

Allergenic Products Advisory Committee (APAC) Meeting December 12, 2013

FDA Briefing Document

Biologic License Application (BLA) for *Timothy Grass Pollen Allergen Extract Tablet for Sublingual Use*

Applicant

Merck Sharp & Dohme Corp

## General Information

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Product Proper Name: Timothy Grass Pollen Allergen Extract Tablet for Sublingual Use

Proposed Trade Name: GRASTEK®

Description: Sublingual tablet comprised of extract from Timothy grass (*Phleum pratense* L.) pollen.

Formulation: Each sublingual tablet contains 2,800 Bioequivalent Allergy Unit (BAU) of the drug substance. The drug substance is a standardized allergen extract from Timothy grass pollen (*Phleum pratense*) sourced from the United States (US).

Dosing Regimen: The recommended dose of GRASTEK for adults and children 5 years of age and older is 1 sublingual tablet daily.

Applicant: Merck Sharp & Dohme Corp

Proposed Indication and Usage: GRASTEK is indicated for the treatment of diagnosed Timothy grass pollen induced allergic rhinitis, with or without conjunctivitis, in adults and children 5 years of age and older.

Abbreviations:

95% CI	95% confidence interval
95% CI UL	upper limit of the 95% CI
AC	allergic conjunctivitis
AE	adverse event (21 CFR 312.32)
AR	allergic rhinitis
ARC	allergic rhinoconjunctivitis
BAU	Bioequivalent Allergy Units
BLA	Biologics License Application
CSR	clinical study report
DMS	Daily Medication Score: see Table 4
DSS	Daily Symptom Score: sum of six RC symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes), each scored daily by the patient using a 4-point scale from 0 to 3 where 0 = absent and 3 = severe symptoms.
FAS	full analysis set (essentially equal to the intent to treat subset)
IND	investigational new drug application
SAE	serious adverse event (21 CFR 312.32)
SCIT	subcutaneous allergen immunotherapy
SLIT	sublingual allergen immunotherapy
TCS	Total Combined Score: sum of DSS (maximum 18) and DMS (maximum 36). The maximum TCS is 54.

## 1.0 Introduction

Allergic rhinoconjunctivitis (ARC) affects over 500 million persons worldwide, including approximately 30 million persons in the US. While allergen avoidance and pharmacotherapy can provide significant relief, for many affected individuals symptoms remain. For some of these patients allergen immunotherapy is a reasonable alternative. Subcutaneous allergen immunotherapy (SCIT) has been practiced since the early 20th century; the administration of allergen extracts orally or sublingually is a more recent development, increasing in popularity in Europe and the US. However, US-licensed allergen extracts for pollens, mold spores, animal danders, insects and inhalants are only approved for use in SCIT.

Merck Sharp & Dohme Corp. has submitted a Biologics License Application (BLA) to FDA for GRASTEK®, a sublingual tablet comprised of extract from Timothy grass (*Phleum pratense*) pollen. GRASTEK is a sublingual tablet for oromucosal delivery. This tablet is intended to be administered for sublingual immunotherapy (SLIT) in adults, adolescents, and children (5 years of age and older) for treatment of allergic rhinitis with or without conjunctivitis due to sensitivity to Timothy or a related grass pollen. Timothy grass belongs to the taxonomic (botanical) family *Poaceae* (formerly known as *Gramineae*) and subfamily *Pooideae*. Timothy grass pollen extract made by other manufacturers has been licensed by FDA for SCIT of allergic rhinoconjunctivitis (ARC), and distributed as extracts that are standardized according to potency in Bioequivalent Allergy Units (BAU)<sup>1</sup>.

The dosage of the tablets proposed for use in the US is 2800 BAU of standardized extract derived from Timothy grass (*Phleum pratense*) pollen. The applicant proposes that patients initiate treatment with GRASTEK at least 8-12 weeks prior to and throughout the grass pollen season. The first dose is taken at the healthcare provider's office, and the remaining doses are taken at home.

GRASTEK is marketed in Europe under the trade name GRAZAX®. A Marketing Authorization Application for GRAZAX® was filed by the Mutual Recognition Procedure in the European Union (EU) which was first approved in 2006. GRAZAX is now marketed in 30 countries.

## 2.0 Summary of Clinical Studies

The BLA includes clinical study reports (CSRs) of five Phase 1 studies, two Phase 2 studies, six Phase 3 studies and two studies identified as Phase 4 European studies. All studies enrolled persons with a clinical history of grass pollen-induced moderate-to-severe allergic rhinoconjunctivitis, a positive skin prick test and serum specific IgE to *Phleum pratense* pollen.

Three of the phase 1 studies evaluated the safety of different doses of GRASTEK (93 BAU to 37,592 BAU) administered to adults 18-65 years of age [Studies GT-01 ( 93 BAU-14,097 BAU), GT-03 (933 BAU-37, 592 BAU)and GT-04(2800-BAU-18,666 BAU)]; two of the phase 1 studies evaluated the safety of GRASTEK 2800 BAU administered daily for 28 days outside the grass pollen season to children 5-12 years of age (Studies GT-09 and GT-11). In phase 1 studies, 179 subjects received GRASTEK (134 adults 18-65 years of age, 45 children 5-12 years of age), 55 subjects received placebo (40 adults 18-65 years of age, 15 children 5-12 years of age).

