Prednisone 5 mg tablet (Day 1, 1 mg/kg/day, max 50 mg/day) | 1.6 | 16 |
| **3** | Prednisone 5 mg tablet (Day 2+, 0.5 mg/kg/day, max 25 mg/day) | 3.2 (= 1.6 × 2) | 16 |
| | Maximum possible daily rhinoconjunctivitis medication score | | |

BID = twice daily; QD = once daily.

**TABLE 19: RHINOCONJUNCTIVITIS MEDICATION SCORING SYSTEM FOR GT-12**

| Step in Rescue Medication Pathway | Medication | Score/Dose | Maximum Score |
|---|---|---|---|
| **1** | Loratadine (5 mg for 5 to 12 years & ≤ 30 kg; 10 mg for 5 to 12 years & > 30 kg, 13 to 16 years) | 6 | 6 |
| **1b** | Levocabastine eye drops (0.5 mg/mL) | 1 | 2 |
| **2** | Budesonide nasal spray (Day 1: 100 mcg/dose for 5 to 12 years) | 2 | 8 |
| **2** | Budesonide nasal spray (Day 2+: 50 mcg/dose for 5 to 12 years) | 4 | 8 |
| **2** | Budesonide nasal spray (Day 1: 200 mcg/dose for 13 to 16 years) | 1 | 8 |
| **2** | Budesonide nasal spray (Day 2+: 100 mcg/dose for 13 to 16 years) | 2 | 8 |
| **3** | Prednisone 5 mg tablet (Day 1, 1 mg/kg/day, max 50 mg/day) | 1.6 | 16 |
| **3** | Prednisone 5 mg tablet (Day 2+, 0.5 mg/kg/day, max 50 mg/day, max 25 mg/day) | 3.2 (= 1.6 × 2) | 16 |
| | Maximum possible daily rhinoconjunctivitis medication score | | 32 |

**TABLE 20: RHINOCONJUNCTIVITIS MEDICATION SCORING SYSTEM FOR P05239**

| Step in Rescue Medication Pathway | Medication | Score/Dose | Maximum Score |
|---|---|---|---|
| **1** | Loratadine syrup 1 mg/mL — 5 mL QD (5 to < 6 years) | 6 | 6 |
| **1** | Loratadine RediTabs tablet 10 mg — 1 tablet QD; Claritin syrup 1 mg/mL — 10 mL QD (≥ 6 to < 18 years) | 6 | 6 |
| **1b** | Olopatadine hydrochloride 0.1% ophthalmic solution — 1 drop in the affected eye BID | 1.5 per drop | 6 |
| **2** | Mometasone furoate monohydrate nasal spray 50 mcg — 1 spray in each nostril QD (5 to < 12 years) | 4 per spray | 8 |
| **2** | Mometasone furoate monohydrate nasal spray 50 mcg — 2 sprays in each nostril QD (≥ 12 to < 1 8 years) | 2 per spray | 8 |
| **3** | Prednisone 5 mg tablet (Day 1, 1 mg/kg/day, max 50 mg/day) | 1.6 | 16 |
| **3** | Prednisone 5 mg tablet (Day 2+, 0.5 mg/kg/day, max 50 mg/day, max 25 mg/day) | 3.2 (= 1.6 × 2) | 16 |
| | Maximum possible daily rhinoconjunctivitis medication score | | 36 |

BID = twice daily; QD = once daily.

**TABLE 21: RHINOCONJUNCTIVITIS MEDICATION SCORING SYSTEM FOR P08067**

| Step in Rescue Medication Pathway | Medication | Score/Dose | Maximum Score |
|---|---|---|---|
| **1** | Loratadine syrup 1 mg/mL — 5 mL QD (5 to < 6 years) | 6 | 6 |
| **1** | Loratadine 10 mg — 1 tablet QD ≥ 18 years); Claritin syrup 1 mg/mL — 10 mL QD (≥ 6 to < 18 years) | 6 | 6 |
| **1b** | Olopatadine hydrochloride 0.1% ophthalmic solution — 1 drop in the affected eye BID | 1.5 per drop | 6 |
| **2** | Mometasone furoate monohydrate nasal spray 50 mcg — 1 spray in each nostril QD (5 to < 12 years) | 4 per spray | 8 |
| **2** | Mometasone furoate monohydrate nasal spray 50 mcg — 2 sprays in each nostril QD (≥ 12 years) | 2 per spray | 8 |
| **3** | Prednisone tablet 5 mg (Day 1 — 1 mg/kg/day, max 50 mg/day) | 1.6 | 16 |
| **3** | Prednisone tablet 5 mg (Day 2+ — 0.5 mg/kg/day, max 25 mg/day) | 3.2 (= 1.6 × 2) | 16 |
| | Maximum possible daily rhinoconjunctivitis medication score | | 36 |

BID = twice daily; QD = once daily.

**TABLE 22: AVERAGE DAILY SYMPTOM SCORE FOR ENTIRE GRASS POLLEN SEASON (ADULTS)**

| | GT-07 | | GT-02[a] | | | | GT-08[b] | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 74 | Placebo N = 40 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) N = 153 | Placebo (no L) N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 208 | Placebo N = 225 |
| **No. included in analysis** | 68 | 39 | 131 | 129 | 144 | 142 | 282 | 286 | 139 | 150 | 184 | 207 |
| **Median (min, max) or (5%Q, 95%Q)** | 1.90 (0.02, 9.50) | 2.66 (0, 7.28) | 2.13 (0.0, 11.9) | 2.53 (0.0, 10.3) | 2.40 (0.0, 10.3) | 2.83 (0.0, 13.7) | 2.6 (0.2, 6.2)[c] | 3.8 (0.4, 9.2)[c] | 5.47 (0.00, 15.61) | 5.88 (0.00, 17.23) | 3.43 (0.0, 16.1) | 4.52 (0.0, 14.7) |
| **Adjusted mean (SE)** | 2.27 | 3.04 | 2.474 (0.180) | 2.935 (0.180) | 2.894 (0.201) | 3.339 (0.201) | 2.85 | 4.14 | 5.69 (0.39) | 6.06 (0.40) | 3.83 (0.3) | 4.69 (0.3) |
| **Difference vs. placebo (95% CI)** | –0.78 | | –0.462 (–0.093, 0.040) | | –0.445 (–0.956 , 0.067) | | –1.29 (–1.68, –0.90) | | –0.37 (–1.16, 0.41) | | –0.86 (–1.46, –0.26) | |
| ***P* value** | 0.0503 | | 0.071 | | 0.088 | | < 0.0001 | | 0.348 | | 0.015 | |
| **% Difference relative to placebo (95% CI)** | –25 | | –15.74[d] | | –13.33[d] | | –31 (–38.8, –23.4) | | –6.18 (–19.77, 6.83) | | –18.3 (–29.4, –5.7) | |

ANOVA = analysis of variance; CI = confidence interval; L = loratadine; PPAE = *Phleum pratense* allergen extract; Q = quantile; SE = standard error.
[a]For GT-02, in the treatment groups PPAE (no L) and Placebo (no L), if step 1 loratadine was needed, placebo was given instead.
[b]For GT-08, the one-year data are used here in order to be comparable with the other studies in the table.
[c]Range expressed as (5%Q, 95%Q).
[d]Calculated by Common Drug Review reviewer.
Note: Analysis by ANOVA.
Source: Clinical study reports.[26-30]

**TABLE 23: AVERAGE DAILY SYMPTOM SCORE FOR ENTIRE GRASS POLLEN SEASON (CHILDREN OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 173 | Placebo N = 167 | PPAE N = 752 | Placebo N = 749 |
| **No. included in analysis** | 117 | 121 | 149 | 158 | 629 | 672 |
| **Median (min, max)** | 2.1 (0.0, 14.4) | 2.8 (0.1, 9.8) | 3.39 (0.0, 14.22) | 4.34 (0.0, 17.95) | 2.49 (0.00, 18.00) | 3.13 (0.00, 17.67) |
| **Adjusted mean (SE or 95% CI)** | 2.18 (1.82 to 2.58) | 2.80 (2.45 to 3.18) | 3.71 (0.40 SE) | 4.91 (0.41 SE) | 3.11 | 3.58 |
| **Difference vs. placebo (95% CI)** | –0.62 (–1.15 to –0.10) | | –1.20 (–1.95 to –0.45) | | –0.47 (–0.79 to –0.16) | |
| ***P* value** | 0.022 | | 0.005 | | 0.004 | |
| **% Difference relative to placebo (95% CI)** | –22.24 (–37.59 to –3.74) | | –25 (–36.4 to –9.1) | | –13 (–22.0% to –4.7%) | |

ANOVA = analysis of variance; CI = confidence interval; PPAE = *Phleum pratense* allergen extract; SE = standard error.
Note: Analysis by ANOVA.
Source: Clinical study reports,[34-36] Common Drug Review submission.[39]

**TABLE 24: AVERAGE DAILY SYMPTOM SCORE OVER PEAK GRASS POLLEN SEASON (ADULTS)**

| | GT-07 | | GT-02[a] | | | | GT-08[b] | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 68 | Placebo N = 39 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) N = 153 | Placebo (no L) N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 208 | Placebo N = 225 |
| **No. included in analysis** | | | 131 | 127 | 144 | 138 | 278 | 281 | 137 | 143 | 183 | 201 |
| **Median (min, max) or (5%Q, 95%Q)** | NR | NR | 2.13 (0.0, 11.9) | 2.53 (0.0, 10.3) | 3.37 (0.0, 16.6) | 3.83 (0.0, 13.7) | 3.9 (0.0, 8.4)[c] | 4.9 (0.1, 11.7)[c] | 5.38 (0.00, 16.36) | 6.29 (0.00, 16.67) | 3.67 (0.0, 16.6) | 5.00 (0.0, 16.9) |
| **Adjusted mean (SE)** | NR | NR | 3.584 (0.232) | 4.243 (0.235) | 4.053 (0.250) | 4.397 (0.254) | 3.81 | 5.27 | 5.99 (0.42) | 6.49 (0.43) | 4.16 (0.3) | 5.24 (0.3) |
| **Difference vs. placebo (95% CI)** | NR | | –0.659 (–1.308 to –0.009) | | –0.344 (–0.982 to 0.294) | | –1.46 (–1.95 to –0.98) | | –0.50 (–1.38 to 0.38) | | –1.08 (–1.81 to –0.36) | |
| ***P* value** | NR | | 0.047 | | 0.290 | | < 0.0001 | | 0.265 | | 0.003 | |
| **% Difference relative to placebo (95% CI)** | NR | | –15.53[d] | | –7.82[d] | | –28 | | –7.72 (–22.37 to 5.62) | | –21 | |

