SUBLINGUAL SOLUTION OF ALLERGEN EXTRACTS
FOR IMMUNOTHERAPY

Staloral®

Evidence is difference

MONOGRAPH

STALLERGENES
Allergen vaccines worldwide

Table of Contents

I Introduction

Allergy:
A Worldwide Burden

Allergic rhinitis is a global health problem that causes major illness and disability worldwide. A conservatively estimated **25% of the adult population suffers from allergic rhinitis, which has significant repercussions on the professional, educational and economic lives of patients.**[1,2]
The worldwide prevalence of allergic rhinitis and asthma has increased significantly in recent decades.[1]
1 in 4 people suffer from respiratory allergies.[3]
500 million people in the world suffer from allergic rhinitis[2], of whom 15 to 20% have severe symptoms.[4]

Allergic rhinitis and asthma:
Two manifestations of the same disease

Allergic rhinitis is not a static condition, but often changes in its clinical presentation over time.[5] In addition to the tendency of patients to develop new allergen sensitizations, **allergic rhinitis often constitutes an early stage in the natural history of asthma, with up to 40% of rhinitis patients developing asthma later in life.**[5] Asthma is three times more common in those with allergic rhinitis than in the general population (10.5% *versus* just 3.6%), and **over 80% of allergic asthmatics have allergic rhinitis.**[2,6]

Extensive research has revealed tight links between these two diseases and their underlying pathogenic mechanisms. The need to consider and manage these diseases together was the impetus behind the Allergic Rhinitis and its Impact on Asthma (ARIA) Consensus formulated in 2001.[1]

The ARIA guidelines outline four basic principles of treating allergic rhinitis and asthma:[1]

1 · Allergen avoidance
2 · Drug treatment
3 · Allergen immunotherapy
4 · Patient education

The guidelines advise that allergic rhinitis should be treated as early as possible to prevent the potential for it to develop into full-blown asthma later. However, all currently available drugs address only the symptoms of allergy without affecting its underlying causes or the disease's natural tendency to deteriorate.

Only interventions that can alter the progression of allergic rhinitis may reduce the risk of developing asthma or prevent the onset of new allergen sensitizations.[5] **According to the World Health Organization (WHO), allergen immunotherapy represents "the only treatment that alters the natural course of allergic disease".**[7]

Allergen immunotherapy has proven:

- **Efficacy in allergic rhinitis and asthma**
- **Prevention from the onset of new sensitizations in monosensitized patients**
- **Prevention from the deterioration of rhinitis into full-blown asthma**
- **Long-term therapeutic benefits**

Allergen Immunotherapy:

The only treatment proven to alter the natural history of allergic disease

Allergen immunotherapy, or allergen vaccination, is the practice of administering increasing amounts of allergen(s) to reduce the symptoms occurring during the natural exposure to the allergen(s) itself.

For the better part of the 20th century, allergen immunotherapy was primarily administered by subcutaneous injection (subcutaneous immunotherapy, SCIT). And while it was the reference treatment, evidence for the efficacy and safety of SCIT remained a concern due to the practice of non-standardized allergen production, as well as the occurrence of adverse reactions.[8] The widespread availability of cheaper and effective symptom management drugs also minimized interest in allergen immunotherapy.

More recently, a simpler mode of allergen administration has been optimized and is coming into favor: sublingual immunotherapy (SLIT). SLIT is considered to be a safer and more convenient route of administration than SCIT. For these reasons, SLIT has raised the level of interest in immunotherapy among practicing allergists and primary care physicians.

There are 3 reasons why allergy specialists and patients alike prefer sublingual administration:

- **Better safety profile**
- **Ease of use**
- **Outstanding acceptance of the treatment (improved adherence)**

Sublingual Immunotherapy (SLIT):
From experimentation to proven efficacy

The first documented application of allergen immunotherapy dates back to the early 1900s, when it was found to be an effective means of reducing hay fever symptoms.[9] Although the administration of allergens by the subcutaneous route was the original standard of practice, the practice of non injectable routes of administration was also investigated at this time.

It was not until 1986 that the first randomized clinical trial (RCT) assessing the sublingual route was published.[10] **Soon after, the efficacy of SLIT was evaluated in several controlled studies using either drops or tablets.[11,12] There have now been more than 60 double-blind, placebo-controlled (DBPC)-RCTs of SLIT, of which 41 were conducted with grass pollen or house dust mite extracts.[5]** In recent years, large well-designed DBPC-RCTs have confirmed the efficacy and safety of SLIT. These studies primarily used grass pollen drops or tablets and have demonstrated a dose-effect relationship.

Several meta-analyses have concluded that SLIT is significantly efficacious compared with placebo for allergic rhinitis and asthma in adults and children[13-16]

SLIT has been recognized as both effective and safe by experts in the field:

- **WHO Position Paper 1998[7]**
- **ARIA Guidelines 2001 and 2008[1,2]**
- **World Allergy Organization (WAO) Position Paper 2009[5]**

Both ARIA and the WAO recommend SLIT for the same indications as SCIT, namely allergic rhinitis and asthma[1,2,5]

II

Staloral®

Sublingual solution of allergen extracts for immunotherapy

History & Evolutionary Milestones

Staloral®

An Extensive Clinical Trial Programme

The safety and efficacy of Staloral® have been established on the basis of a clinical dossier composed of a large number of double-blind and placebo-controlled clinical trials conducted in both adults and children with allergic rhinitis and/or asthma due to pollen from grasses, weeds (wall pellitory and ragweed) or trees (olive, cypress and birch), and mites.

Authors/year of publication	Pathologies	Protocol	Patients	Number of patients		Efficacy significance* p
				Placebo	Staloral®	
GRASS POLLEN						
Sabbah 1994 [12]	Rhinoconjunctivitis	Pre- and coseasonal	Children Adults	29	**29**	<0.05 to <0.01
Clavel 1998 [18]	Rhinoconjunctivitis and asthma	Pre- and coseasonal	Children Adults	58	**62**	<0.02
Pradalier 1999 [19]	Rhinoconjunctivitis and asthma	Pre- and coseasonal	Children Adults	61	**62**	<0.05
Smith 2004 [20]	Severe rhinitis	Pre- and coseasonal	Adults	45 (placebo only)	**44** (Staloral® only) **47** (Staloral® 1st year & Placebo 2nd year)	<0.05 to <0.01
Ott 2009 [21]	Rhinoconjunctivitis	Coseasonal	Children Adults	46	**99**	<0.05
WEED POLLEN						
La Rosa 1999 [22]	Rhinoconjunctivitis and asthma	Pre- and coseasonal	Children	21	**20**	=0.02
André 2003 [23]	Rhinoconjunctivitis and asthma	Pre- and coseasonal	Children Adults	55	**55**	=0.005 to =0.004
Bowen 2004 [24]	Rhinoconjunctivitis and asthma	Pre- and coseasonal	Children Adults	39	**37**	<0.04
TREE POLLEN						
Vourdas 1998 [25]	Rhinoconjunctivitis and asthma	Pre- and coseasonal	Children	32	**34**	<0.05 to <0.03
Khinchi 2004 [26]	Rhinoconjunctivitis and asthma	Pre- and coseasonal	Adults	19	**18****	<0.002 to <0.01
Vervloet 2007 [27]	Rhinoconjunctivitis and asthma	Coseasonal	Adults	38	**38**	<0.03
MITES						
Bousquet 1999 [28]	Asthma	Perennial	Children Adults	43	**42**	=0.02 to =0.01
Guez 2000 [29]	Rhinoconjunctivitis and asthma	Perennial	Children Adults	36	**36**	>0.05
Mortemousque 2003 [30]	Conjunctivitis	Perennial	Children Adults	30	**30**	<0.01 to <0.0007
Tonnel 2004 [31]	Rhinitis and asthma	Perennial	Children Adults	17	**15**	<0.02

* Based on symptom and/or medication scores
** Kinchi: + 21 SCIT patients in the protocol

Staloral®

A Proven Optimal Dose[33]

Data from these clinical trials were used to establish the minimal concentration of Staloral®.
240 IR/day corresponding to 8 pressures with the 300IR/ml vial concentration was determined to be the dose with the best benefit-to-risk ratio.
Some Staloral® clinical studies have confirmed that a dose of 10 pressures daily with the 300 IR/ml vial concentration (300 IR/day) are well tolerated.[36]

Allergic Rhinitis and its Impact on Asthma (ARIA) Consensus – 2001 & 2008[1,2]

The ARIA guidelines are based on concrete clinical evidence obtained in both adults and children for diverse allergens, including mites and pollen of grasses, weeds and trees.