Study GT-02 was a Phase 2 dose-ranging proof-of-concept efficacy study in which 569 adults received one of three doses of GRASTEK (93, 933 and 2800 BAU) and 286 subjects received placebo. This study

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<sup>1</sup> Turkeltaub PC. Use of Skin Testing for Evaluation of Potency, Composition, and Stability of Allergenic Products. *Arb Paul Ehrlich* 1994; 87:79-87

identified the GRASTEK 2800 BAU dose as the dose for further evaluation in Phase 3 studies. Phase 2 Study GT-07 was conducted in 114 adult subjects with a clinical history of mild-to-moderate grass pollen-induced asthma during the previous two pollen seasons. Subjects were randomized to receive GRASTEK 2800 BAU (74 subjects) or placebo (40 subjects).

The BLA includes study reports for four Phase 3 non-efficacy studies conducted in Europe from 2006 to 2009 to assess:

- subject compliance with daily GRASTEK 2800 BAU dosing when a compliance device was provided (Study GT-10, 460 subjects);
- changes in antibody levels associated with GRASTEK 2800 BAU treatment [Study GT-16 (GRASTEK 2800 BAU in 52 subjects, placebo in 26) and Study GT-18 (GRASTEK 2800 BAU in 219 subjects, placebo in 57)]; and
- whether oral antihistamine administered immediately prior to GRASTEK 2800 BAU is associated with fewer treatment-related adverse events on the first day of exposure (Study GT-19, 46 subjects).

The BLA also contains reports for two additional studies conducted in Europe and identified as Phase 4 studies. The goals of these studies were to assess the safety of GRASTEK 2800 and compliance with daily dosing when a compliance device was provided (Study GT-15 and GT-17 respectively).

Finally, the BLA provides reports of six Phase 3 placebo-controlled studies that were conducted to assess the efficacy and safety of GRASTEK 2800 BAU (Studies GT-14, GT-08, GT-12, P05238, P05239 and P08067). In five of these studies the efficacy of GRASTEK was evaluated over one pollen season in adults (Studies GT-14 and P05238), children (Studies GT-12 and P05239) or in children, adolescents and adults (Study P08067). In Study GT-08 adult subjects received either GRASTEK or placebo for three consecutive years (beginning 16 weeks prior to the anticipated start of first grass pollen season). Subjects were observed but not treated for the last two years.

Tables 1 and 2 present summaries of the Phase 3 and EU post-marketing clinical studies.

**Table 1: Phase 3 GRASTEK Clinical Efficacy Studies**

Study# Location Year conducted	Objectives	Study design	Study population age range	Treatment Dose and Schedule	Number of subjects	Treatment Duration
GT-08 EU 9/2004-9/2009	Efficacy and Safety	MC, R, DB, PG, PC	18-65y	Year 1: GRASTEK 2800 BAU and placebo  Year 2: GRASTEK 2800 BAU and placebo  Year 3: GRASTEK 2800 BAU and placebo  Years 4 and 5: No treatment	Year 1: 316 active; 318 placebo  Year 2: 189 active; 162 placebo  Year 3: 170 active; 138 placebo  Year 4 <sup>b</sup> : 157 active; 126 placebo  Year 5 <sup>b</sup> : 145 active; 113 placebo	Year 1: 4 to 6 months prior to the grass pollen season and during the 2005 season  Year 2 and 3 <sup>a</sup> : extensions of GT- 08 to end of 2006 and 2007  Year 4 and 5: No treatment
P08067 US, Canada 2012	Efficacy and Safety	MC, R, DB, PG, PC;	5-65y	GRASTEK 2,800 BAU Placebo	752 749	~24 weeks (12 weeks prior to, and during 2012 grass pollen season)
GT-14 US 12/2006-8/2007	Efficacy and Safety	MC, R, DB, PG, PC	18-65y	GRASTEK 2,800 BAU  Placebo	166 163	24-36 wks (At least 8 to 16 weeks prior to and during the 2007 grass pollen season)
P05238 US, Canada 1/2008-9/2009	Efficacy and Safety	MC, R, DB, PG, PC;	18-65y	GRASTEK 2,800 BAU Placebo	166 163	Approx 16 weeks prior to and then during the entire 2009 season (total of approx 24 weeks)
GT-12 Germany 11/2006-11/2007	Efficacy and Safety	MC, R, DB, PC, PG	5-16y	GRASTEK 2,800 BAU Placebo	126 127	At least 16 weeks prior to and then during the entire 2007 grass pollen season  ~ 36 weeks
P05239 US, Canada 1/2008-9/2009	Efficacy and Safety)	MC, R, DB, PC, PG	5-18y	GRASTEK 2,800 BAU Placebo	175 169	Approx 16 weeks prior to and then during the entire 2009 grass pollen season  ~ 36 weeks

Adapted from Original application, Module 2 (Common Technical documents), Folder 2.5 (Clinical Overview). Note: BAU = Bioequivalent Allergen Unit; DB = double-blind; MC = multicenter; PC = placebo-controlled; PG = parallel-group; R = randomized. a: In Study **GT-08**, treatment continued daily throughout the year during Years 1 to 3; no product was administered during Years 4 and 5. b: In Study GT-08 **Years 4 and 5**, number is subjects previously treated in **Years 1 to 3**.