ANOVA = analysis of variance; CI = confidence interval; L = loratadine; NR = not reported; PPAE = *Phleum pratense* allergen extract; Q = quantile; SE = standard error.
[a]For GT-02, PPAE (no L) and Placebo (no L) are treatment groups for which step 1 loratadine was not allowed.
[b]For GT-08, the one-year data are used here in order to be comparable with the other studies in the table.
[c]Range expressed as (5%Q, 95%Q).
[d]Calculated by Common Drug Review reviewer.
Note: Analysis by ANOVA.
Source: Clinical study reports.[26,28-30]

**TABLE 25: AVERAGE DAILY SYMPTOM SCORE OVER PEAK GRASS POLLEN SEASON (CHILDREN OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 173 | Placebo N = 167 | PPAE N = 751 | Placebo N = 749 |
| **No. included in analysis** | 117 | 121 | 147 | 153 | 620 | 663 |
| **Median (min, max)** | 3.9 (0.0, 13.4) | 2.9 (0.0, 13.3) | 3.5 (0.0, 14.5) | 4.73 (0.0, 18.0) | 2.71 (0.00, 18.00) | 3.40 (0.00, 17.57) |
| **Adjusted mean (SE)** | 2.84 | 3.91 | 3.81 (0.4) | 5.30 (0.4) | 3.19 (0.17) | 3.79 (0.18) |
| **Difference vs. placebo** | –1.07 | | –1.49 | | –0.61 | |
| **95% CI** | (–1.81 to –0.32) | | (–2.30 to –0.67) | | (–0.95 to –0.26) | |
| ***P* value** | 0.0059 | | < 0.001 | | < 0.001 | |
| **% Difference relative to placebo** | –27.34 | | –28 | | –16 | |
| **95% CI** | (–42.50 to –8.91) | | NR | | (–25.0 to – 7.4) | |

ANOVA = analysis of variance; CI = confidence interval; NR = not reported; PPAE = *Phleum pratense* allergen extract; SE = standard error.
Note: Analysis by ANOVA.
Source: Clinical study reports.[34-36]

**TABLE 26: AVERAGE DAILY MEDICATION SCORE FOR ENTIRE GRASS POLLEN SEASON (ADULTS)**

| | GT-07 | | GT-02[a] | | | | GT-08 [b] | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 70 | Placebo N = 40 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) N = 153 | Placebo (no L) N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 208 | Placebo N = 225 |
| **No. included in analysis** | 68 | 39 | 131 | 129 | 144 | 142 | 282 | 286 | 139 | 150 | 184 | 207 |
| **Median (min, max) or (5%Q, 95%Q)** | 1.23 (0, 19.9) | 3.19 (0, 14.1) | 0.35 (0.0, 12.0) | 1.24 (0.0, 11.9) | 0.27 (0.0, 14.2) | 0.86 (0.0, 17.8) | 1.0 (0.0, 6.6)[c] | 2.2 (0.0, 8. 9)[c] | 0.22 (0.00, 10.73) | 0.29 (0.00, 10.89) | 0.26 (0.0, 16.5) | 0.50 (0.0, 13.9) |
| **Adjusted mean (SE)** | 2.60 | 3.81 | 1.463 (0.205) | 2.046 (0.206) | 1.741 (0.237) | 2.479 (0.237) | 1.65 | 2.68 | 1.07 (0.20) | 1.47 (0.22) | 1.25 (0.2) | 1.70 (0.2) |
| **Difference vs. placebo (95% CI)** | –1.21 | | –0.582 (–1.156 to –0.008) | | –0.738 (–1.341 to –0.135) | | –1.03 (–1.44 to –0.63) | | –0.40 (–0.85 to 0.05) | | –0.45 (–0.96 to 0.06) | |
| ***P* value** | 0.136 | | 0.047 | | 0.017 | | < 0.0001 | | 0.083 | | 0.084 | |
| **% Difference relative to placebo (95% CI)** | –32 | | –28.45[d] | | –29.77[d] | | –39 (–49.8 to –26.5) | | –27.12 (–48.35 to 10.7 ) | | –26.5 (–49.1 to 5.4) | |

ANOVA = analysis of variance; CI = confidence interval; L = loratadine; PPAE = *Phleum pratense* allergen extract; SE = standard error.
[a]For GT-02, PPAE (no L) and Placebo (no L) are treatment groups for which step 1 loratadine was not allowed.
[b]For GT-08, the one-year data are used here in order to be comparable with the other studies in the table.
[c]Range expressed as (5%Q, 95%Q).
[d]Calculated by Common Drug Review reviewer.
Note: Analysis by ANOVA.
Source: Clinical study reports[26-30] and Common Drug Review submission.[39]

**TABLE 27: AVERAGE DAILY MEDICATION SCORE FOR ENTIRE GRASS POLLEN SEASON (CHILDREN OR MIXED POPULATION)**

| | GT-12[a] | | P05239[b] | | P08067[b] | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 173 | Placebo N = 167 | PPAE N = 752 | Placebo N = 749 |
| **No. included in analysis** | 117 | 121 | 149 | 158 | 629 | 672 |
| **Median (min, max)** | 0.8 (0.0, 21.2) | 1.2 (0.0, 15.3) | 0.12 (0.0, 10.85) | 0.64 (0.0, 11.08) | 0.00 (0.00, 19.67) | 0.26 (0.00, 17.85) |
| **Adjusted mean (SE or 95% CI)** | 0.78 (0.43 to 1.30) | 1.19 (0.74 to 2.64) | 0.91 (0.25) | 1.33 (0.23) | 0.88 | 1.28 |
| **Difference vs. placebo (95% CI)** | –0.41 (–0.68 to –0.01) | | –0.42 (–0.88 to 0.03) | | –0.40 (–0.65 to –0.15) | |
| ***P* value** | 0.016 | | 0.066 | | 0.002 | |
| **% Difference relative to placebo (95% CI)** | –34.25 (–60.4 to 0.1) | | –31.6 (–57.5 to 4.0) | | –31 (–48.0% to –14.0%) | |

ANOVA = analysis of variance; CI = confidence interval; PPAE = *Phleum pratense* allergen extract; SE = standard error.
[a]Results for daily medication score were from a non-parametric analysis using Wilcoxon rank sum test, as parametric ANOVA could not be conducted because normality assumptions were not satisfied with non-transformed or transformed data.
[b]Analysis by ANOVA.
Source: Clinical study reports[34-36] and Common Drug Review submission.[39]

**TABLE 28: AVERAGE DAILY MEDICATION SCORE OVER PEAK GRASS POLLEN SEASON (ADULTS)**

| | GT-07 | | GT-02 | | | | GT-08[a] | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 68 | Placebo N = 39 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) N = 153 | Placebo (no L) N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 208 | Placebo N = 225 |
| **No. included in analysis** | | | 131 | 127 | 144 | 138 | 278 | 281 | 119 | 121 | 183 | 201 |
| **Median (min, max) or (5%Q, 95%Q)[b]** | NR | NR | 0.35 (0.0, 12.0) | 1.24 (0.0, 11.9) | 0.00 (0.0, 14.0) | 0.57 (0.0, 17.8) | 1.3 (0.0, 8.1)[b] | 3.0 (0.0, 10.0)[b] | 0.00 (0.00, 12.00) | 0.00 (0.00, 11.42) | 0.00 (0.00, 19.1) | 0.00 (0.00, 20.0) |
| **Adjusted mean (SE)** | NR | NR | 1.887 (0.254) | 2.638 (0.257) | 2.286 (0.275) | 2.821 (0.279) | 2.12 | 3.46 | 1.17 (0.22) | 1.57 (0.25) | 1.61 (0.3) | 2.07 (0.3) |
| **Difference vs. placebo (95% CI)** | NR | | –0.751 (–1.463 to –0.039) | | –0.536 (–1.238 to 0.166) | | –1.34 (–1.84 to –0.84) | | –0.40 (–0.90 to 0.11) | | –0.46 (–1.17 to 0.26) | |
| ***P* value** | NR | | 0.039 | | 0.134 | | < 0.0001 | | 0.1230 | | 0.211 | |
| **% Difference relative to placebo (95% CI)** | NR | | –28.47[b] | | –18.96[b] | | –39 | | –25.38 (–48.15 to 13.6) | | –22 | |

ANOVA = analysis of variance; CI = confidence interval; L = loratadine; NR = not reported; PPAE = *Phleum pratense* allergen extract; Q = quantile; SE = standard error.
[a]For GT-08, the one-year data are used here in order to be comparable with the other studies in the table.
[b]Calculated by Common Drug Review reviewer.
Note: Analysis by ANOVA.
Source: Clinical study reports.[26,28-30]

**TABLE 29: AVERAGE DAILY MEDICATION SCORE VER PEAK GRASS POLLEN SEASON (CHILDREN OR MIXED POPULATION)**

| | GT-12[a] | | P05239[b] | | P08067[b] | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 173 | Placebo N = 167 | PPAE N = 744 | Placebo N = 744 |
| **No. included in analysis** | 117 | 121 | 147 | 153 | 620 | 663 |
| **Median (min, max)** | 0.87 | 2.40 | 0.0 (0.0, 17.0) | 0.44 (0.0, 16.5) | 0.00 ( 0.00, 27.68) | 0.00 (0.00, 27.61) |
| **Adjusted mean(SE)** | NR | NR | 0.92 (0. 3) | 1.55 (0.3) | 1.01( 0.16) | 1.56( 0.16) |
| **Difference vs. placebo (95% CI)** | –0.80 (–1.53 to –0.13) | | –0.63 (–1.26 to –0.00) | | –0.55 (–0.86 to –0.23) | |
| ***P* value** | 0.0013 | | 0.049 | | < 0.001 | |
| **% Difference relative to placebo (95% CI)** | –33.33 | | –41 | | –35 (–52% to –17%) | |

ANOVA = analysis of variance; CI = confidence interval; DMS = daily medication score; NR = not reported; PPAE = *Phleum pratense* allergen extract; SE = standard error.