The 2001 ARIA Consensus[1]

The value of allergen immunotherapy was recognized as:

- The only treatment modality which can alter the natural course of allergic disease
- Safe and suitable for children five years and above

Moreover, **SLIT was recognized as:**

- **Suitable for the same indications as SCIT** (allergic rhinitis, conjunctivitis and/or asthma due to pollen or mites in patients)
- **Being effective in adults and children when administered at high doses** (at least 50 to 100-fold higher than those used in SCIT)

The 2008 ARIA Consensus Update[2]

Highlights of the update included:

- **The recognition that SLIT is effective for rhinitis and asthma due to birch, cypress, grass, olive, wall pellitory pollens, and house dust mites**
- **That allergen immunotherapy appears to reduce the development of new sensitizations**
- **The confirmation that SLIT is safe in adults and children**

Double-blind, placebo-controlled clinical trials of Staloral® have significantly contributed to:

- **The validation of the high-dose concept (doses at least 50 to 100-fold higher than those used in SCIT)**
- **The confirmation of the efficacy and safety of SLIT**

Controlled studies at the origin of the validation of high-dose SLIT (ARIA 2001)[1]

Horak F, Stubner P, Berger UE, *et al.* Immunotherapy with sublingual birch pollen extract. A short-term double-blind placebo study. *J Investig Allergol Clin Immunol* 1998;8(3):165-171.

Clavel R, Bousquet J, André C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollens extract in rhinitis. *Allergy* 1988;53(5):493-498.

Feliziani V, Lattuada G, Parmiani S, *et al.* Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study. *Allergol et Immunopathol* (Madr) 1995;23(5):224-230.

Hordijk GJ. Sublingual immunotherapy with a standardized grass pollen extract: a double-blind, placebo-controlled study. *Allergol Immunopathol* (Madr) 1998;26(5):234-240.

Sabbah A, Hassoun S, Le Sellin J, *et al.* A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollens extract. *Allergy* 1994;49(5):309-313.

Purello-D'Ambrosio F. Sublingual immunotherapy: a double-blind, placebo-controlled trial with Parietaria judaica extract standardized in mass units in patients with rhinoconjunctivitis, asthma, or both. *Allergy* 1999;54:968-973.

La Rosa M, Ranno C, André C, *et al.* Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999;104:425-432.

Passalacqua G, Albano M, Riccio A, *et al.* Clinical and immunologic effects of a rush sublingual immunotherapy to Parietaria species: A double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 1999;104:964-968.

Troise C, Voltolini S, Canessa A, *et al.* Sublingual immunotherapy in Parietaria pollen-induced rhinitis: a double-blind study. *J Investig Allergol Clin Immunol* 1995;5:25-30.

Bousquet J, Scheinmann P, Guinnepain MT, *et al.* Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. *Allergy* 1999;54(3):249-260.

Mungan D, Misirligil Z, Gurbuz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma: a placebo controlled study. *Ann Allergy Asthma/Immunol* 1999;82(5):485-490.

Passalacqua G, Albano M, Fregonese L, *et al.* Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 1998;351:629-632.

Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite: a double-blind study. *Allergol et Immunopathol* (Madr) 1990;18:277-284.

Controlled studies, reviews and meta-analyses further assessing the efficacy and safety of SLIT (ARIA 2008)[2]

Durham SR, Yang WH, Pedersen MR, *et al.* Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117(4):802-9.

Marogna M, Spadolini I, Massolo A, *et al.* Randomized controlled open study of sublingual immunotherapy for respiratory allergy in reallife: clinical efficacy and more. *Allergy* 2004;59(11):1205-10.

Marogna M, Spadolini I, Massolo A, *et al.* Clinical, functional, and immunologic effects of sublingual immunotherapy in birch pollinosis: a 3-year randomized controlled study. *J Allergy Clin Immunol* 2005;115(6):1184-8.

Tonnel AB, Scherpereel A, Douay B, *et al.* Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004;59(5):491-7.

Bufe A, Ziegler-Kirbach E, Stoeckmann E, *et al.* Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004;59(5):498-504.

Sopo SM, Macchiaiolo M, Zorzi G, *et al.* Sublingual immunotherapy in asthma and rhinoconjunctivitis; systematic review of paediatric literature. *Arch Dis Child* 2004;89(7):620-4.

Pajno GB, Vita D, Parmiani S, *et al.* Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate. *Clin Exp Allergy* 2003;33(12):1641-7.

Smith H, White P, Annila I, *et al.* Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004;114(4):831-7.

Rolinck-Werninghaus C, Wolf H, Liebke C, *et al.* A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004;59(12):1285-93.

Bowen T, Greenbaum J, Charbonneau Y, *et al.* Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2004;93(5):425-30.

Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006;61(2):185-90.

Passalacqua G, Pasquali M, Ariano R, *et al.* Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy* 2006;61(7):849-54.

Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005;60(1):4-12.

Calamita Z, Saconato H, Pela AB, *et al.* Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 2006;61(10):1162-72.

Andre C, Vatrinet C, Galvain S, *et al.* Safety of sublingual-swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000;121(3):229-34.

Pajno GB, Peroni DG, Vita D, *et al.* Safety of sublingual immunotherapy in children with asthma. *Paediatr Drugs* 2003;5(11):777-81.

Agostinis F, Tellarini L, Canonica GW, *et al.* Safety of sublingual immunotherapy with a monomeric allergoid in very young children. *Allergy* 2005;60(1):133.

Pham-Thi N, Scheinmann P, Fadel R, *et al.* Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. *Pediatr Allergy Immunol* 2007;18(1):47-5.

Studies conducted with Staloral® or meta-analysis including studies with Staloral®

SLIT Meta-Analyses [13-17]

1. SLIT meta-analysis in allergic rhinitis

Wilson DR, et al. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev 2003;2:CD002893.[13]

The aim of the meta-analysis by Wilson *et al.* was to evaluate the efficacy of sublingual allergen immunotherapy on allergic rhinitis symptoms and drug consumption, as recorded in a series of placebo-controlled clinical trials.
In order to ensure a systematic review of all the relevant literature (up till September 2002), all the following bibliographical databases were searched:

- Cochrane Registry of controlled clinical trials
- MEDLINE (1966-2002)
- EMBASE (1974-2002)
- Scisearch

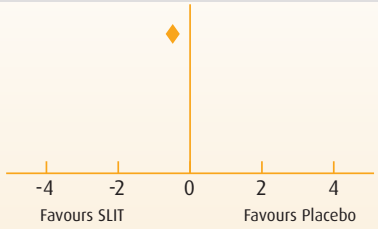
The meta-analysis, according to the Cochrane method, included 22 double-blind, randomised, placebo-controlled studies, all conducted according to stringent guidelines. The studies were carried out on a total of 979 patients (adults and children) suffering from allergic rhinitis to pollens and/or mites.