**Table 2: Phase 3 Non-efficacy and Phase 4 GRASTEK Clinical Studies**

Study# Location Year conducted	Objectives	Study design	Age range (years)	Treatment dose and schedule	Number of Subjects	Treatment Duration
GT-10 EU 2006	Compliance (w/wo device) and safety	MC, R, PG, OL;	17-66	Grastek: 2,800 BAU	460	Approximately 6 to 12 weeks prior to and during the 2006 grass pollen season, follow for ~ 1 year
G10 extension EU 8/2006-11/2007	Compliance and safety	MC,OL;	19-67	Grastek: 2,800 BAU	264	Approximately 1 year or until marketed product GRASTEK available
GT-16 Spain 2007	Investigate changes in immunological parameters and cutaneous reactivity	MC, R, DB, PC, PG	18-61	Grastek: 2,800 BAU Placebo	52 26	2-4 months prior to, and during 2007 grass pollen season
GT-18 German, Austria 2008	PD effect and tolerability of GRASTEK	MC, R, DB, PC, PG	18-66	Grastek: 2,800 BAU Placebo	219 57	At least 8 weeks of treatment initiated during the grass pollen season
GT-15 France 2008	Safety, Tolerance	MC, R*, OL	18-73	Grastek: 2,800 BAU	628	At least 4 months prior to and during the 2008 grass pollen season (maximum 10 months)
GT-17 Italy 3/2007-4/2009	Compliance(w/wo compliance device)	MC, R, PG, OL	18-63	Grastek: 2,800 BAU	261	48 weeks of treatment
GT-19 Germany 2008	Safety (local allergic reactions) of GRASTEK in combination with desloratadine	SC, R, DB, Crossover	21-65	Grastek: 2,800 BAU + desloratadine 2.5mg or placebo	46, all received single doses of each treatment	Single doses

BAU = Bioequivalent Allergen Unit; DB = double-blind; MC = multicenter; MD = multiple dose; OL = open label; PC = placebo-controlled; PG = parallel-group; QD = once daily; R = randomized; SC = single center; PD= pharmacodynamics.

\*GT-15 (from registry of eligible patients into enrolled or not enrolled)

### 3.0 Summary of Efficacy

#### 3.1 Clinical Scores for Assessment of Efficacy

Several clinical scoring algorithms have been developed to assess the efficacy of allergen immunotherapy. Some of these consider only symptoms or quality of life, some consider medication use, and some take both symptoms and medication use into account. In the Phase 3 efficacy studies conducted by the applicant, the primary efficacy endpoint was either the average rhinoconjunctivitis Daily Symptom Score (DSS), the average rhinoconjunctivitis Daily Medication Score (DMS), or the average combined rhinoconjunctivitis DSS and DMS (Total Combined Score, TCS) over the entire grass pollen season.

The DSS is the sum of six individual rhinoconjunctivitis symptom scores with possible values of 0 (absent) to 3 (severe). The six symptoms that are scored are: runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes. The maximum DSS is 18.

The DMS is the sum of scores that are assigned to each medication as presented in Table 3.

**Table 3: Scoring of Rescue Medication Usage for DMS calculation**

Step	Rescue Medication	Score/ Dose Unit	Max Daily Score
1a	Loratadine syrup 1 mg/mL – 5 mL QD (5 to <6 yr)	6 (per 5 mL)	6
1a	Loratadine Reditabs tablet 10 mg – 1 tablet QD $\geq$ 18 yr); Claritin syrup 1 mg/mL – 10 mL QD ( $\geq$ 6 to <18 yr)	6 (per tablet or 10 mL)	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 yr)	4 (per spray)	8
2	Mometasone furoate monohydrate nasal spray 50 mcg - 2 sprays in each nostril QD ( $\geq$ 12 yr)	2 (per spray)	8
3	Prednisone tablet 5 mg (Day 1 - 1 mg/kg/day, Max 50 mg/day)	1.6 (per tablet)	16 <sup>a</sup>
3	Prednisone tablet 5 mg (Day 2+ - 0.5 mg/kg/day, Max 25 mg/day)	1.6 x 2 (per tablet)	16 <sup>a</sup>
Maximum daily rhinoconjunctivitis medication score			36

<sup>a</sup>: use of prednisone will be counted in the rhinoconjunctivitis medication score and/or the asthma medication score depending on the symptoms. In the combined score, use of prednisone was counted only once.

From BLA Application STN 125473/000; Module 5, CSR p05238, Vol 1, Page 65

TCS is the sum of DSS (maximum 18) and DMS (maximum 36). The maximum TCS is 54. Note that the TCS is weighted towards the use of rescue medication.



### 3.2 Clinical Studies Efficacy Analyses

This section presents the primary analyses for efficacy in the six Phase 3 studies conducted to assess the efficacy of the GRASTEK 2800 BAU dose relative to placebo.