[a]Results for DMS were from a non-parametric analysis using Wilcoxon rank sum test with the associated Hodges–Lehmann estimate for a difference, as parametric ANOVA could not be conducted since normality assumptions were not satisfied with non-transformed or transformed data.

[b]Analysis by ANOVA.

Source: Clinical study reports.[34-36]

**TABLE 30: RHINOCONJUNCTIVITIS COMBINED SCORE FOR ENTIRE GRASS POLLEN SEASON (ADULTS)**

| | GT-07 | | GT-02 | | | | GT-08[a] | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 74 | Placebo N = 40 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) N = 153 | Placebo (no L) N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 208 | Placebo N = 225 |
| **No. included in analysis** | | | | | | | 282 | 286 | 139 | 150 | 184 | 207 |
| **Median (min, max)** | NR | NR | NR | NR | NR | NR | NR | NR | 6.12 (0.00, 25.37) | 6.84 (0.00, 20.25) | 4.62 (0.0, 32.6) | 6.13 (0.0, 25.0) |
| **Adjusted mean (SE)** | NR | NR | NR | NR | NR | NR | 4.46 | 6.78 | 6.74 | 7.53 | 5.08 (0.4) | 6.39 (0.4) |
| **Difference vs. placebo (95% CI)** | NR | | NR | | NR | | –2.32 (–2.98 to –1.67) | | –0.78 (–1.83 to 0.26) | | –1.31 (–2.22 to –0.40) | |
| ***P* value** | NR | | NR | | NR | | < 0.001 | | 0.142 | | 0.005 | |
| **% Difference relative to placebo (95% CI)** | NR | | NR | | NR | | –34.2 (–42.0 to –26.3) | | –10.4 (–23.9 to 4.0) | | –20.5 (–33.0 to –6.0) | |

ANOVA = analysis of variance; CI = confidence interval; L = loratadine; NR = not reported; PPAE = *Phleum pratense* allergen extract; SE = standard error.
[a]For GT-08, the one-year data are used here in order to be comparable with the other studies in the table.
Note: Analysis by ANOVA.
Source: Clinical study report[30] and Common Drug Review submission.[39]

**TABLE 31: TOTAL COMBINED SCORE FOR ENTIRE GRASS POLLEN SEASON (CHILDREN OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 173 | Placebo N = 167 | PPAE N = 752 | Placebo N = 749 |
| **No. included in analysis** | 117 | 121 | 149 | 158 | 629 | 672 |
| **Median (min, max)** | 3.4 (0.0, 35.7) | 4.9 (0.2, 18.6) | 3.82 (0.0, 22.66) | 5.81 (0.0, 23.95) | 3.24 (0.00, 24.10) | 4.22 (0.00, 23.16) |
| **Adjusted mean (SE or 95% CI)** | 3.70 (2.94 to 4.54) | 4.87 (4.08 to 5.73) | 4.62 (0.52) | 6.25 (0.51) | 3.99 | 4.86 |
| **Difference vs. placebo (95% CI)** | –1.18 (–2.17 to –0.19) | | –1.63 (–2.60 to –0.66) | | –0.87 (–1.32 to –0.42) | |
| ***P* value** | 0.022 | | 0.001 | | < 0.001 | |
| **% Difference relative to placebo (95% CI)** | –24.2 (–40.55 to –4.10) | | –26.1 (–38.2 to –10.1) | | –18 (–27.0% to –9.3%) | |

ANOVA = analysis of variance; CI = confidence interval; PPAE = *Phleum pratense* allergen extract; SE = standard error.
Note: Analysis by ANOVA.
Source: Clinical study reports[34-36] and Common Drug Review submission.[39]

**TABLE 32: AVERAGE RHINOCONJUNCTIVITIS COMBINED SCORE OVER PEAK GRASS POLLEN SEASON (ADULTS)**

| | GT-07 | | GT-02 | | | | GT-08[a] | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 68 | Placebo N = 39 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) N = 153 | Placebo (no L) N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 208 | Placebo N = 225 |
| **No. included in analysis** | | | | | | | | | 137 | 143 | 183 | 201 |
| **Median (min, max)** | NR | NR | NR | NR | NR | NR | NR | NR | 6.23 (0.00, 25.92) | 7.43 (0.00, 22.00) | 4.47 (0.0, 35.8) | 6.20 (0.0, 33.8) |
| **Adjusted mean (SD/SE)** | NR | NR | NR | NR | NR | NR | NR | NR | 7.13 (0.53 SE) | 8.05 (0.5 SE) | 5.76 (0.5 SE) | 7.31 (0.5 SE) |
| **Difference vs. placebo (95% CI)** | NR | | NR | | NR | | NR | | –0.91 (–2.09 to 0.27) | | –1.55 (–2.74 to –0.35) | |
| ***P* value** | NR | | NR | | NR | | NR | | 0.1290 | | 0.011 | |
| **% Difference relative to placebo (95% CI)** | NR | | NR | | NR | | NR | | –11.32 (–25.45 to 3.91) | | –21 | |

ANOVA = analysis of variance; CI = confidence interval; L = loratadine; NR = not reported; PPAE = *Phleum pratense* allergen extract; Q = quantile; SD = standard deviation; SE = standard error.
[a]For GT-08, the one-year data are used here in order to be comparable with the other studies in the table.
Note: Analysis by ANOVA.
Source: Clinical study reports.[29,30]

**TABLE 33: AVERAGE RHINOCONJUNCTIVITIS COMBINED SCORE OVER PEAK GRASS POLLEN SEASON (CHILDREN OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 173 | Placebo N = 167 | PPAE N = 744 | Placebo N = 744 |
| **No. included in analysis** | | | 147 | 153 | 620 | 663 |
| **Median (min, max)** | NR | NR | 4.00 (0.0, 29.1) | 6.53 (0.0, 28.9) | 3.33 (0.00, 30.88) | 4.67 (0.00, 34.21) |
| **Adjusted mean (SE)** | NR | | 4.73 (0.6) | 6.85 (0.6) | 4.20 (0.26) | 5.35 (0.27) |
| **Difference vs. placebo (95% CI)** | NR | | –2.12 (–3.30 to –0.95) | | –1.15 (–1.67 to –0.63) | |
| ***P* value** | NR | | < 0.001 | | < 0.001 | |
| **% Difference relative to placebo (95% CI)** | NR | | –31 | | –22 (–30% to –13%) | |

ANOVA = analysis of variance; CI = confidence interval; NR = not reported; PPAE = *Phleum pratense* allergen extract; SE = standard error.
Note: Analysis by ANOVA.
Source: Clinical study reports.[35,36]

**TABLE 34: PERCENTAGE WELL DAYS OR MINIMAL SYMPTOM DAYS (ADULTS)**

| | GT-07 | | GT-02[a] | | | | GT-08 | | GT-14 | | P05238[b] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 68 | Placebo N = 39 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) N = 153 | Placebo (no L) N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 208 | Placebo N = 225 |
| **No. included in analysis** | | | 131 | 129 | 144 | 142 | 282 | 286 | 139 | 150 | 184 | 207 |
| **Median (min, max) or (5%Q, 95%Q)** | NR | NR | 58.33 (0.0, 100.0) | 43.48 (0.0, 100.0) | 55.54 (0.00, 100.00) | 40.59 (0.00, 97.18) | 40.0 (0.0, 94.0)[c] | 21.6 (0.0, 90.7)[c] | 12.1 (0.0, 100.0) | 15.6 (0.0, 100.0) | 35.60 (0.0, 100.0) | 24.32 (0.0, 100.0) |
| **Adjusted mean (SD/SE/ [95% CI])** | NR | NR | 52.27 (2.70) | 44.43 (2.71) | 48.965 (2.824 SE) | 43.505 (2.833 SE) | 45.02 | 32.61 | 27.44 (3.29 SE) | 26.03 (3.13 SE) | 40.21 (3.1) | 33.78 (2.9) |
| **Difference vs. placebo (95% CI)** | NR | | 7.85 (0.32 to 15.38) | | 5.460 (–1.731 to 12.650) | | 12.41 (7.63 to 17.18) | | 1.42 (–5.73 to 8.56) | | 6.44 (–0.38 to 13.25) | |
| ***P* value** | NR | | 0.041 | | 0.136 | | < 0.0001 | | 0.6965 | | 0.064 | |
| **% Difference relative to placebo (95% CI)** | NR | | 17.67[d] | | NR | | 38 | | 5.44 (–19.44 to 40.0) | | 19 | |

ANOVA = analysis of variance; CI = confidence interval; L = loratadine; NR = not reported; PPAE = *Phleum pratense* allergen extract; SD = standard deviation; SE = standard error.
[a]A well day is defined as a day without any intake of step 1-3 medication and step A-B medication, as well as a rhinoconjunctivitis symptom score ≤ 2 (for GT-02).
[b]Minimal symptom day: daily symptom score less than or equal to 2 and without taking any rescue medication (P05238).
[c]Range expressed as (5%Q, 95%Q).
[d]Calculated by Common Drug Review reviewer.
Note: Analysis by ANOVA.
Source: Clinical study reports.[26,28-30]