RESULTS: EFFICACY

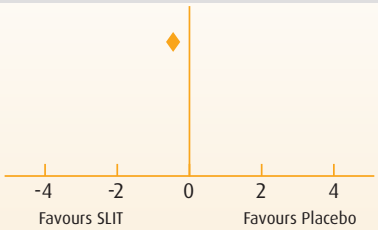
Results were calculated using the Standardized Mean Difference (SMD)* and showed a significant difference in the benefit of SLIT:

- **A reduction in the symptoms of rhinitis:** SMD = -0.42; p = 0.002
- **A decrease in drug consumption:** SMD = -0.43; p = 0.00003

Allergic Rhinitis symptom scores (SLIT *vs.* placebo)

	SLIT N	Placebo N	SMD Mean Difference IV, Random, 95% CI	SMD Mean Difference IV, Random, 95% CI
Total of studies (95% CI)	484	475		-0.42 [-0,69; -0.15]
Heterogeneity: Tau²=0.26; Chi²=75.36, df=20 (p<0.00001); I²=73% Test for overall effect: Z=3.09 (p=0.002)				

Medication scores (SLIT *vs* placebo)

	SLIT N	Placebo N	SMD Mean Difference IV, Random, 95% CI	SMD Mean Difference IV, Random, 95% CI
Total of studies (95% CI)	405	398		-0.43 [-0,63; -0.23]
Heterogeneity: Tau²=0.07; Chi²=28.48, df=15 (p=0.0029); I²=44% Test for overall effect: Z=4.17 (p=0.000031)				

* The Standardized Mean Difference (SMD) involves taking the difference between the means of two groups and dividing it by the estimated standard deviation for the entire population. This takes into account the fact that different measurement methods might have been used in the various studies; each result is converted into a so-called "reduced, centered" figure which can be meaningfully compared with other values generated in the same way.

RESULTS: SAFETY

- **The good safety profile of SLIT** was also proven, as the review **showed the complete absence of any form of systemic reactions and only minor local undesirable effects.**

NOTE

Staloral®'s contribution to the meta-analysis by Wilson *et al.* is illustrated by a single, informative figure:

- Nearly 50% of all patients covered in the review had been treated with Staloral®

2. SLIT meta-analysis in allergic asthma

Calamita Z, et al. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 2006:61:1162-72.[14]

The objective of the meta-analysis by Calamita *et al.* was to assess the efficacy and safety of SLIT in allergic asthma following the Cochrane Collaboration method.

The following bibliographical databases were searched for all the relevant literature up to September 2005: The Cochrane Controlled Trials Register, MEDLINE (1966–2005), EMBASE (1974–2005), LILACS (1982–2005).

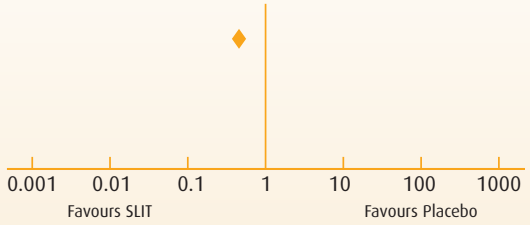
Randomised, controlled clinical trials on SLIT in asthma treatment for adults and children were selected. From 119 citations, 25 studies with 1,706 patients were included in this meta-analysis. All types of allergen, doses, and lengths of treatment were considered.

For each report, quality scores were assigned and data were extracted in relation to the outcomes analyzed: asthmatic symptoms, use of asthma medications, lung function, bronchial provocation.

RESULTS: EFFICACY

- **Significant improvement of overall asthma parameters** (asthmatic symptoms, respiratory function test, symptom relief medication, lung reactivity) **favouring SLIT (p < 0.00001).**

Meta-analysis of overall asthma parameter improvements (asthmatic symptoms, respiratory function test, symptom relief medication, lung reactivity) from placebo-controlled trials: relative risk (RR) with 95% confidence interval (CI)

	Treatment N	Control N	RR (fixed) 95% CI	RR (fixed) 95% CI
Total of studies (95% CI)	497	379		0.48 [0.40; 0.57]
Total events 116 (treatment), 195 (control) Test for heterogeneity: Chi^2=9.41, df=6 (p=0.15), I^2=36.3% Test for overall effect: Z=8.01 (p<0.00001)				

RESULTS: SAFETY

An important issue addressed by the review is in relation to adverse effects. Indeed, **the absence of severe reactions in 20 trials and 1,501 patients demonstrates the highly favourable safety profile of SLIT.**

NOTE

- The meta-analysis by Calamita *et al.* showed that in allergic asthma treatment, SLIT is not only beneficial but also safe, which makes it a safe alternative to the subcutaneous route
- However, because of the heterogeneity of the studies, Calamita *et al.* pointed to the need for more RCTs with standardized symptom scores and medications

3. SLIT meta-analysis of allergic rhinitis in children

Penagos M, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. Ann Allergy Asthma Immunol 2006;97:141-8.[15]

The objective of the meta-analysis by Penagos *et al.* was to evaluate the efficacy of SLIT in the treatment of allergic rhinitis in paediatric patients (3-18 years).

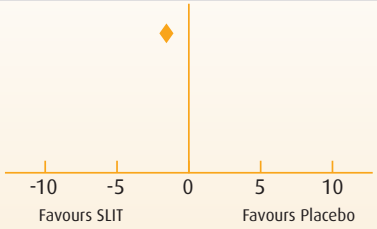
This review was conducted following the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUOROM) guidelines standards. Databases (MEDLINE, EMBASE, LILACS, CINAHL) were searched for randomised, double-blind, placebo-controlled trials assessing SLIT in paediatric cases from 1966 to February 10, 2006.

Ten studies fulfilled the selection criteria and a total of 484 patients were included in the analysis: 245 received SLIT and 239 received placebo. All patients suffered from allergic rhinitis, with or without allergic asthma and/or conjunctivitis.

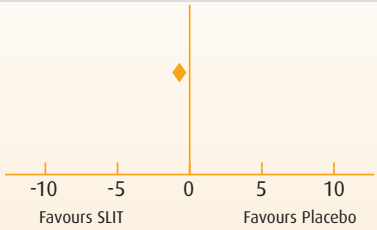
RESULTS: EFFICACY

- **Overall, SLIT was significantly more effective than placebo, as assessed by the reduction in symptom scores and rescue medication usage.**

Comparison SLIT vs. placebo: Nasal symptom scores

	SLIT N	Placebo N	SMD* (random) 95% CI	SMD* (random) 95% CI
Total of studies (95% CI)	**245**	**239**		**-0.56 [-1.01; -0.10]**
Test for heterogeneity: Chi²=47.73, df=9 (p<0.00001); I²=81.1% Test for overall effect: Z=2.39 (p=0.02)				

Comparison SLIT vs. placebo: Medication scores

	SLIT N	Placebo N	SMD* (random) 95% CI	SMD* (random) 95% CI
Total of studies (95% CI)	**141**	**139**		**-0.76 [-1.46; -0.06]**
Test for heterogeneity: Chi²=41.52, df=6 (p<0.00001); I²=85.5% Test for overall effect: Z=2.14 (p=0.03)				

* The SMD (Standardized Mean Difference) involves taking the difference between the means of two groups and dividing it by the estimated standard deviation for the entire population.