#### *Study GT-08 (5 year study)*

This study was conducted in Europe from September 2004 to September 2009. A total of 634 subjects 18-65 years of age were randomized 1:1 to receive placebo or GRASTEK 2800 BAU. Subjects were treated for 16-35 weeks (median 27 weeks) prior to the first grass pollen season and continued treatment during three consecutive pollen seasons. The primary objective was to assess the efficacy of SLIT with GRASTEK on the average rhinoconjunctivitis DSS and the DMS during the entire 2005 pollen season and the four subsequent seasons. The analysis of efficacy after the 2005 season was considered the primary efficacy analysis of the trial. In study year 1 (2005) the percent changes in the average rhinoconjunctivitis DSS and DMS in the GRASTEK group compared to placebo were -31.2 % (95% CI -38.8, -23.4%) and -38.4% (95% CI -49.8%, -26.5%) respectively. The efficacy of GRASTEK in reducing DSS and DMS during the first pollen season and subsequent seasons is presented in Table 4.

**Table 4: Study GT-08: Average DSS and DMS During the Entire Grass Pollen Season for each Year 2005 – 2009 (FAS population).**

Study GT-08	Number of subjects		% change in DSS (95% CI)	% change in DMS (95% CI)
Year	GRASTEK	Placebo		
1 (2005 season)	282	286	-31.2 % (-38.3, -23.4)	-38.4% (-49.8, -26.5)
2 (2006 season)	172	144	-36.2% (-46.5, -26.2)	-45.5% (-60.4, -28.2)
3 (2007 season)	160	127	-29.0% (-40.3, -16.3)	-40.1% (-55.4, -21.2)
4 (2008 season) [no treatment]	142	115	-26.2% (-37.6, -12.2)	-28.6% (-46.3, -6.0)
5 (2009 season) [no treatment]	137	104	-24.7% (-37.7, -9.7)	-20.4% (-39.8, +4.3)

Note that, in Year 5, which was the second year following treatment discontinuation, there was no significant difference in average DMS between the GRASTEK and placebo groups.

#### *Study GT-14 (US efficacy study)*

This study was conducted in the US in 2007. A total of 329 adults 18-65 years of age were randomized 1:1 to receive either placebo or GRASTEK 2800 BAU. Subjects were treated for 6-24 (median ~16) weeks prior to the grass pollen season and continued treatment during the season. The primary objective was to assess the efficacy of SLIT with GRASTEK on the average rhinoconjunctivitis DSS during the entire grass pollen period. In this study the percent change in average DSS in the GRASTEK group was -6.1% (95% CI -19.8, +7.1); efficacy was not demonstrated. The applicant performed a number of post-hoc analyses to explore the failure to demonstrate efficacy in this study. Although none were conclusive the applicant suggested that the subjects' pre-seasonal symptom scores, and overlapping pollen seasons/allergies may have affected the results.

#### *Study GT-12 (Pediatric study conducted in Germany)*

This study was conducted in Germany from December 2006 to December 2007. A total of 253 children and adolescents 5-16 years of age were randomized 1:1 to receive either placebo or GRASTEK 2800 BAU. Subjects initiated treatment with placebo or GRASTEK approximately 17 weeks (range 8 to 23 weeks) prior to and then during the entire 2007 grass pollen season. The primary objective was to assess the efficacy of SLIT with GRASTEK on the average rhinoconjunctivitis DSS during the entire grass pollen period. In this study the percent change in average DSS in the GRASTEK group relative to the placebo group was -22.1% (95% CI -38.7, -4.8). The percent change in average DMS in the GRASTEK group relative to the placebo group was -34.5% (95% CI -60.4, +0.1).

#### *Study P05238 (Adult US and Canada efficacy study)*

This study was conducted in the US and Canada from January 2008 to September 2009. During 2008 there was an observational grass pollen season period during which no investigational product was administered. In 2009 439 subjects 18-63 years of age (189 from the Year 1 observational period and an additional 250) were randomized 1:1 to treatment with either GRASTEK or placebo. Subjects initiated treatment 7-24 weeks (median 17 weeks) prior to the start of the grass pollen season. The primary objective was to assess the efficacy of SLIT with GRASTEK on the average rhinoconjunctivitis TCS (the sum of the DSS and DMS averaged over the entire grass pollen period). In this study the percent change in TCS during the entire grass pollen season in the GRASTEK group relative to the placebo group was -20.5% (95% CI -33.0, -6.0).

#### *Study P05239 (Pediatric US and Canada study)*

This study was conducted in the US and Canada from January 2008 to September 2009. During 2008 there was an observational grass pollen season period during which no investigational product was administered. In 2009 345 subjects 5-18 years of age (76 from the Year 1 observational period and an additional 269) were randomized 1:1 to either GRASTEK or placebo. Subjects initiated treatment 2 days -22 weeks (median 16 weeks) prior to the start of the grass pollen season. The primary objective was to assess the efficacy of SLIT with GRASTEK on the average rhinoconjunctivitis TCS (the sum of the DSS and DMS averaged over the entire grass pollen period). In this study the percent change in TCS during the entire grass pollen season in the GRASTEK group relative to placebo group was -26.1% (95% CI -38.2, -10.1).

#### *Study P08067 (Adult and Pediatric US and Canada Study)*

This study was conducted in the US and Canada from December 2011 to August 2012. A total of 1501 subjects 5-65 years of age were randomized to 1:1 to GRASTEK or placebo. Subjects initiated treatment 11-27 weeks (median 19 weeks) prior to the start of the grass pollen season. The primary efficacy

objective was to assess the efficacy of SLIT with GRASTEK on the average rhinoconjunctivitis TCS (the sum of the DSS and DMS averaged over the entire grass pollen period). In this study the percent change in TCS during the entire grass pollen season in the GRASTEK group relative to placebo group was -23.2% (95% CI -36.0, -13.0). This study was powered to detect a treatment difference of at least 10% between GRASTEK and placebo groups (i.e. 95% CI UL < -10%).