**TABLE 35: PERCENTAGE WELL DAYS OR MINIMAL SYMPTOM DAYS (CHILDREN OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 173 | Placebo N = 167 | PPAE N = 534 | Placebo N = 582 |
| **No. included in analysis** | 117 | 121 | 149 | 158 | | |
| **Median (min, max)** | 53.2 (0.0, 100.0) | 41.6 (0.0, 98.1) | 40.63 (0.0, 100.0) | 20.71 (0.0, 100.0) | NR | NR |
| **Adjusted mean (SE or 95% CI)** | 51.57 (44.93 to 58.21) | 42.33 (36.02 to 48.64) | 47.37 (4.0) | 35.33 (3.7) | NR | NR |
| **Difference vs. placebo (95% CI)** | 9.24 (1.32 to 17.16) | | 12.05 (4.83 to 19.27) | | NR | |
| ***P* value** | 0.0225 | | 0.001 | | NR | |
| **% Difference relative to placebo (95% CI)** | 21.83 (2.96 to 44.77) | | 34 | | NR | |

ANOVA = analysis of variance; CI = confidence interval; NR = not reported; PPAE = *Phleum pratense* allergen extract; SE = standard error.
Note: Analysis by ANOVA.
Source: Clinical study reports.[34,35]

**TABLE 36: VISUAL ANALOGUE SCALE SCORE DURING GRASS POLLEN SEASON (ADULTS)**

| | GT-07 | | GT-02[a] | | | | GT-08 | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 68 | Placebo N = 39 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) N = 153 | Placebo (no L) N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 208 | Placebo N = 225 |
| **No. included in analysis** | | | 129 | 125 | 135 | 137 | 282 | 286 | 139 | 150 | 184 | 207 |
| **Median (min, max) or (5%Q, 95%Q)** | NR | NR | 14.14 (0.0, 75.6) | 17.67 (0.0, 95.8) | 16.00 (0.0, 71.0) | 22.11 (0.0, 84.0) | 12.1 (1.0, 40.6)[b] | 18.2 (1.5, 54.8)[b] | 27.0 (0.0, 98.1) | 32.5 (0.0, 98.4) | 14.12 (0.0, 98.6) | 20.08 (0.0, 84.2) |
| **Adjusted mean (SE)** | NR | NR | 17.78 (1.39) | 19.77 (1.41) | 18.334 (1.635) | 24.488 (1.618) | 14.62 | 21.27 | 32.23 (2.97) | 35.85 (3.05) | 18.92 (1.7) | 24.18 (1.7) |
| **Difference vs. placebo (95% CI)** | NR | | –2.33 (–6.22 to 1.56) | | –6.154 (–10.27 to –2.036) | | –6.65 (–9.08 to –4.21) | | –3.62 (–8.76 to 1.52) | | –5.26 (–9.19 to –1.34) | |
| ***P* value** | NR | | 0.240 | | 0.004 | | < 0.0001 | | 0.1670 | | 0.009 | |
| **% Difference relative to placebo (95% CI)** | NR | | –11.79[c] | | –25.13[c] | | –31 | | –10.10 (–26.06 to 4.90) | | –22 | |

ANOVA = analysis of variance; CI = confidence interval; NR = not reported; PPAE = *Phleum pratense* allergen extract; SE = standard error; VAS = visual analogue scale.
[a]Hay fever score (for GT-02).
[b]Range presented as (5%Q, 95%Q)
[c]Calculated by Common Drug Review reviewer.
Note: VAS total score: 0 to 100, where 0 represented no symptoms and 100 represented a high level of symptoms.
Note: Analysis by ANOVA.
Source: Clinical study reports.[26,28-30]

**TABLE 37: VAS SCORE DURING GRASS POLLEN SEASON (CHILDREN OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 173 | Placebo N = 167 | PPAE N = 534 | Placebo N = 582 |
| **No. included in analysis** | 117 | 121 | 149 | 158 | | |
| **Median (min, max)** | 9.0 (0.0, 96.9) | 13.0 (0.0, 62.4) | 15.67 (0.0, 88.1) | 21.10 (0.0, 99.8) | NR | NR |
| **Adjusted mean (SE or 95% CI)** | 11.03 (8.69 to 13.64) | 13.82 (11.68 to 16.14) | 21.62 (2.7) | 27.91 (2.7) | NR | NR |
| **Difference vs. placebo (95% CI)** | –2.80 (–6.10 to 0.50) | | –6.28 (–11.2 to –1.33) | | NR | |
| ***P* value** | 0.1018 | | 0.013 | | NR | |
| **% Difference relative to placebo (95% CI)** | –20.23 (–39.77 to 4.39) | | –23 | | NR | |

ANOVA = analysis of variance; CI = confidence interval; NR = not reported; PPAE = *Phleum pratense* allergen extract; SE = standard error; VAS = visual analogue scale.
Note: The VAS score was evaluated on a scale from 0 to 100, where 0 represented no symptoms and 100 represented a high level of symptoms.
Note: Analysis by ANOVA.
Source: Clinical study reports.[34-36]

**TABLE 38: RQLQ(S) TOTAL SCORE DURING GRASS POLLEN SEASON (ADULTS)**

| | GT-07 | | GT-02[a] | | | | GT-08[b] | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 74 | Placebo N = 40 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) N = 153 | Placebo (no L) N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 208 | Placebo N = 225 |
| **No. included in analysis** | | | 136 | 136 | 153 | 150 | 267 | 268 | N-ob = 801 | N-ob = 840 | 172 | 197 |
| **Median (min, max) or (5%Q, 95%Q)** | NR | NR | 0.64 (0.0, 2.9) | 1.50 (0.0, 4.0) | 0.57 (0.0, 4.7) | 0.75 (0.0, 5.2) | 0.9 (0.1, 2.4)[c] | 1.4 (0.3, 3.0)[c] | 1.42 (0.00, 5.19) | 1.57 (0.00, 5.01) | 1.01 (0.0, 5.1) | 1.45 (0.0, 5.8) |
| **Adjusted mean (SE)** | NR | NR | 0.844 (0.067) | 1.052 (0.068) | 0.843 (0.085) | 1.072 (0.084) | 1.03 | 1.40 | 1.36 (0.12) | 1.44 (012) | 1.30 (0.1) | 1.57 (0.1) |
| **Difference vs. placebo (95% CI)** | NR | | –0.208 (–0.384 to –0.033) | | –0.229 (–0.424 to –0.035) | | –0.37 (–0.50 to –0.23) | | –0.08 (–0.32 to 0.16) | | –0.27 (–0.48 to –0.05) | |
| ***P* value** | NR | | 0.020 | | 0.021 | | < 0.0001 | | 0.5293 | | 0.022 | |

ANOVA = analysis of variance; BAU = bioequivalent allergy unit; CI = confidence interval; L = loratadine; N-ob = number of observations (patients × weeks); NR = not reported; PPAE = *Phleum pratense* allergen extract; RQLQ(S) = Rhinoconjunctivitis Quality of Life Questionnaire with standardized activities; SE = standard error.

[a]RQLQ data for second seasonal visit.

[b]For GT-08, the one-year data are used here in order to be comparable with the other studies in the table.

[c]Range expressed as (5%Q, 95%Q)..

Note: Analysis by ANOVA.

Source: Clinical study reports.[27-30]

**TABLE 39: RQLQ(S) TOTAL SCORE DURING GPS (CHILDREN OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE N = 117 | Placebo N = 121 | PPAE N = 173 | Placebo N = 167 | PPAE N = 744 | Placebo N = 744 |
| **No. included in analysis** | | | 109 | 111 | 534 | 582 |
| **Median (min, max)** | NR | NR | 1.36 (0.0, 4.91) | 1.69 (0.0, 4.70) | 0.83 (0.00, 5.93) | 1.03 (0.00, 4.80) |
| **Adjusted mean (SE)** | NR | NR | 1.45 (0.11) | 1.77 (0.12) | 1.07 (0.06) | 1.22 (0.06) |
| **Difference vs. placebo (95% CI)** | NR | | –0.32 (–0.60 to –0.03) | | –0.15 (–0.26 to –0.03) | |
| ***P* value** | NR | | 0.042 | | 0.017 | |

ANOVA = analysis of variance; CI = confidence interval; GPS = grass pollen season; N-ob = number of observations (patients × weeks); NR = not reported; PPAE = *Phleum pratense* allergen extract; RQLQ(S) = Rhinoconjunctivitis Quality of Life Questionnaire with standardized activities; SE = standard error.
Note: Analysis by ANOVA.
Source: Clinical study reports.[35,36]

**TABLE 40: TCS, DSS, AND DMS SCORE DURING GPS CALCULATED BY DIFFERENT METHODS**

| Study | Population, Country | Mean Difference (95% CI); % Difference | |
|---|---|---|---|
| | | ANOVA | LDA |
| **TCS** | | | |
| P08067 | Adult & Pediatric; Canada/US | –0.87 (–1.32 to –0.42); –18% | –0.85 (–1.30 to –0.41); –18% |
| P05239 | Pediatric; Canada/US | –1.63 (–2.60 to –0.66); –26.1% | –1.65 (–2.61 to –0.70); –26% |
| P05238 | Adult; Canada/US | –1.31 (–2.22 to –0.40); –20.5% | –1.23 (–2.12 to –0.35); –19% |
| GT-14 | Adult; US | –0.78 (–1.83 to 0.26); –10.4% | –0.69 (–1.76 to 0.38); –9% |
| GT-08 | Adult; Europe | –2.32 (–2.98 to –1.67); –34.2% | –2.21 (–2.84 to –1.58); –31% |
| **DSS** | | | |
| P08067 | Adult & Pediatric; Canada/US | –0.47 (–0.79 to –0.16); –13% | –0.46 (–0.78 to –0.15); –13% |
| P05239 | Pediatric; Canada/US | –1.20 (–1.95 to –0.45); –25% | –1.22 (–1.97 to –0.48); –25% |
| P05238 | Adult; Canada/US | –0.86 (–1.46 to –0.26); –18.3% | –0.81 (–1.41 to –0.22); –18% |
| GT-14 | Adult; US | –0.37 (–1.16 to 0.41); –6.2% | –0.30 (–1.10 to 0.51); –5% |
| GT-08 | Adult; Europe | –1.29 (–1.68 to –0.90); –31.2% | –1.24 (–1.61 to –0.86); –29% |
| **DMS** | | | |
| P08067 | Adult & Pediatric; Canada/US | –0.40 (–0.65 to –0.15); –31% | –0.40 (–0.64 to –0.15); –31% |
| P05239 | Pediatric; Canada/US | –0.42 (–0.88 to 0.03); –31.6% | –0.43 (–0.87 to 0.02); –32% |
| P05238 | Adult; Canada/US | –0.45 (–0.96 to 0.06); –26.5% | –0.42 (–0.91 to 0.07); –25% |
| GT-14 | Adult; US | –0.40 (–0.85 to 0.05); –27.1% | –0.39 (–0.85 to 0.07); –27% |
| GT-08 | Adult; Europe | –1.03 (–1.44 to –0.63); –38.4% | –0.97 (–1.35 to –0.59); –32% |