RESULTS: SAFETY

- All trials reported the occurrence of adverse effects:
  - SLIT groups: n=132
  - Placebo groups: n=28
- **The most common adverse effects in the SLIT group were oral, nasal-ocular and gastro-intestinal symptoms**
- **No fatal or severe systemic reactions were reported**

NOTE

The meta-analysis by Penagos *et al.* showed that SLIT is effective in the treatment of allergic rhinitis in paediatric patients (3-18 yrs old)

4. SLIT meta-analysis of allergic asthma in children

Penagos M, et al. Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. Chest 2008;133:599-609.[16]

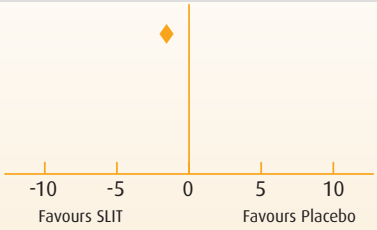
The objective of the 2008 meta-analysis by Penagos *et al.* was to evaluate the efficacy of SLIT in the treatment of allergic asthma in children.

This review was conducted following the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUOROM) guidelines standards. Databases (MEDLINE, EMBASE, LILACS, CINAHL) were searched for randomised, double-blind, placebo-controlled trials assessing SLIT in paediatric cases of asthma from 1966 to May 31, 2006.
Nine studies fulfilled the selection criteria and a total of 441 patients were included in the analysis. 232 patients received SLIT and 209 patients received placebo. All patients suffered from asthma, with or without rhinitis and/or conjunctivitis.

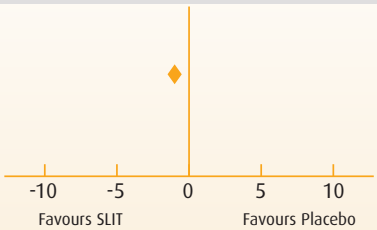
RESULTS: EFFICACY

- **Overall, SLIT resulted in significant reductions in symptoms and medication use.**

Comparison SLIT vs. placebo: Asthma score

	SLIT N	Placebo N	SMD* (random) 95% CI	SMD* (random) 95% CI
Total of studies (95% CI)	**232**	**209**		**-1.14 [-2.10; -0.18]**
Test for heterogeneity : Chi^2=144.10, df=8 (p<0.00001) ; I^2=94.4% Test for overall effect : Z=2.32 (p=0.02)				

Comparison SLIT vs. placebo: Medication score

	SLIT N	Placebo N	SMD* (random) 95% CI	SMD* (random) 95% CI
Total of studies (95% CI)	**192**	**174**		**-1.63 [-2.83; -0.44]**
Test for heterogeneity : Chi^2=130.85, df=6 (p<0.00001) ; I^2=95.4% Test for overall effect : Z=2.68 (p=0.007)				

* The SMD (Standardized Mean Difference) involves taking the difference between the means of two groups and dividing it by the estimated standard deviation for the entire population.

RESULTS: SAFETY

- Most of the trials reported the occurrence of adverse effects in some patients:
  - SLIT groups: n=81
  - Placebo groups: n=23
- **In the SLIT groups, oral, nasal-ocular and gastro-intestinal symptoms were the most common**
- **No fatal or severe systemic reactions were reported**

NOTE

The meta-analyses by Penagos *et al.* (allergic rhinitis and asthma):

- **Showed that SLIT is both effective and safe in the treatment of allergic rhinitis and allergic asthma in children (3-18 years old)**
- **Suggested more SLIT trials need to be conducted in children to determine optimal dosing and administration protocol**

5. SLIT meta-analysis for mites allergy

Compalati E, et al. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA²LEN meta-analysis. Allergy 2009;64:1570-9.[17]

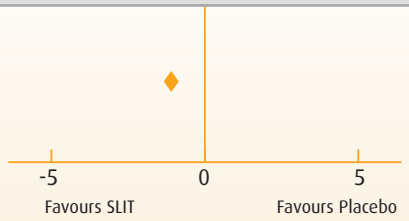
The aim of the recent meta-analysis by Compalati *et al.* was to evaluate the efficacy of SLIT in the treatment of allergic rhinitis and allergic asthma related to mites.

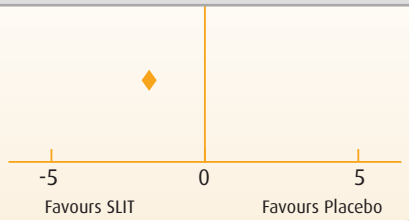
Databases (MEDLINE, EMBASE, LILACS, and SCOPUS) were searched to identify all randomised, double-blind, placebo-controlled trials of SLIT with house dust mite extracts published up to the end of March 2008. Eight studies for allergic rhinitis and nine for allergic asthma fulfilled the selection criteria and a total of 382 patients with allergic rhinitis and 476 patients with allergic asthma were included in the analysis. Patients ranged in age from 5 to 56 years and suffered from either allergic asthma alone or allergic rhinitis, with or without allergic conjunctivitis and/or asthma.

RESULTS: EFFICACY

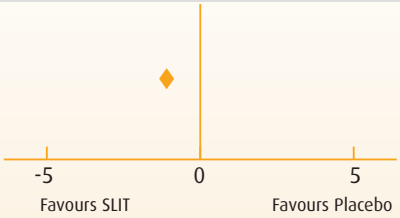
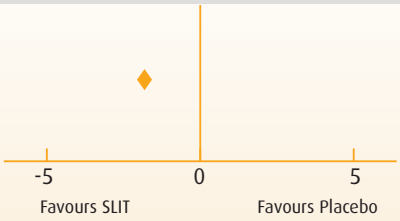
- **Overall, SLIT was significantly more effective than placebo in relieving symptoms and in reducing the need for medications in both pediatric and adult population.**

Efficacy of SLIT in allergic rhinitis: Effect on total symptoms score (A) and medication requirement (B)

A	SLIT N	Placebo N	SMD* (IV, Random, 95% CI)	SMD* (IV, Random, 95% CI)
Total of studies (95% CI)	194	188	-0.95 [-1.77; -0.14]	
Test for heterogeneity: Chi²=82.81, df=7 (p<0.00001), I²=92% Test for overall effect: Z=2.31 (p=0.02)				

B	SLIT N	Placebo N	SMD* (IV, Random, 95% CI)	SMD* (IV, Random, 95% CI)
Total of studies (95% CI)	89	86	-1.88 [-3.65; -0.12]	
Test for heterogeneity Chi²=57.21, df=3 (p<0.00001), I²=95% Test for overall effect Z=2.09 (p=0.04)				

* The SMD (Standardized Mean Difference) involves taking the difference between the means of two groups and dividing it by the estimated standard deviation for the entire population

Efficacy of SLIT in Asthma: Effect on total symptoms score (A) and medication requirement (B)				
A	**SLIT N**	**Placebo N**	**SMD* (IV, Random, 95% CI)**	**SMD* (IV, Random, 95% CI)**
Total of studies (95% CI)	**243**	**233**	**-0.95 [-1.74; -0.15]**	
Test for heterogeneity: Chi^2=113.86, df=8 (p<0.00001), I^2=93% Test for overall effect: Z=2.34 (p=0.02)				
B	**SLIT N**	**Placebo N**	**SMD* (IV, Random, 95% CI)**	**SMD* (IV, Random, 95% CI)**
Total of studies (95% CI)	**202**	**195**	**-1.48 [-2.70; -0.26]**	
Test for heterogeneity Chi^2=145.92, df=6 (p<0.00001), I^2=96% Test for overall effect Z=2.38 (p=0.02)				

* The SMD (Standardized Mean Difference) involves taking the difference between the means of two groups and dividing it by the estimated standard deviation for the entire population

NOTE

- The meta-analysis by Compalati *et al.* showed that SLIT improves symptoms and reduces rescue medication use in patients with allergic rhinitis and allergic asthma related to mites
- However, because of heterogeneity, Compalati *et al.* pointed out the need for large-population-based high quality studies

Staloral®

Sublingual solution of allergen extracts for immunotherapy

Clinical Evidence in Allergic Rhinitis and Asthma Due to Pollen

Staloral® Efficacy in Grass Pollen Allergy

The first form of allergy in which Staloral® was demonstrated to be safe and effective was grass pollen allergy - a relatively reproducible allergenic model. Five studies have been conducted with Staloral® in the treatment of grass pollen allergy.