### **3.3 Post-hoc Efficacy Analyses Using the Total Combined Score**

In studies P05238, P05239 and P08067 the primary efficacy endpoint was the average TCS during the entire grass pollen season. To permit a comparison of efficacy of GRASTEK across all studies the applicant performed post-hoc analyses of the average TCS during the entire grass pollen season for Studies GT-14, GT-08 and GT-12. The results of these analyses and the primary analyses for P05238, P05239 and P08067 are presented in Table 5.

**Table 5: Analyses of Efficacy During the Entire Pollen Season Using the Total Combined Score (FAS Population)** (\*Average Combined Score x2 (ACS = (DSS/DMS)/2 = TCS/2)

Treatment	Number of Subjects	Total Combined Score	Percent change in TCS relative to placebo	
			Point estimate	95% CI
<b>Study P08067 (Adult and Pediatric US and Canada Study)</b>				
Grastek	629	3.24 (median)	-23.2%	-36.0%, -13.0%
Placebo	672	4.22 (median)		
<b>Study P05239 (Pediatric US and Canada study)</b>				
Grastek	149	4.62 (adjusted mean)	-26.1%	-38.2%, -10.1%
Placebo	158	6.25 (adjusted mean)		
<b>Study P05238 (Adult US and Canada efficacy study)</b>				
Grastek	184	5.08 (adjusted mean)	-20.5%	-33.0%, -6.0%
Placebo	207	6.39 (adjusted mean)		
<b>Study GT-12 (Pediatric study conducted in Germany) post-hoc analysis</b>				
Grastek	117	3.70 Adjusted mean)	-24.2 %	-41.3%, -4.5%
Placebo	121	4.87 (adjusted mean)		
<b>Study GT-14 (US efficacy study) –post hoc analysis</b>				
Grastek	139	6.74 (adjusted mean)	-10.4%	-23.9%, + 4.0%
Placebo	150	7.53 (adjusted mean)		
<b>Study GT-08 (5 year study) Year 1 post hoc analysis</b>				
Grastek	282	4.46 (adjusted mean)	-34.2%	-42.0%, -26.3%
Placebo	286	6.78 (adjusted mean)		
<b>Study GT-08 (5 year study) Year 2 post hoc analysis</b>				
Grastek	172	4.10 (adjusted mean)	-40.9%	-51.8%, -29.5%
Placebo	144	6.94 (adjusted mean)		
<b>Study GT-08 (5 year study) Year 3 post hoc analysis</b>				
Grastek	160	4.39 (adjusted mean)	-34.0%	-45.5%, -21.4%
Placebo	127	6.64 (adjusted mean)		
<b>Study GT-08 (5 year study) Year 4 post hoc analysis</b>				
Grastek	142	6.42 (adjusted mean)	-27.2%	-39.9%, -12.4%
Placebo	115	6.81 (adjusted mean)		
<b>Study GT-08 (5 year study) Year 5 post hoc analysis</b>				
Grastek	137	4.96 (adjusted mean)	-22.7%	-37.1%, -6.3%
Placebo	104	6.42 (adjusted mean)		

## 4.0 Summary of Safety

### 4.1 Overall Clinical Studies Safety Database

Across 13 clinical trials (phase 1, 2, and 3) that comprised the pivotal clinical development program for GRASTEK, a total of 4,704 participants were randomized to receive GRASTEK (2,568 participants) or placebo (2,136 participants). Safety analyses presented herein are based on two pooled analyses:

- all adults  $\geq 18$  years of age at entry randomized to receive GRASTEK at a daily dose of 2800 BAU or placebo in phase 2 or 3 studies (includes participants from 6 studies)
- all children and adolescents 5 to 17 years of age at entry randomized to receive GRASTEK at a daily dose of 2800 BAU or placebo in phase 3 studies (includes participants from 3 studies).

These pooled analyses included 2,116 persons randomized to receive GRASTEK at a daily dose of 2800 BAU: 1,669 adults aged 18 through 65 years, 239 adolescents aged 12 through 17 years, and 207 children aged 5 through 11 years<sup>2</sup>. The pooled analyses included 2,080 persons randomized to receive placebo: 1,645 adults aged 18 through 65 years, 245 adolescents aged 12 through 17 years, and 190 children aged 5 through 11 years. Among adult study participants, the mean age was 36.2 years in both the GRASTEK and placebo groups. Among child and adolescent study participants, the mean age was 11.7 years in the GRASTEK group and 11.9 years in the placebo group. Three adult subjects randomized to placebo and 2 pediatric subjects randomized to GRASTEK did not receive treatment.

In the pooled analyses, the mean duration of exposure to GRASTEK was 175 days (range 1-317 days) for adults and 176.9 days (range 1-258 days) for children and adolescents. The average duration of exposure in the respective placebo recipients was similar to that observed in the GRASTEK recipients.