ANOVA = analysis of variance; CI = confidence interval; DMS = daily medication score; DSS = daily symptom score; LDA = longitudinal data analysis; TCS = total combined score.
Source: Clinical study reports[28-30,35,36] and product monograph.[11]

**TABLE 41: PROPORTION OF PATIENTS WITH ASTHMA REPORTED AS AN ADVERSE EVENT (ADULTS)**

| | GT-07 | | GT-02 | | | | GT-08 | | GT-14 | | P05238 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PPAE N = 74 | Placebo N = 40 | PPAE N = 141 | Placebo N = 136 | PPAE (no L) N = 153 | Placebo (no L) N = 150 | PPAE N = 316 | Placebo N = 318 | PPAE N = 163 | Placebo N = 166 | PPAE N = 213 | Placebo N = 225 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Asthma** | **8 (11)** | 4 (10) | 0 (0.0) | 2 (1.47) | 0 (0.0) | 0 (0.0) | 4 (1) | 2 (1) | **2 (1)** | 2 (1) | 2 (0.9) | 2 (0.9) |

L = loratadine; PPAE = *Phleum pratense* allergen extract.
Source: Clinical study reports.[26-30]

**TABLE 42: PROPORTION OF PATIENTS WITH ASTHMA REPORTED AS AN ADVERSE EVENT (CHILDREN OR MIXED POPULATION)**

| | GT-12 | | P05239 | | P08067 | |
|---|---|---|---|---|---|---|
| | PPAE N = 126 | Placebo N = 127 | PPAE N = 175 | Placebo N = 169 | PPAE N = 753 | Placebo N = 745 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Asthma** | 7 (6) | 12 (9) | 2 (1.1) | 3 (1.8) | 10 (1.3) | 5 (0.7) |

PPAE = *Phleum pratense* allergen extract.
Source: Clinical study reports.[34-36]

**TABLE 43: SUMMARY OF EFFICACY WITH PPAE IN COMPARISON WITH LORATADINE IN STUDY GT-02**

| Outcome | PPAE + Placebo | Placebo + Loratadine (10 mg) | Difference vs. Loratadine | | | % Difference vs. Loratadine |
|---|---|---|---|---|---|---|
| | Adjusted Mean (SE) | Adjusted Mean (SE) | Estimate | 95% CI | *P* value | |
| **DSS — entire GPS** | 2.894 (0.201) | 2.813 (0.266) | 0.082 | (–0.657 to 0.821) | 0.828 | 2.88[a] |
| **DSS — peak GPS** | 4.053 (0.250) | 3.991 (0.335) | 0.062 | (–0.867 to 0.992) | 0.895 | 1.55[a] |
| **DMS — entire GPS** | 1.741 (0.237) | 1.960 (0.313) | –0.219 | (–1.090 to 0.653) | 0.622 | –11.17[a] |
| **DMS — peak GPS** | 2.286 (0.275) | 2.386 (0.368) | –0.100 | (–1.123 to 0.923) | 0.848 | –4.19[a] |
| **RQLQ — 2nd seasonal visit** | 0.843 (0.085) | 1.134 (0.078) | –0.292 | (–0.524 to –0.059) | 0.014 | –25.66[a] |
| **% Well days — entire GPS** | 48.965 (2.824) | 46.656 (3.737) | 2.309 | (–8.092 to 12.709) | 0.663 | 4.95[a] |
| **VAS — entire GPS** | 18.334 (1.635) | 19.951 (2.139) | –1.617 | (–7.619 to 4.385) | 0.597 | –8.10[a] |

CI = confidence interval; DMS = daily rhinoconjunctivitis medication score; DSS = daily rhinoconjunctivitis symptom score; GPS = grass pollen season; PPAE = *Phleum pratense* allergen extract; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; VAS = visual analogue scale.
[a]Calculated by Common Drug Review reviewer.
Note: The VAS score was for hay fever and was evaluated on a scale from 0 to 100, where 0 represented no symptoms and 100 represented a high level of symptom.
Source: Clinical study report.[26]

**TABLE 44: HARMS WITH PPAE IN COMPARISON WITH LORATADINE IN STUDY GT-02**

| | PPAE + Placebo | Placebo + Loratadine (10 mg) |
|---|---|---|
| | N (%)[a] | N (%)[a] |
| **AE** | 137 (89.54) | 100 (73.53) |
| **Ear Pruritus** | 25 (16.34) | 0 (0.00) |
| **Eye Pruritus** | 7 (4.58) | 5 (3.68) |
| **Edema Mouth** | 17 (11.11) | 0 (0.00) |
| **Oral Pruritus** | 75 (49.02) | 15 (11.03) |
| **Asthma** | 2 (1.47) | 0 (0.00) |
| **Throat Irritation** | 44 (28.76) | 2 (1.47) |
| **Nasopharyngitis** | 25 (16.34) | 25 (18.38) |
| **Upper Respiratory Tract Infection** | 6 (3.92) | 2 (1.47) |
| **SAE** | 2 (1.31) | 0 (0.00) |
| **WDAE** | 7 (4.58) | 1 (0.74) |

AE = adverse event; PPAE = *Phleum pratense* allergen extract; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a]Percentage of patients in each treatment group having the event.
Source: Clinical study report.[26]

# APPENDIX 5: VALIDITY OF OUTCOME MEASURES

## Aim

The World Allergy Organization (WAO) recommends that clinical trials of specific immunotherapy for respiratory allergy include a measurement of the symptoms and the use of concomitant medication.[41] Various such instruments are available, either patient-rated or clinician-rated. The purpose of this appendix is to describe the instruments used to measure symptoms, concomitant medication use, and quality of life in the trials included in the Common Drug Review (CDR) systematic review of *Phleum pratense* allergen extract (PPAE), as well as to provide information regarding their validity and minimal clinically important difference (MCID).

## Findings

### Rhinoconjunctivitis Daily Symptom Score

For allergic rhinitis (AR) trials, patient-rated symptom scores are recommended by the FDA and the European Medical Agency as the primary measures of clinical efficacy. Most common nasal symptoms and eye symptoms related to AR should be recorded.[59,60] The scores should be presented as a main symptom sum-score, nasal symptom sum-score, and/or eye symptom sum-score, depending on the condition studied.[59] Symptom scores in the included randomized controlled trials were measured using a four-point severity rating scale, from 0 to 3: 0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; and 3 = severe symptoms. The daily symptom score (DSS) consists of six individual symptom scores: four nasal symptoms (runny nose, blocked nose, sneezing, and itchy nose) and two ocular symptoms (gritty feeling or red or itchy eyes, and watery eyes). Each day, the patient rates the severity of each individual symptom using this scale. Results are entered in an electronic diary. The main symptom sum-score is calculated for each patient as the sum of all individual symptom scores, representing the sum of the severity of the most common symptoms in AR. The maximum DSS is 18.

The average DSS is a calculation of the mean of all non-missing rhinoconjunctivitis DSSs during the pollen season on treatment. No information was found on the validity of this instrument, or the MCID.

### Daily Medication Score

Measurement of the use of concomitant medications besides the specific immunotherapy is recommended by the WAO for the assessment of immunotherapy in clinical trials.[41] In the randomized controlled trials of PPAE included in the CDR systematic review, rescue medications for rhinoconjunctivitis and asthma were administered in a stepwise manner, as described below. Patients recorded their medication using an electronic diary.

In general, for patients who need rescue medications for adequate symptom control, the first step is oral antihistamine (loratadine or desloratadine) or antihistamine eye drops (olopatadine); the second step is corticosteroid nasal spray (budesonide or mometasone furoate); and the third step is oral corticosteroid (prednisone or prednisolone). Calculation of a rescue medication score varied across the trials. The total medication score in a day depends on the type of medication used, the dosing, and the days that the rescue medications are needed (APPENDIX 4: DETAILED OUTCOME DATA, Table 14 to Table 21, for details on daily medication score calculation). Higher scores indicate greater use of rescue medications, or a higher step. No information regarding the accuracy, reliability, validity, or MCID of these medication scoring systems could be found by CDR.