Authors/ year of publication	Pathologies	Allergens	Protocol	Patients	Staloral®				
					Sublingual form	Maintenance concentration	Major allergen dose	Cumulative dosage	Duration of treatment
Sabbah, 1994 [12]	Rhino-conjunctivitis	5 grasses	Pre- and coseasonal	Children Adults	Drops	100 IR	Not specified	4,500 IR	4 months
Clavel, 1998 [18]	Rhino-conjunctivitis and asthma	5 grasses	Pre- and coseasonal	Children Adults	Drops	300 IR	Phl p5: 2.6 mg (cumulative dose)	40,700 IR	7 months
Pradalier, 1999 [19]	Rhino-conjunctivitis and asthma	5 grasses	Pre- and coseasonal	Children Adults	Drops + tablets	100 IR	Phl p5: 8.5 µg/ml Phl p5: 0.935 mg (cumulative dose)	11,000 IR	4 months
Smith, 2004 [20]	Rhinitis	5 grasses	Pre- and coseasonal	Adults	Drops + tablets	300 IR	Lol p1: 24 µg/ml Dac g5: 14 µg/ml	26,100 IR (annual)	Feb to July for 1 or 2 years
Ott 2009 [21]	Rhino-conjunctivitis	5 grasses	Coseasonal	Children Adults	Drops	300 IR	Phl p5: 21 µg/ml	66,000 IR (total) 22,000 IR (per season)	2.5 to 3 months for 3 years in a row

1. Sabbah A *et al.* A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollens extract. Allergy 1994;49:309-13.[12]

First efficacy and safety study in seasonal allergic rhinitis

The study by Sabbah *et al.*[12] was the first double-blind, placebo-controlled study conducted with Staloral®. This pilot study was aimed at assessing the efficacy and safety of Staloral® in seasonal rhinoconjunctivitis induced by grass pollen.

Design

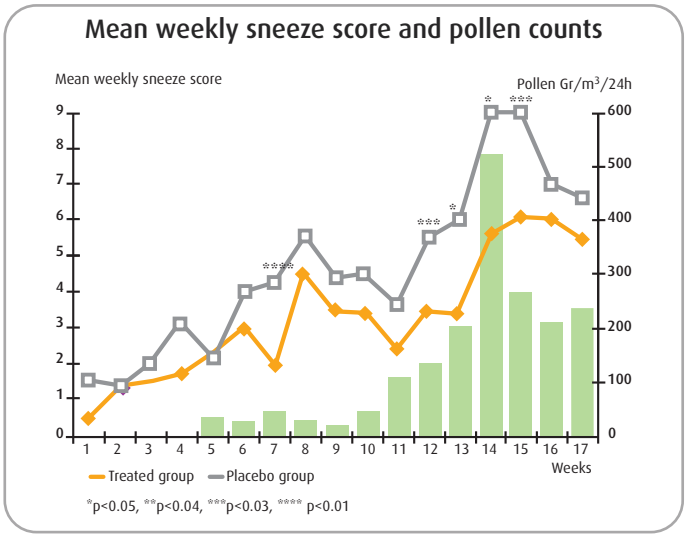
- Randomized, double-blind, placebo-controlled study
- Patients 13 to 51 years old with seasonal rhinoconjunctivitis induced by grass pollen
- **Treatment:** Staloral® 100 IR Grasses: n=29, Placebo: n=29

Protocol

- **Pre- and coseasonal**
- **Duration :** 4 months
- A prolonged titration phase was deliberately chosen because of the absence of data on the safety of this new route of administration at that time.

RESULTS: EFFICACY

- **Significant decrease in the symptoms of rhinitis and conjunctivitis ($p < 0.05$ to $p < 0.01$)**
  - **↘ Runny nose**
  - **↘ Sneezing**
  - **↘ Eye watering**
  - **↘ Red eyes**



- **Significant reduction in drug consumption ($p<0.01$) (cromoglicate, betamethasone and dexchlorpheniramine)**

RESULTS: SAFETY

- **Only minor adverse reactions were reported with Staloral® and placebo, with similar incidence in both groups.**

NOTE This pilot study was the first to generate evidence that Staloral® is effective and safe in the treatment of seasonal rhinitis and conjunctivitis due to grass pollen.

2. Clavel R *et al.* Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. Allergy 1998;53:493-8.[18]

First high-dose study in seasonal allergic rhinitis with or without asthma

The objective of the study by Clavel *et al.*[18] was to assess the efficacy and safety of Staloral® in seasonal rhinoconjunctivitis induced by grass pollen.

Design

- Randomized, double-blind, placebo-controlled study
- Patients 8 to 55 years old with rhinoconjunctivitis (with or without asthma) induced by grass pollen
- **Treatment:** Staloral® 300 IR Grasses: n=62, Placebo: n=58

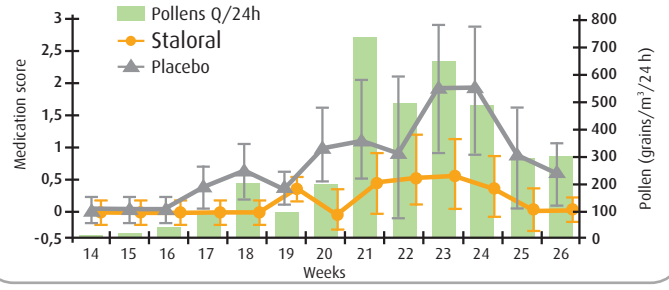
Protocol

- **Pre- and coseasonal**
- **Duration :** 7 months

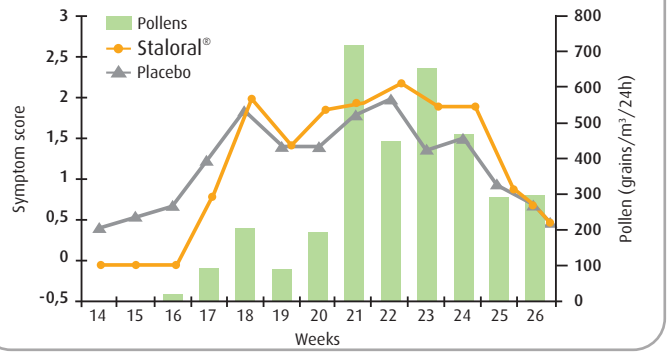
RESULTS: EFFICACY

- **Significant reduction in drug consumption (betamethasone) during the pollen season (p<0.02) and reduction in the frequency of asthma attacks (p<0.02)**
- **Nasal and conjunctival symptoms did not differ significantly between both groups**

Medication scores (median ± 95% CI) and pollen counts



Rhinitis scores (median ± 95% CI) and pollen counts



- The AUC of medication score was significantly (p<0.01) lower in the SLIT group.
- Significant increase in the median post seasonal timothy-specific level of IgG4 antibodies in the Staloral® group *vs.* the placebo group (p<0.03).