Persons with a self-reported history of controlled asthma and an  $FEV_1 \geq 70\%$  of predicted value at screening and randomization visits were allowed to enroll in the trials. Persons needing year-round maintenance inhaled corticosteroids or long-acting beta2 agonists treatment were generally excluded. Among the adults included in the pooled analyses, 415 (25%) of those who received GRASTEK and 383 (23%) of those who received placebo had a medical history of asthma at baseline. Among children and adolescents included in the pooled analyses, 140 (31%) of those who received GRASTEK and 136 (31%) of those who received placebo had a medical history of asthma at baseline.

### Safety Monitoring/Definitions

Safety was monitored by observation in the physician's office for 30 minutes following the first dose (also after the second and third doses in two studies), phone calls to capture adverse events over the first

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<sup>2</sup> For pediatric participants, data on age were derived from an analysis of 446 out of 447 participants randomized to receive GRASTEK.

2-4 days of home administration in some studies, safety assessments at study visits, paper diary comment cards and electronic diaries<sup>3</sup>.

Treatment-related adverse events refer to those events considered by the investigator as possibly related (temporal association, but other etiologies were likely to be the cause; study drug involvement could not be excluded) or probably related (temporal association, other etiologies possible, but unlikely) to the study drug.

Severity of adverse events was graded as:

- Mild: awareness of sign, symptom, or event, but easily tolerated
- Moderate: discomfort enough to cause interference with usual activity and may have warranted intervention
- Severe: incapacitating with inability to do usual activities or significantly affected clinical status, and warranted intervention.

A serious adverse event was any event that:

- was fatal
- was life-threatening (i.e., immediate risk of death from the event as it occurred)
- was significantly or permanently disabling
- required in-patient hospitalization, or prolonged hospitalization
- was a congenital abnormality or birth defect

Important medical events that may not have resulted in death, been life-threatening, or required hospitalization may have been considered serious when, on the basis of appropriate medical judgment, they may have jeopardized the subject or the subject may have required medical or surgical intervention to prevent one of the outcomes listed in the definition.

#### **4.1.2 Clinical Studies Pooled Safety Analyses - Adults**

##### ***Discontinuation due to Treatment-Related Adverse Events***

In the adult pooled analysis, 4.9% (81/1669) of GRASTEK recipients and 0.9% (15/1,645) of placebo recipients discontinued study participation due to a treatment-related adverse event. The most commonly reported treatment-related adverse events that led to study discontinuation in GRASTEK recipients were oral pruritus (12 study participants), mouth edema (7 study participants), and swollen tongue (6 study participants). Treatment-related adverse events that led to study discontinuation in 2 to 5 GRASTEK recipients were eye pruritus, dyspepsia, dysphagia, lip swelling, nausea, oral mucosal blistering, salivary gland enlargement, stomatitis, chest discomfort, chest pain, hypersensitivity, headache, asthma, cough, dysphonia, dyspnea, pharyngeal erythema, pharyngeal edema, throat irritation, throat tightness, angioedema, pruritus, swelling face, and urticaria.

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<sup>3</sup> Electronic diaries were utilized to capture efficacy data and only limited safety-related information

### ***Treatment-Related Adverse Events, Overall***

Treatment-related adverse events were reported at a higher frequency following GRASTEK than placebo. Onset of treatment-related adverse events typically occurred within the first 1-2 weeks of treatment, with the highest percentage of subjects having onset on Day 1. The most commonly reported treatment-related adverse events were oral pruritus (26.7% GRASTEK; 3.5% placebo), throat irritation (22.6% GRASTEK; 2.8% placebo), ear pruritus (12.5% GRASTEK; 1.1% placebo), and mouth edema (11.1% GRASTEK; 0.8% placebo). Other treatment-related adverse events reported in  $\geq 2.5\%$  of GRASTEK recipients and at a higher frequency than placebo recipients included eye pruritus, lip swelling, oral paresthesia, swollen tongue, tongue pruritus, and pharyngeal edema.

In an analysis of treatment-related adverse events that occurred at an incidence of 2% or greater, a severe event was reported in 49 (2.9%) GRASTEK recipients. Of these 49 participants, 15 participants had severe treatment-related oral swellings, with mouth edema (n=7) and pharyngeal edema (n=5) affecting most of the participants. Severe swollen tongue was reported in 2 participants and severe throat tightness was reported in 1 participant. Such events typically occurred within the first several weeks of treatment. In this analysis, the latest onset of severe oral swelling (swollen tongue) was day 74. In these 15 participants, none of the severe oral swellings resulted in airway compromise. One event (swollen tongue) was treated with epinephrine.

### ***Serious Adverse Events***

In the pooled analysis, at least one serious adverse event was reported in 25 (1.5%) GRASTEK recipients and 22 (1.3%) placebo recipients. None of the serious adverse events in GRASTEK recipients included in the pooled analysis were considered treatment-related.

One subject who received GRASTEK 933 BAU (not included in the pooled analysis of 2800 BAU) experienced a serious adverse event considered by the investigator to be probably related to GRASTEK. The subject experienced itching of the tongue with localized edema of the uvula 20 minutes after taking the first GRASTEK tablet. The subject was observed in the clinic for 2 hours and then released to home. No treatment was given and the subject completed the study according to the protocol.