**Combined Score or Total Combined Score**

Severity and frequency of symptoms and use of rescue medications are interdependent. Specific allergen immunotherapy is expected to reduce both symptom and rescue medication scores.[41] Rescue medications relieve AR symptoms; therefore, their use may bias the results in trials of immunotherapy. Thus, ideally, the primary end point in AR trials should reflect both rescue medication intake and symptom severity to evaluate the global efficacy of the study drug. Since the publication of European Medical Agency (2004)[59] and FDA (2000)[60] guidelines on clinical development programs for drug products for AR, the WAO recommended that a combined symptom plus medication score be utilized as the primary outcome measure in AR trials in 2007.[41]

Different approaches to combine symptom scores and rescue medication scores have been proposed, but none have been standardized.[41,61]

An MCID is not available for total combined score, even though a difference of 23% in this outcome from placebo was the basis for the sample size calculations in studies P08067, P05238, and P05239. The WAO recommends that the relative difference between specific immunotherapy and placebo on the combined scores be at least 20% to be considered clinically important.[41]

**Visual Analogue Scale**

The visual analogue scale (VAS) is a simple tool for evaluating the severity of disease as well as the efficacy of therapeutic interventions.[62] In general, a 10 cm line to grade the severity of symptoms from "no symptoms" (0 cm) to "the highest level of symptoms" (10 cm) is utilized.[41] Clinical practice guidelines have suggested a classification in which "mild" AR = 0 to 3 cm, "moderate" AR = 3.1 to 7 cm, and "severe" AR = 7.1 to 10.[63] In a French study,[62] from the results of 3,052 patients with AR (seasonal or perennial), VAS and health-related quality of life measurement (measured by the Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]) were correlated, although the correlation was not high ($P = 0.46$, $P < 0.0001$). Test-retest validity of VAS or changes of VAS depending on treatment was not assessed in this study. The VAS employed in the included studies answered the question "How has your hay fever been today/this week?", and the patient indicated a point on a scale from 0 to 100. CDR could identify no information regarding what constitutes an MCID for the VAS to assess AR symptom severity.

**Rhinoconjunctivitis Quality of Life Questionnaire**

The RQLQ is a self-administered questionnaire that contains 28 questions in seven domains: activities limitation (three questions), sleep problems (three questions), nose symptoms (four questions), eye symptoms (four questions), non-nose or 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. It has been validated in adult patients with seasonal or perennial rhinoconjunctivitis. The MCID is 0.5 in the overall or individual domain score.[64]

## Conclusion

Recommended and universally accepted outcome measures in allergen immunotherapy trials include symptom scores and medication scores, or a combination of the two. However, there are no validated scores for AR symptom or rescue medication use in such trials. MCIDs were not identified in the literature for the symptom score, medication score, or combined score. The WAO recommends that the relative difference between specific immunotherapy and placebo on the combined score be at least 20% to be considered clinically meaningful. The RQLQ is a health-related quality of life measure that has been validated in adults with seasonal or perennial rhinoconjunctivitis. The MCID is 0.5 for both the overall and individual domain scores.

# APPENDIX 6: SUMMARY OF GT-08 EXTENSION STUDIES

The objective of the original GT-08 study was to assess the efficacy and safety of *Phleum pratense* allergen extract (PPAE) compared with placebo, in participants with grass pollen–induced rhinoconjunctivitis, during the grass pollen season of 2005. The study was later amended in order to extend the treatment to a total of three years of treatment (until the end of the grass pollen season of 2007) with an additional two years of follow-up (after the end of each grass pollen season in 2008 and 2009) to examine long-term and sustained efficacy and safety of PPAE. At the end of the grass pollen season 2005, the participating patients were offered continued treatment for an additional two years. Of the 634 participants randomized in year 2005, approximately 50% (N = 316) agreed to continue treatment in year 2006, and by 2009, the participant number had decreased to 241. The participants remained in their respective groups during the study and were treated with PPAE or placebo in a similar fashion as in year 2005. Double blinding was maintained throughout the study.

Results for the additional four years reveal statistically significant between-treatment mean differences, for rhinoconjunctivitis daily symptom score (DSS), daily medication score (DMS), and total combined score (TCS; DSS + DMS) favouring PPAE, except in year five, when the between-treatment mean difference for DMS was not statistically significant (shown in Table 45). The extent of reduction in DSS, DMS, and TCS with PPAE in comparison with placebo further increased in year two and then declined closer to year one values in year three, and subsequently declined in years four and five. In the PPAE group, there appears to be an increase in rescue medication use in years four and five. Therefore, the relative stability observed in DSS in the PPAE group may be related to increase rescue medication use rather than a sustained effect.

For RQLQ, over the additional four years there was a statistically significant between-treatment mean difference, for RQLQ favouring PPAE, except in year five, when the between-treatment mean difference was not statistically significant (Table 46). The between-treatment mean difference increased slightly in year two and then declined in year three, remained stable in year four, and then declined further in year five.

The internal validity of findings for years two to five is limited by the large proportion of participants originally randomized to GT-08 who chose not to continue the study after year one, and the fact that study discontinuation was not equal across treatment groups. However, for year two through year five, the dropout rates were low and similar across the treatment groups.

Adverse events were generally higher in the PPAE group compared with the placebo group (Table 47). No deaths occurred in year two to year four. In year five, one patient in the placebo group, diagnosed with a subarachnoid haematoma/ subarachnoid haemorrhage, died during hospitalization.

**TABLE 45: SUMMARY OF DSS, DMS, AND TCS FOR GT-08 EXTENSION STUDIES FOR YEARS 2 TO 5**

| Outcome | PPAE | Placebo | Difference vs. Placebo | Difference vs. Placebo | % Difference Relative to Placebo |
|---|---|---|---|---|---|
| | (N) Adjusted Mean | (N) Adjusted Mean | Mean Difference 95% CI | *P* Value | % Difference 95% CI |
| **DSS** | | | | | |
| Year 2 (2006) | (172) 2.40 | (144) 3.76 | –1.36 (–1.86 to –0.86) | < 0.0001 | –36.2 (–46.5 to –26.2) |
| Year 3 (2007) | (160) 2.56 | (127) 3.59 | –1.04 (–1.56 to –0.52) | 0.0001 | –29.0 (–40.3 to –16.3) |
| Year 4 (2008) | (142) 2.68 | (115) 3.63 | –0.95 (–1.50 to –0.40) | 0.0007 | –26.2 (–37.6 to –12.2) |
| Year 5 (2009) | (137) 2.56 | (104) 3.40 | –0.84 (–1.41 to –0.28) | 0.0037 | –24.7 (–37.7 to –9.7) |
| **DMS** | | | | | |
| Year 2 (2006) | (172) 1.74 | (144) 3.19 | –1.45 (–2.16 to –0.75) | < 0.0001 | –45.5 (–60.4 to –28.2) |
| Year 3 (2007) | (160) 1.82 | (127) 3.04 | –1.22 (–1.92 to –0.52) | 0.0007 | –40.1 (–55.4 to –21.2) |
| Year 4 (2008) | (142) 2.32 | (115) 3.25 | –0.93 (–1.72 to –0.14) | 0.0215 | –28.6 (–46.3 to –6.0) |
| Year 5 (2009) | (137) 2.42 | (104) 3.04 | –0.62 (–1.38 to 0.15) | 0.1136 | –20.4 (–39.8 to 4.3) |
| **TCS** | | | | | |
| Year 2 (2006) | (172) 4.10 | (144) 6.94 | –2.84 (–3.88 to –1.79) | < 0.0001 | –40.9 (–51.8 to –29.5) |
| Year 3 (2007) | (160) 4.39 | (127) 6.64 | –2.26 (–3.26 to –1.25) | < 0.0001 | –34.0 (–45.5 to –21.4) |
| Year 4 (2008) | (142) 4.96 | (115) 6.81 | –1.85 (–2.97 to –0.73) | 0.0014 | –27.2 (–39.9 to –12.4) |
| Year 5 (2009) | (137) 4.96 | (104) 6.42 | –1.46 (–2.61 to –0.31) | 0.0128 | –22.7 (–37.1 to –6.3) |

CI = confidence limit; DMS = rhinoconjunctivitis daily medication score; DSS = rhinoconjunctivitis daily symptom score; PPAE = *Phleum pratense* allergen extract; TCS = total combined score (DSS+DMS).
Source: CDR submission.[39]

**TABLE 46: SUMMARY OF RQLQ FOR GT-08 EXTENSION STUDIES FOR YEARS 2 TO 5**

| Outcome | PPAE | Placebo | Difference vs. Placebo | Difference vs. Placebo | % Difference Relative to Placebo |
|---|---|---|---|---|---|
| | (N) Adjusted Mean | (N) Adjusted Mean | Mean Difference 95% CI | *P* Value | % Difference 95% CI |
| **RQLQ** | | | | | |
| **Year 2 (2006)** | (168) 0.85 | (137) 1.26 | –0.41 (–0.59 to –0.23) | < 0.0001 | –33 NR |
| **Year 3 (2007)** | (157) 0.78 | (122) 1.01 | –0.23 (–0.40 to –0.07) | 0.0058 | –23.1 NR |
| **Year 4 (2008)** | (139) 0.82 | (112) 1.07 | –0.25 (–0.41 to –0.08) | 0.0041 | –23 NR |
| **Year 5 (2009)** | (134) 0.69 | (102) 0.85 | –0.16 (–0.33 to 0.01) | 0.0587 | –19 NR |

CI = confidence interval; NR = not reported; PPAE = *Phleum pratense* allergen extract; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.
Source: Clinical study report.[28]

**TABLE 47: HARMS FOR GT-08 EXTENSION STUDIES FOR YEARS 2 TO 5**

| | Year 2 (2006) | | Year 3 (2007) | | Year 4 (2008) No Treatment | | Year 5 (2009) No Treatment | |
|---|---|---|---|---|---|---|---|---|
| | PPAE N = 189 | Placebo N = 162 | PPAE N = 170 | Placebo N = 138 | PPAE N = 157 | Placebo group N = 126 | PPAE N = 145 | Placebo N = 113 |
| | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) |
| **AE** | 126 (67) | 98 (60) | 108 (64) | 88 (64) | 45 (29) | 43 (34) | 139 (96) | 100 (88) |
| **Ear Pruritus** | NR | NR | NR | NR | NR | NR | 15 (10) | 1 (< 1) |
| **Eye Pruritus** | 3 (2) | 3 (2) | 2 (1) | 7 (5) | NR | NR | 8 (6) | 10 (9) |
| **Edema Mouth** | NR | NR | NR | NR | NR | NR | 31 (21) | 1 (< 1) |
| **Oral Pruritus** | 20 (11) | 3 (2) | 13 (8) | 3 (2) | NR | NR | 70 (48) | 7 (6) |
| **Asthma** | 4 (2) | 3 (2) | 9 (5) | 5 (4) | 6 (4) | 7 (6) | 16 (11) | 16 (14) |
| **Throat Irritation** | 6 (3) | 2 (1) | NR | NR | NR | NR | 18 (12) | 4 (4) |
| **Nasopharyngitis** | 36 (19) | 27 (17) | 23 (14) | 26 (19) | 12 (8) | 5 (4) | 59 (41) | 46 (41) |
| **Upper Respiratory Tract Infection** | NR | NR | NR | NR | NR | NR | 8 (6) | 4 (4) |
| **SAE** | 0[a] | 0[a] | 5 | 5 | 4 | 4 | 1 | 4 |
| **WDAE** | 1 (< 1) | 2 (1) | 1 (< 1) | 1 (< 1) | 0 | 0 | 0 | 0 |