RESULTS: SAFETY

- **No severe, systemic reactions were reported with Staloral®,** only minor adverse reactions with the same frequency in the Staloral® and placebo groups.

NOTE

- **The study by Clavel *et al.*[18] brought new ground by demonstrating the efficacy and safety of a high-dose Staloral® protocol (300 IR)**
- **The demonstration of the efficacy and safety of Staloral® at doses ten-fold higher than those administered in the Sabbah study[12] confirmed the validity of the high-dose protocol**

3. Pradalier A *et al.* Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. Allergy 1999;54:819-28.[19]

First study with Staloral® drops and tablets

Pradalier *et al.*[19] investigated the efficacy and safety of Staloral® in adults and children suffering from rhinoconjunctivitis (with or without asthma) induced by grass pollen.

Design

- Randomized, double-blind, placebo-controlled study
- Patients 7 to 58 years old with rhinoconjunctivitis (with or without allergic asthma) induced by grass pollen
- **Treatment:** Staloral® 100 IR 5 Grasses and 5 Grasses tablet: n=62, Placebo: n=61

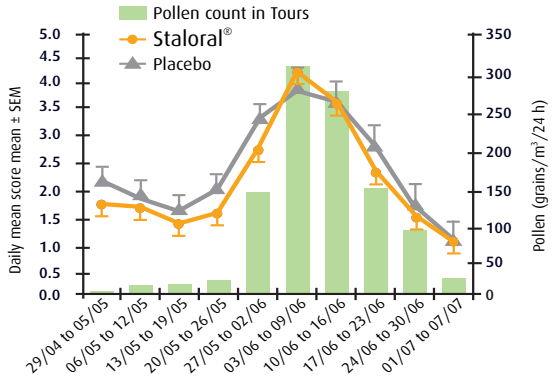
Protocol

- **Pre- and coseasonal**
- **Duration :** 4 months
- In the maintenance phase, the dose was deliberately limited to 100 IR per day because this was the first trial involving the tablet form (During titration: drops were used).

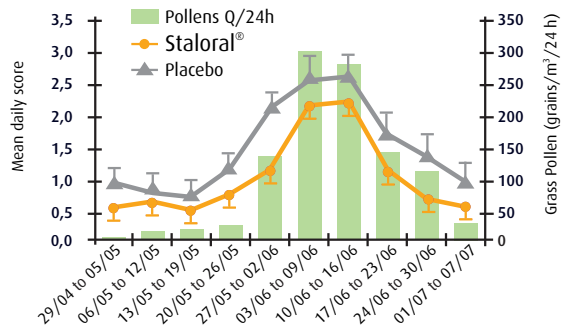
RESULTS: EFFICACY

- Non-significant improvement in the symptoms of rhinitis, but a **significant reduction in symptoms of conjunctivitis (p<0.05)**

Total rhinitis symptom score (mean ± SEM) in relation to pollen counts

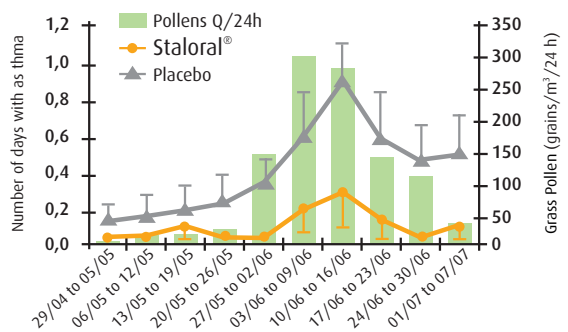


Total conjunctivitis symptom score (mean ± SEM, P<0.05) in relation to pollen counts



- **Significant reduction in the eye redness score (p<0.05) and eye watering score (p=0.05)**
- **Significantly more patients treated with Staloral® were free of asthma symptoms (p<0.005)** for a significantly higher number of days (p<0.02)
- **Significant reduction in the consumption of inhaled salbutamol (p<0.01)** and a trend towards the reduction in prednisolone consumption (p=0.059)

Number of days with asthma (mean ± SEM, P<0.02) in relation to pollen counts



RESULTS: SAFETY

- Adverse reactions involving the respiratory system (sneezing, rhinitis and dyspnea) were minor and short-lived (lasting minutes or at most one hour) in the great majority of patients
- Most adverse reactions were minor mouth

NOTE

The study by Pradalier *et al.* was the first to use drops and tablets and to demonstrate that Staloral®:
- **Improves symptoms of grass pollen allergic conjunctivitis**
- **Prevents asthma symptoms**
- **Is safe and well-tolerated**

4. Smith H *et al.* Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. J Allergy Clin Immunol 2004;114:831-7.[20]

First study conducted exclusively in patients with severe rhinitis

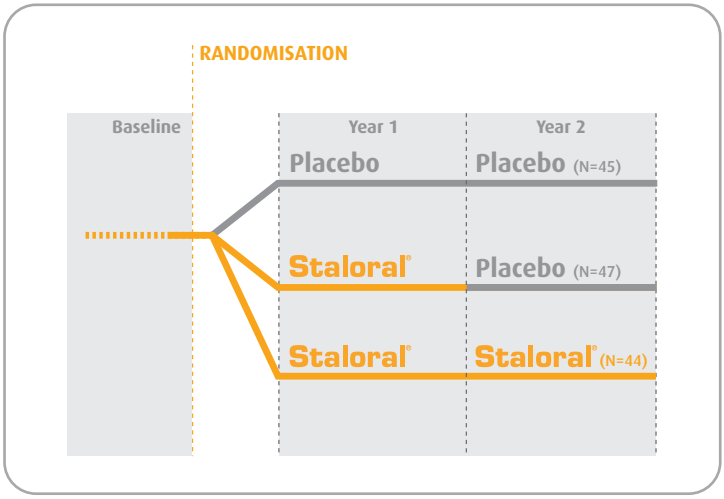
The study by Smith *et al.*[20] investigated the efficacy and safety of Staloral® in adults suffering from severe seasonal allergic rhinitis and asthma induced by grass pollen in a general practice setting in the UK.

Design

- Randomized, double-blind, placebo-controlled study
- Patients 18 to 58 years old with grass pollen allergic rhinitis who were uncontrolled with symptomatic medications
- **Treatment:** Staloral® 300 IR Grasses *vs.* Placebo

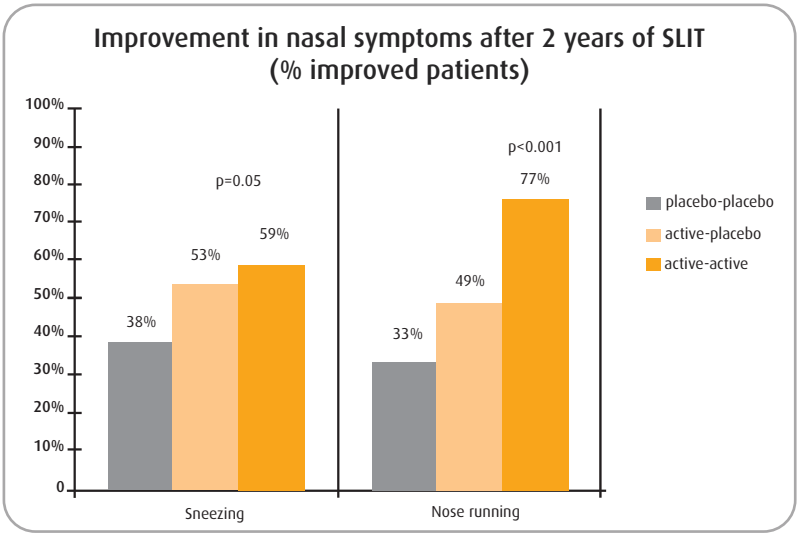
Protocol

- **Pre- and coseasonal**
- **Duration of study :**
  24 months (treatment from February to end of July)