Death was reported in 2 GRASTEK recipients. One death due to multiple drug overdose occurred  $\approx 6$  days after the last dose of GRASTEK. One death due to arteriosclerotic cardiovascular disease with combined drug toxicity occurred  $\approx 6$  days after the last dose of GRASTEK.

### ***Systemic Allergic Reactions***

For an analysis of systemic allergic reactions, the applicant searched the database for: anaphylaxis, anaphylactic reactions, and hypersensitivity reactions using specified MedDRA terms; events that could indicate possible systemic allergic reactions when applying criteria proposed by the Food Allergy and Anaphylaxis Network (FAAN); and administrations of epinephrine. Based on review of the identified events, guided by FAAN criteria and excluding participants with local symptoms only, the applicant determined that 6 adult participants who received GRASTEK experienced a convincing treatment-related systemic allergic reaction. All events (7 events total) were assessed as non-serious and none were considered severe in intensity. Four events had onset on the first day of GRASTEK treatment. One event

had onset on Day 2 in a participant who also had a reported systemic allergic reaction on Day 1. One event had onset on Day 2 in a participant who tolerated the first dose of GRAFTK with mild local adverse events. One reaction (chest tightness and shortness of breath) had onset on Day 42. Epinephrine was administered for 2 of the 7 reactions.

#### **4.1.3 Clinical Trials Studies Pooled Safety Analyses - Children and Adolescents**

##### ***Discontinuation due to Treatment-Related Adverse Events***

In the pediatric pooled analysis, 6.3% (28/447) of GRAFTK recipients and 0.7% (3/434) of placebo recipients discontinued study participation due to a treatment-related adverse event. The most commonly reported treatment-related adverse events that led to study discontinuation in GRAFTK recipients were throat irritation (6 study participants) and mouth edema (5 study participants). Treatment-related adverse events that led to study discontinuation in 2 to 4 GRAFTK recipients were dyspepsia, dysphagia, lip swelling, oral discomfort, oral pruritus, swollen tongue, chest discomfort, cough, and dyspnea.

##### ***Treatment-Related Adverse Events, Overall***

Treatment-related adverse events were reported at a higher frequency following GRAFTK than placebo. Onset of treatment-related adverse events typically occurred within the first 1-2 weeks of treatment, with the highest percentage of subjects having onset on Day 1. The most commonly reported treatment-related adverse events were oral pruritus (24.4% GRAFTK; 2.1% placebo), throat irritation (21.3% GRAFTK; 2.5% placebo), mouth edema (9.8% GRAFTK; 0.2% placebo), and tongue pruritus (9.2% GRAFTK; 0.9% placebo). Other treatment-related adverse events reported in  $\geq 2.5\%$  of GRAFTK recipients and at a higher frequency than placebo recipients included ear pruritus, eye pruritus, lip pruritus, lip swelling, oral mucosal erythema, oral paresthesia, swollen tongue, headache, cough, dry throat, oropharyngeal pain, pharyngeal erythema, and pharyngeal edema.

In an analysis of treatment-related adverse events that occurred at an incidence of 2% or greater, at least one severe event was reported in 8 (1.8%) GRAFTK recipients. The severe events included ear pruritus, lip swelling, mouth edema, oral pruritus, tongue disorders, dyspnea, and throat irritation). The event of severe mouth edema had onset on Day 17 and was treated with an antihistamine. It did not result in airway compromise.

##### ***Serious Adverse Events***

In the pooled pediatric analysis, at least one serious adverse event was reported in 5 (1.1%) GRAFTK recipients and 7 (1.6%) placebo recipients. Serious adverse events reported in GRAFTK recipients included viral myocarditis (1 participant), synovitis (1 participant), and asthma (3 participants). One of the asthma events occurred prior to randomization. The other serious asthma events are described in detail below:

- A 9-year old male with a history of asthmatic bronchitis experienced a severe, life-threatening asthmatic reaction (62 days after first intake of GRAFTK), 10 minutes after ingestion of an



herbal mixture for cough. The last dose of GRASSTEK had been >24 hours before the reaction. The event led to hospitalization.

- A 16-year old female with a history of allergic asthma experienced 2 asthma exacerbations (1 event on Day 52 and 1 event on Day 199 following initiation of GRASSTEK). Both events led to hospitalization.

None of the serious adverse events in GRASSTEK recipients included in the pooled analysis were considered treatment-related.

There were no deaths reported in the pediatric studies.

### ***Systemic Allergic Reactions***

Using the same methodology described above for the adult pooled analysis, the applicant determined that 1 participant who received GRASSTEK experienced a convincing treatment-related systemic allergic reaction. Within minutes of the first intake of GRASSTEK, this 13-year old participant developed lip angioedema, dysphagia due to sensation of a lump in the throat, and intermittent cough. The events were assessed as moderate in severity. The participant was treated with epinephrine, recovered, and was discontinued from the trial.

## **4.2 Post-Marketing Safety Data**

The applicant's sublingual formulation of the allergen extract from Timothy grass pollen is currently marketed under the trade name GRAZAX in Europe. GRAZAX was first approved in Sweden in 2006 and as of September 2012 was approved and marketed in 30 European countries.

The applicant provided safety data from 6 post-EU registration market support trials, 24 completed or ongoing non-interventional, observational studies, and spontaneous reports.