AE = adverse event; No. = number of patients with event; NR = not reported; PPAE = *Phleum pratense* allergen extract; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a]No treatment-related SAE was reported.
Note: Treatment-emergent adverse events are reported in the table above, unless otherwise stated.
Source: Clinical study report.[28]

# APPENDIX 7: CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS BETWEEN SUBLINGUAL IMMUNOTHERAPY TABLETS AND SUBCUTANEOUS IMMUNOTHERAPY

## 1. Objectives

The manufacturer submitted an indirect comparison (IDC) between sublingual immunotherapy tablets (SLIT-T) and other immunotherapy modalities, including subcutaneous immunotherapy (SCIT) and SLIT drops (SLIT-D), in the treatment of grass pollen allergic rhinitis (AR). The objective of this review is to provide a summary and critical appraisal of the manufacturer-provided IDC.

## 2. Summary of Indirect Comparison Analysis

### Rationale

As no head-to-head randomized trials comparing SLIT-T with SLIT-D or SCIT treatment were identified through a systematic literature search, an indirect analysis of placebo-controlled trials was performed by the manufacturer to estimate the comparative efficacy of SLIT-T to SCIT and SLIT-D.[65]

### Methods

#### Eligibility Criteria

The inclusion criteria for the IDC consisted of the following: double-blind, placebo- or active-controlled randomized controlled trials (RCTs) evaluating SLIT-T (*Phleum pratense* allergen extract [PPAE], five-grass pollen allergen extract [5GPAE], or other), SLIT-D (single or multiple grass pollen extracts), or SCIT in patients with seasonal grass pollen AR, rhinoconjunctivitis, or seasonal asthma; and measured the outcome of symptom scores and/or medication scores. A systematic literature search on multiple databases was performed until May 17, 2013. Unpublished data were also searched.

#### Interventions and Comparators

The interventions included in the IDC analysis were SLIT-T (including PPAE and 5GPAE), SLIT-D, and SCIT. The active treatments utilized in the trials had to be products that were commercialized in at least one country.

#### Outcomes

The outcomes of interest included symptom score and medication scores. Symptom scores were measured differently across studies and were made up of combinations of individual symptoms. The scores that were of interest for inclusion in the analysis were preferentially listed as follows: rhinoconjunctivitis symptom scores, rhinitis or nasal symptom scores only, and total scores (including eye, nose, and lower airway symptoms). Data included in the IDC analysis were specific to the first grass pollen season following the commencement of immunotherapy treatment.

#### Analysis

Traditional direct pairwise meta-analyses using the inverse weighted method were used to examine the efficacy of the immunotherapies compared with placebo.

Network meta-analysis (NMA) was used to provide an estimate of the relative efficacy of SLIT-T compared with SCIT and SLIT-D. Bayesian methods were used to combine the available RCT data as a function of the likelihood, with a prior probability distribution, to obtain a posterior probability distribution of the outcomes of interest from which summary measures (mean and credible intervals [CrIs]) can be estimated. The manufacturer base-case analysis combined different sublingual immunotherapies (i.e., PPAE and 5GPAE) into one node. Perennial and seasonal SCIT were also included as one node. Both fixed effect and random effect models were used. Furthermore, estimates of the probability that each treatment is best were derived. WinBUGS software was employed to perform the NMA.

Efficacy outcomes were analyzed as standardized mean differences (SMDs) of the continuous variables (such as symptom score) where different scales of measure were combined. Uncertainty was presented using upper and lower limits of 95% CIs or CrIs, for the direct pairwise and network meta-analysis, respectively.

Sensitivity analysis was also performed to explored the degree to which base-case findings were affected by changes in methods (alternative prior distributions) or in data from individual studies (use of total symptom scores as first preference of score).

Subgroup analyses, including PPAE versus 5GPAE, were also performed to address issues of between-study heterogeneity.

Publication bias was explored using a funnel plot or other statistical tests.

**Results**

**Study and Patient Characteristics**

A total of 37 RCTs were included in the NMA: 14 for SLIT-T (eight of these were PPAE [Grazax] trials,[14-16,24,25,31-33] all of which are included in this Common Drug Review (CDR) review; five were 5GPAE [Oralair] trials, with the drug in one trial unspecified), 14 for SLIT-D, and nine for SCIT. The products assessed in the SCIT trials included Staloral, Alutard SQ, Allergovit, and Pollinex, either administered pre-seasonally or perennially. Skin prick test was performed in the included studies to confirm the diagnosis of grass pollen AR, but it was not specified whether an immunoglobulin E test was required. All trials were placebo controlled. Of these, all 37 were included in the analysis for symptoms scores and 33 in the analysis of medication scores. Sample size in these studies ranged from 48 to 1,501. Treatment effect of the immunotherapy was evaluated over different time periods. For example, most of the trials of SLIT-T were conducted after 2005, while the trials of SCIT were conducted before 2000. SLIT-T and SCIT-D were assessed in adult and pediatric populations, while SCIT enrolled adult patients only. The symptom scales for AR symptoms in the PPAE trials were the same as the 5GPAE trials.[42-45] The symptom scales used in the SCIT included trials were not reported.

The duration of treatment with immunotherapy for SLIT-T ranged from greater than two months to greater than eight months (range of 8 to 35 weeks for pre-seasonal treatment; range of 0 to 11 weeks for co-seasonal treatment). Treatment duration ranged from two months to eight months in the PPAE trials, five to six months in the 5GPAE trials, and three weeks to one year in the SCIT trials; five, two, and one PPAE trials were conducted in adult, pediatric, and mixed populations, while four and one 5GPAE trials were conducted in adult and pediatric populations, respectively; permitted rescue medications were similar between the PPAE trials and 5GPAE trials (the details of rescue medication use in SCIT trials were not reported).

**Results of the Indirect Comparison Analysis**
Given that SCIT-D drugs are not available in Canada, these data are not provided in this CDR review.

***Symptom Score***
The IDCs calculated from the Bayesian NMA suggest that SLIT-T had a similar effect on symptom control as SCIT, given that no statistically significant differences were detected for standardized mean difference (SMD) between SLIT-T and SCIT (SMD of symptom score: 0.01, 95% credible interval [CrI], –0.19 to 0.23). The probability of being ranked as the best treatment in the study population was 44% for SLIT-T, and 54% for SCIT. Consistency between direct and indirect estimates for SLIT-T versus placebo, and for SCIT versus placebo, was demonstrated.

**Medication Score**
There was no statistically significant difference in medication scores between SLIT-T and SCIT based on the NMA (SMD of medication score: 0.13, 95% CrI, –0.31 to 0.57). The probability of being ranked as the best treatment for this outcome was 7.5% for SLIT-T and 37% for SCIT. Consistency between direct and indirect estimates for SLIT-T versus placebo, and for SCIT versus placebo, was demonstrated.

A subgroup analysis within the SLIT-T modality was conducted to investigate the potential differences that may be present between PPAE and 5GPAE. Thirteen RCTs (eight for PPAE, five for 5GPAE) included these treatments versus placebo. Compared with placebo, both sublingual tablets significantly reduced both symptom and medication scores relative to placebo, but there were no statistical differences between the two products; SMD (95% CI) for symptom score of 0.14 (–0.08 to 0.37) and SMD for medication score of 0.07 (–0.09 to 0.37).

The detailed results are presented in Table 48.

**TABLE 48: FINDINGS FROM TRADITIONAL PAIRWISE COMPARISON AND NETWORK META-ANALYSIS**

| | Comparator Treatment | Reference Treatment | |
|---|---|---|---|
| | | Placebo | SCIT |
| **Symptom scores (SMD, 95% CI or CrI)[a]** | SLIT-T | TPC: –0.32 (–0.41 to –0.23), favouring SLIT-T | NA |
| | | NMA: –0.33 (–0.46 to –0.22), favouring SLIT-T | NMA: 0.01 (–0.19 to 0.23), favouring SCIT |
| | SCIT | TPC: –0.32 (–0.45 to –0.18), favouring SCIT | NA |
| | | NMA: –0.35 (–0.53 to –0.18), favouring SCIT | |
| | PPAE vs. 5GPAE: 0.14 (–0.08 to 0.37), favouring 5GPAE | | |
| **Medication scores (SMD, 95% CI or CrI)[a]** | SLIT-T | TPC: –0.23 (–0.29 to –0.17), favouring SLIT-T | NA |
| | | NMA: –0.26 (–0.51 to –0.07), favouring SLIT-T | NMA: 0.13 (–0.31 to 0.57), favouring SCIT |
| | SCIT | TPC: –0.33 (–0.52 to –0.13), favouring SCIT | NA |
| | | NMA: –0.39 (–0.76 to –0.04), favouring SCIT | |
| | PPAE vs. 5GPAE: 0.07 (–0.09 to 0.37), favouring 5GPAE | | |

5GPAE = five-grass pollen allergen extract; CI = confidence interval; CrI = credible interval; NA = not applicable; NMA = network meta-analysis; PPAE = *Phleum pratense* allergen extract; SCIT = subcutaneous immunotherapy; SLIT-T = sublingual immunotherapy; SMD = standardized mean difference; TPC = traditional pairwise comparison.
[a]Results for TPC and NMA both from random effects model.