RESULTS: EFFICACY

- **After 2 years of Staloral® treatment, patients experienced significant improvements in nasal symptoms**
- Patients were 6.8 times more likely to have reduced runny scores ($p<0.001$) and 2.4 times more likely to have reduced sneezing ($p<0.05$) compared with placebo
- Benefits for nasal blockage were identified only at the height of the season
  - Improvement in nose blocking after 2 years of SLIT: placebo-placebo: 40%; active-placebo: 57%; active-active: 52%
- Rescue medication use was reduced in all groups, with greater reductions in active groups than the placebo group



RESULTS: SAFETY

- Most adverse reactions with Staloral® were mild and easily tolerated
- In the active treatment group, most adverse reactions (86%) occured during the titration phase, and only 14% of events occured during maintenance
- For both groups, fewer adverse reactions occurred in year 2

NOTE

- **2 years of high-dose grass pollen SLIT confers clinical benefit in patients with severe seasonal allergic rhinitis.**
- **At least 2 years of treatment are required to show a benefit.**

5. Ott H *et al.* Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. Allergy 2009;64:179-86.[21]

First ultra-rush coseasonal protocol for 3 consecutive seasons

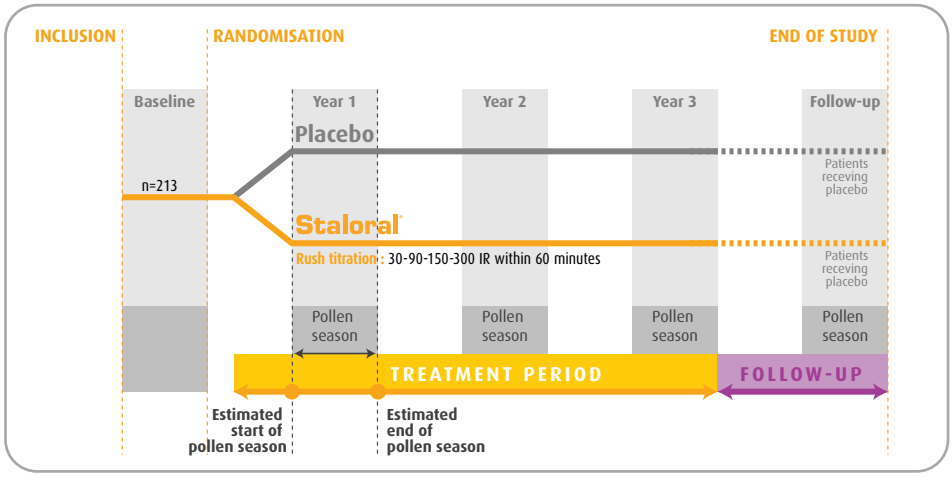
In the ECRIT study, Ott *et al.*[21] evaluated the efficacy, safety and sustained effect of a coseasonal regimen with Staloral® in patients with grass pollen allergic rhinoconjunctivitis over 3 consecutive pollen seasons and one follow-up pollen season post treatment-end.

Design

- Randomized, double-blind, placebo-controlled study
- Patients 8 to 65 years old with grass pollen allergic rhinoconjunctivitis
- **Treatment:** Staloral® 300 IR 5 Grasses: n=99, Placebo: n=46

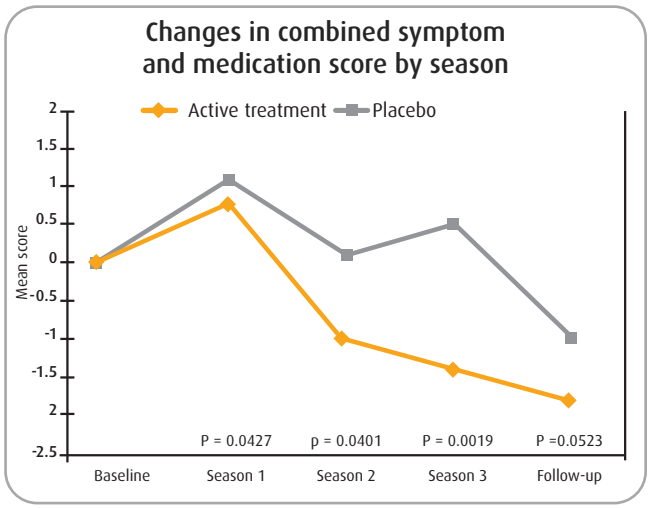
Protocol

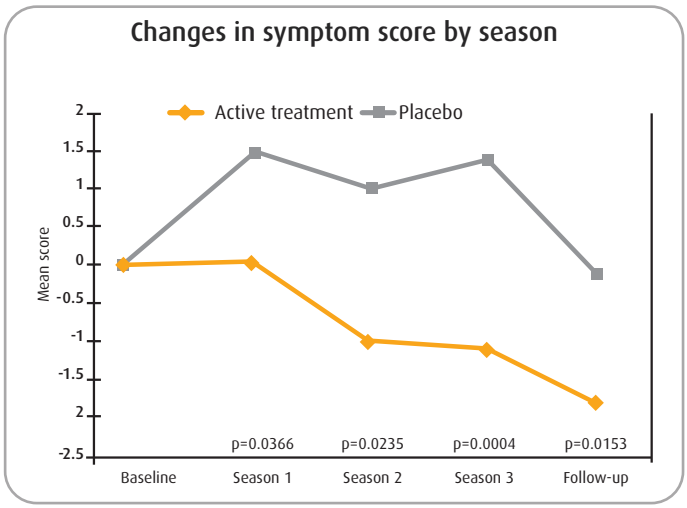
- **Coseasonal**
- **Duration of treatment:** 3 pollen seasons



RESULTS: EFFICACY

- **Significant and progressive improvement in the combined symptom and medication score**
- Sustained effect in the 4th year (without significance) showing a trend towards carry-over effect
- **Significant and progressive improvement in symptom score alone, sustained in the post-treatment year**





- Increases in specific IgG4 observed in the first season were sustained with Staloral® *vs.* placebo throughout treatment (p=0.0001)

RESULTS: SAFETY

- Ultra-rush and daily SLIT with Staloral® were well-tolerated. No serious systemic or anaphylactic reactions were reported.

NOTE

The ECRIT study confirmed that coseasonal SLIT with ultra-rush titration is effective and well-tolerated from the first treatment season onwards and results are indicative of a carry-over effect

Efficacy in weed pollen allergy

The following 3 studies have been conducted with weed pollen allergens using a pre- and coseasonal protocol.