### ***Post-EU Registration Market Support Trials***

In the post-EU registration market support trials, GRAZAX at a daily dose of 2800 BAU was administered to 1,666 persons ranging in age from 17 through 66 years. Overall, the pattern of adverse events was similar to those previously described. There was one systemic anaphylactic reaction that was considered life-threatening that occurred 1 minute after the first intake of GRAZAX in a 30 year old male with a medical history of active asthma. He had ongoing treatment with fluticasone propionate + salmeterol and terbutaline for his asthma. Reaction symptoms included mouth itching, swelling in the mouth and pharynx, and acute asthma. The participant was treated with a beta2-agonist, subcutaneous epinephrine, and prednisolone.

### ***Non-Interventional Studies***

Based on a summary of data through April 30, 2013, in 24 non-interventional, observational post-marketing surveillance studies (20 completed; 4 ongoing as of the cut-off date) in Europe, approximately 11,000 persons were exposed to at least one dose of GRAZAX. The majority of subjects were adults.

Subjects were monitored for 30 minutes after the first intake of GRAZAX, and adverse events were recorded at this and at all follow-up visits that were part of the normal course of care.

The proportion of withdrawals due to adverse events varied between 1% and 18.6% across studies. In completed studies, 32 of approximately 11,000 subjects reported a serious adverse event, including 25 subjects who had a serious adverse event assessed as treatment-related. Six subjects had events assessed by the reporting physician as treatment-related anaphylactic reactions or hypersensitivity reactions. Epinephrine was administered to 3 of these 6 subjects. Three of the 6 subjects had events at the first dose with the other subjects experiencing the events at Day 17, 2 months following treatment, and at Day 95.

Eight of the 25 treatment-related allergic serious adverse events occurred at the time of the first tablet administration, 16 subjects experienced events that occurred within the first 2 months following treatment initiation, and one subject experienced the event on Day 95. Of the 17 subjects experiencing events at a dose after the first dose, 13 subjects had events characterized by lower airway symptoms and local oral symptoms. The other 4 subjects had local allergic symptoms without lower airway symptoms.

### ***Post-Marketing Spontaneous Adverse Event Reports***

Through September 30, 2012, 3,927 events were reported following GRAZAX. These events, of which 116 were serious, were reported in 1,268 individuals. Across all age groups (5 years of age and older), the most frequently reported non-serious events included mouth edema, oral pruritus, and dyspnea. Across all age groups, the most frequently reported serious event was dyspnea.

Twenty-seven serious systemic allergic reaction cases were reported, including 16 coded as anaphylactic reaction and 11 coded as hypersensitivity. Of the 27 reports, 10 occurred in children or adolescents. For 22 reports with information on time to onset available, 17 events occurred on Day 1 of tablet administration (14 “within minutes” or “up to 20 minutes”; 2 without exact timing specified; and 1 at 6 hours after tablet ingestion), 2 events occurred on Day 2, one event occurred on Day 9, one event occurred 4 weeks after first intake, and one event occurred on Day 47.

Thirty-five serious local reactions with throat symptoms were reported. Eleven of the 35 cases overlapped with serious systemic allergic reactions described above. For the remaining 24 reports, 23 had age reported, including 3 that occurred in children or adolescents. Of 22 reports with information on time to onset, 13 occurred after first intake (ranging from 2 minutes to 10 minutes except for one with onset at 1 hour). The other cases ranged in first occurrence of serious symptoms from Day 2 to Day 86. One of the events was assessed as life-threatening with severe edema of the tongue, hoarseness and a blurred voice on Day 1 of tablet administration.

In an update that also included information regarding serious adverse events spontaneously reported during the period October 1, 2013 to April 30, 2013, the applicant reported a cumulative total of 139 serious spontaneous postmarketing reports. During the update period, 10 serious systemic allergic reaction cases had been spontaneously reported. One case, considered clinically important by the applicant, is summarized below:

A 65 year old male patient developed symptoms reported as consciousness disorder with any loss of consciousness (Glasgow 9). Symptoms included heart rate increase to 126 beats per minute (bpm), blood pressure decrease to 60 mm Hg SBP (no baseline was reported), wheezing, urticaria, and face edema within 2 minutes of the first dose of GRAZAX. The patient was in the physician’s office at the time of the event and was immediately treated with epinephrine, steroids, and oxygen. After 10

minutes, the patient's level of consciousness was back to normal (Glasgow 12) and systolic blood pressure was measured at 110 mm Hg. The patient was observed in the clinic for an additional 2 hours without further reaction. The patient fully recovered and GRAZAX therapy was discontinued.

## **5.0 Allergenic Products Advisory Committee**

The BLA includes data evaluating the safety and efficacy of GRASTEK, 2800 BAU per dose, for immunotherapy of diagnosed Timothy grass pollen induced allergic rhinitis, with or without conjunctivitis. The proposed treatment regimen is daily dosing with GRASTEK for at least 8-12 weeks prior to the onset of grass pollen season, to be continued through the duration of the season.

On December 12, 2013, the Allergenic Products Advisory Committee will be asked whether the available data support the safety and the efficacy of the product in persons 5 years of age and older. In addressing this question, the Committee should address safety and efficacy for adult and pediatric patients separately.

The Committee will be asked to discuss recommendations regarding the need, if any, for additional studies.