### 3. Critical Appraisal of Indirect Comparison Analysis

The quality of the manufacturer-submitted indirect analyses was assessed according to the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[66] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 49.

**Limitations**

Only a high-level summary of methods and results of the NMA was provided in the manufacturer's submission. The lack of details led to the following concerns:

- Insufficient details were provided with respect to the key patient characteristics (e.g., geographic region, mono- or poly-sensitization, disease severity, previous treatment for AR, and number of asthmatic patients) and trial characteristics (specific symptom scales used in the individual studies, particularly whether the use of rescue medications had been adjusted for in those symptom scales). Thus, it was impossible to evaluate the consistency with which the primary outcome (symptom control) was measured or reported, or whether there was substantial heterogeneity on important

factors across the included studies. This is important because the validity of IDCs rests on a sufficient degree of comparability in methods, populations, and outcome definitions across studies.
- No data were reported on patient withdrawal. Quality assessment of the included studies was not provided; therefore, it is difficult to evaluate the internal validity of individual trials included in the NMA.
- The outcome measures in the individual studies were standardized to SMD; however, there were no data on how the standardization was performed, and the assumption that the variations in outcome scores would be similar across the studies was not justified. The clinical significance of the observed difference in SMD was not addressed, either.

In terms of clinical heterogeneity, the treatment duration (from weeks to months), length of grass pollen season (from weeks to months), and publication year (from 1989 to 2013) varied substantially across the included studies of immunotherapy. Studies of SLIT-T were conducted more recently. It appeared that mono or poly-sensitization, uni- or multi-study centres, and disease severity at baseline were not considered in the analysis. No sensitivity analyses were conducted to assess the effects of these sources of heterogeneity.

A number of key outcomes identified in the CDR systematic review were not evaluated in the NMA. These included health-related quality of life, and systemic reactions or episodes of anaphylaxis. These gaps limit the ability to assess the comparative benefit and harms of SLIT-T or PPAE specifically versus other immunotherapies. In addition, reporting of results from just the first pollen season does not allow for an assessment of longer-term effects.

**Strengths**

A systematic literature search was performed and a search strategy was provided to ensure the comprehensiveness and transparency of data retrieval.

Subgroup analysis and sensitivity analysis were conducted to explore the degree to which base-case findings were affected by changes in methods or in data used from individual studies.

**TABLE 49: APPRAISAL OF THE INDIRECT COMPARISON ANALYSES USING ISPOR CRITERIA**

| ISPOR Checklist Item | | Details and Comments |
|---|---|---|
| 1. | Are the rationale for the study and the objectives stated clearly? | • The rationale for conducting an IDC analysis and the study objectives were clearly stated. |
| 2. | Does the methods section include the following?<br>• Eligibility criteria<br>• Information sources<br>• Search strategy<br>• Study selection process<br>• Data extraction<br>• Validity of individual studies | • The eligibility criteria for individual RCTs were presented.<br>• The databases of MEDLINE, Embase, and the Cochrane Library were searched to May 17, 2013. Search terms were provided. A detailed search strategy was provided.<br>• Study selection was performed using a structured form; unclear whether the studies were selected by 2 independent reviewers.<br>• Data were extracted by 2 reviewers using data extraction form. Key information included publication year, trial duration, length of grass pollen season, symptom scores, and medication scores. No data were reported on changes in patient quality of life, patient compliance, geographic region, previous pharmacological treatment for AR, number of asthmatic patients, and number of withdrawals due to adverse effects. |

| ISPOR Checklist Item | | Details and Comments |
|---|---|---|
| | | • Quality assessment of included studies was not provided. |
| 3. | Are the outcome measures described? | • Outcomes assessed in the IDC analysis (symptom scores and medication scores) were briefly described.<br>• No explanation for why other outcomes were not extracted from the included studies.<br>• No detailed information on the specific symptom scales and scores used in the analysis. Consequently, the consistency of these symptom control outcomes across the studies was not reported. |
| 4. | Is there a description of methods for analysis or synthesis of evidence?<br>• Description of analyses methods or models<br>• Handling of potential bias or inconsistency<br>• Analysis framework | • Network meta-analysis using the Bayesian method was reported for the IDC analysis on the symptom scores and medication scores. Both fixed and random effect models were developed. Traditional pairwise comparisons between active treatment and placebo were also performed.<br>• To account for the differences in scales used to assess outcomes, SMDs were used to express effect sizes for continuous dependent variables.<br>• Description and justification of the Bayesian approach were provided.<br>• Heterogeneity was examined, but inadequately (use of multiple different scoring tools was considered, but other factors were not addressed).<br>• Publication bias was not detected based on assessments using various statistical methods. |
| 5. | Are sensitivity analyses presented? | • Sensitivity analyses were conducted using alternative prior distributions in the model, and total scores including symptom scores related to the lower airway. |
| 6. | Do the results include a summary of the studies included in the network of evidence?<br>• Individual study data?<br>• Network of studies? | • A table with trial characteristics of all included studies was provided. There was no information regarding patient baseline characteristics in the included trials. In addition, no data were presented on the definition of symptom scores and medication scores.<br>• A figure showing the network of studies was not provided. However, forest plots of meta-analysis results between each of the three active comparators and placebo were presented.<br>• Tables with raw data by study and treatment were provided for the IDC analysis. |
| 7. | Does the study describe an assessment of model fit? Are competing models being compared? | • Methods to examine model fit were described, and the report indicated that model fit parameters suggested a better fit with the use of the random effect model but without providing any data. |
| 8. | Are the results of the evidence synthesis presented clearly? | • The results of the analysis were clearly reported for each outcome measure, including point estimates and 95% confidence intervals or credible intervals as a measure of uncertainty. |
| 9. | Sensitivity or scenario analyses | • Sensitivity analysis was reported. |

AR = allergic rhinitis; IDC = indirect comparison; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; RCT = randomized controlled trial; SMD = standardized mean difference.

**Comparison With Other Indirect Analysis**

In a recently published indirect analysis[2] conducted by Canadian researchers, efficacy and safety of Grazax (PPAE), Oralair (5GPAE), and SCIT were compared in patients with seasonal AR. This study was sponsored by the manufacturer of Oralair (Paladin Labs Inc.). A systematic literature search was performed to identify relevant double-blind placebo-controlled RCTs up to December 2012. A meta-regression model and a Bucher method were used. Effect size for continuous dependent variables such

as AR symptom control was expressed as SMD in the meta-regression approach, while it was expressed as absolute difference between active drugs in the Bucher method. In total, 20 RCTs were included in this IDC: eight Grazax and Grastek trials (six RCTs [GT-07, GT-02, GT-08, GT-12, P05238, and P05239] and two follow-up evaluations of GT-08), five Oralair trials, and seven SCIT trials. By using the meta-regression approach, the results indicated statistically improved AR symptom control with Oralair over SCIT (SMD for AR symptom control= –0.21, 95% CI, –0.36 to –0.066; *P* = 0.007) and Grazax and Grastek (SMD for AR symptom control= –0.18, 95% CI, –0.32 to –0.035; *P* = 0.018), but there were no significant differences in the risk of discontinuation due to adverse events between treatment groups (point estimates for Oralair, Grazax and Grastek, and SCIT were 5.6% [95% CI, 3.8% to 7.3%], 3.5% [1.7% to 5.2%] and 2.7% [1.3% to 4.2%], respectively). With the Bucher approach, Oralair was superior to SCIT (mean difference = –0.18, 95% CI, –0.31 to –0.047; *P* = 0.033) and Grazax and Grastek in reducing AR symptoms (mean difference = –0.13, 95% CI, –0.29 to –0.025; *P* > 0.05). There was no statistically significant difference in the risk of treatment discontinuations between Oralair and SCIT (relative risk = 1.55, 95% CI, 0.54 to 4.44; *P* > 0.05), while Oralair-treated patients were associated with higher risk of discontinuation due to adverse events versus Grazax and Grastek (relative risk = 2.58, 95% CI, 1.14 to 5.80; *P* = 0.035).

The point estimates of efficacy results between the NMA provided by Merck Inc. (in its Grastek submission to CDR) and the IDC sponsored by Paladin Inc. regarding the comparison of Grazax and Grastek versus Oralair were similar, but differences in statistical significance were observed. This may be partially explained by the differences in the adopted statistical techniques, and the various numbers of included SLIT-T studies in the two reports: 13 studies in the Paladin report (six were on Grastek and Grazax) versus 14 in the Merck report (eight were on Grastek and Grazax, and approximately 1,800 more patients were involved than the Paladin report).

**4. Summary**

The manufacturer undertook a systematic review of RCTs and performed a network meta-analysis using the Bayesian method to compare SLIT-T (including both PPAE and 5GPAE) with SCIT and SLIT-D (not available in Canada). The results suggested that SLIT-T is not statistically different from SCIT in decreasing AR symptom and medication scores for the treatment of grass pollen allergy. Findings from the subgroup analysis suggest that within the SLIT-T group, PPAE is also not statistically different from 5GPAE in decreasing symptom and medication scores. Given that no head-to-head trials of immunotherapies were identified, and that study-level information in the NMA suggests that important heterogeneity exists across studies, the results of the NMA should be interpreted with caution. Further research such as meta-regression that includes covariates, which may influence the clinical outcomes, was suggested by the authors, who said that this may help to further explain any heterogeneity and identify differences between the various immunotherapy modalities. Because other efficacy and safety outcomes were not evaluated in this NMA, we are not able to estimate the other clinical benefits and risks for SLIT relative to SCIT.

Ultimately, considerable uncertainty remains regarding the comparative efficacy and safety between SLIT and SCIT, and between the different SLIT-T products. High-quality trials directly comparing the active treatments would provide more certainty regarding their comparative benefits and harms.

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