Authors/ year of publication	Pathologies	Allergens	Protocol	Patients	Staloral®				
					Sublingual form	Maintenance concentration	Major allergen dose	Cumulative dosage	Duration of treatment
La Rosa, 1999 (22)	Rhino-conjunctivitis and asthma	Wall pellitory pollen	Pre- and coseasonal	Children	Drops	300 IR	Par J 1: 52.5 mg over 2 years	150,000 IR over 2 years	24 months
André, 2003 (23)	Rhino-conjunctivitis and asthma	Ragweed pollen	Pre- and coseasonal	Children Adults	Drops + tablets	300 IR	Amb a1 : 160 µg/ 100 IR	23,000 IR	7 months
Bowen, 2004 (24)	Rhino-conjunctivitis and asthma	Ragweed pollen	Pre- and coseasonal	Children Adults	Drops	300 IR	Amb a1: 116 µg/ 100 IR 314 µg/ 300 IR	17,450 IR	2 1/2 months

1. La Rosa M *et al.* Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 1999; 104(2 Pt 1):425-32.[22]

First study conducted exclusively in children with rhinoconjunctivitis to wall pellitory pollen

La Rosa *et al.*[22] conducted the first study assessing the efficacy of Staloral® 300 IR in children with rhinoconjunctivitis (with or without asthma) induced by wall pellitory pollen.

Design

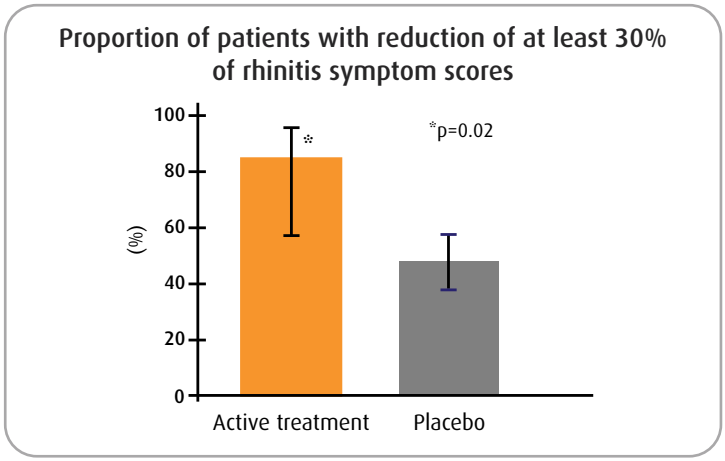
- Randomized, double-blind, placebo-controlled study
- Children 6 to 14 years old with rhinoconjunctivitis (with or without moderate asthma) induced by the pollen of *Parietaria judaica*
- **Treatment:** Staloral® 300 IR wall pellitory: n=20, Placebo: n=21

Protocol

- **Duration :** 2 pollen seasons (24 months)

RESULTS: EFFICACY

- **Significant improvement of rhinitis symptoms during the second season (p=0.02)**
  - 87.5% of children treated with Staloral® experienced a reduction of at least 30% in the symptom score



- **Staloral® provided a decreased reactivity to allergen:**
  - Significant increase in the reactivity threshold in conjunctival challenge test after two years of treatment (p = 0.02)
  - Significant reduction in skin reactivity after two years of treatment (p = 0.002)
  - Significant increase in the level of specific IgG4 (p = 0.02)
- **No difference between Staloral® and placebo in the medication score**

RESULTS: SAFETY

- Staloral® 300 IR was well-tolerated, as all adverse reactions were minor and easily managed

NOTE

The study by La Rosa *et al.* demonstrated that in children with rhinoconjunctivitis induced by wall pellitory pollen, Staloral®:
- **Reduces symptoms of rhinitis, skin reactivity and conjunctival reactivity**
- **Has a good safety profile**

2. André C *et al.* A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. Int Arch Allergy Immunol 2003;131:111-8.[23]

First efficacy and safety study in ragweed pollen rhinoconjunctivitis

Staloral® and ragweed extract tablets were demonstrated to be effective against rhinoconjunctivitis induced by ragweed pollen in a study by André *et al.*[23]

Design

- Randomized, double-blind, placebo-controlled study
- Adults and children 8 to 62 years old with rhinoconjunctivitis induced by ragweed pollen (with or without moderate asthma)
- **Treatment:** Staloral® 300 IR Ragweed and ragweed extract tablets: n=55, Placebo: n=55

Protocol

- **Duration:** 7 months
- 54.2% of patients in the treatment group reached a maintenance dose of 3 tablets 3 times a week, i.e. 900 IR/week (During escalation phase: Staloral® drops were used)

RESULTS: EFFICACY

- **Significant reduction in the global symptom scores for both rhinitis and conjunctivitis (p=0.05 and p=0.04, respectively)**

Efficacy parameters (daily mean over the pollen period) (n=48)			
Symptom	**Active treatment**	**Placebo**	**p**
Total rhinitis symptom score Mean ± SD Range	**2.27 ± 1.42** **0-5.52**	**3.09 ± 2.14** **0-10.05**	**0.05**
Total conjunctivitis symptom score Mean ± SD Range	**1.11 ± 0.91** **0-3.43**	**1.69 ± 1.48** **0-7.52**	**0.04**
Total medication score Mean ± SD Range	**2.41 ± 3.09** **0-12.00**	**2.00 ± 4.24** **2.01-14.78**	**0.09**

- **Significant reduction in corticosteroid consumption (flunisolide and prednisolone) (p=0.05)**
- An analysis of sub-populations based on the size of the maintenance dose showed that efficacy results were significantly better in patients administered a high dose of ragweed extract.
- According to the perceptions of both patients and investigators, Staloral® and ragweed extract tablets were significantly more effective than placebo at all doses throughout the pollen season (p=0.004 and p=0.005, respectively).

RESULTS: SAFETY

- No serious adverse reactions occurred in the course of the study
- Most adverse reactions were mild or moderate and mainly confined to the titration phase

NOTE

- **The results of the study by André *et al.* confirm that Staloral® and ragweed extract tablets are effective and safe (in different galenic forms: drops and tablets) and highlight the dose-dependent efficacy**

3. Bowen T *et al.* Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. Ann Allergy Asthma Immunol 2004; 93:425-30.[24]

First Canadian SLIT study

Bowen *et al.*[24] conducted the first Canadian trial with sublingual immunotherapy to evaluate the efficacy and safety of high dose Staloral® in patients with allergic rhinoconjunctivitis induced by ragweed pollen.

Design

- Randomized, double-blind, placebo-controlled study
- Adults and children 14 to 58 years old with rhinoconjunctivitis and mild to moderate asthma induced by ragweed pollen
- **Treatment:** Staloral® 300 IR Ragweed: n=37, Placebo: n=39

Protocol

- **Duration :** 2 ½ months

RESULTS: EFFICACY

- **Significant reduction in the rhinitis symptoms score:**
  - Sneezing score ($p<0.04$)
  - Nasal pruritus score ($p<0.04$)
- No significant difference between the 2 groups in medication and conjunctivitis scores

Rhinitis, Conjunctivitis, and Medication Scores during the Ragweed Pollen Peak (mean±SD)

Symptom	Placebo group	Treatment group	P value
Total rhinitis score	5.03 ± 2.54	3.95 ± 2.45	0.09
Total conjunctivitis score	2.38 ± 1.92	1.96 ± 1.90	0.35
Total medication score	1.26 ± 1.24	1.05 ± 1.60	0.36

- Significant increase in the levels of IgG4 ($p<0.001$)

RESULTS: SAFETY

- No serious adverse events or systemic reactions were reported with Staloral®

NOTE

- **The study by Bowen *et al.* is the first Canadian double blind, placebo-controlled trial published about sublingual immunotherapy**
- **This study showed that Staloral® given shortly before the pollen season is effective and safe in the treatment of seasonal allergic rhinoconjunctivitis to ragweed**

Efficacy in tree pollen allergy

Studies have been conducted to investigate the use of Staloral® in the treatment of allergies to various tree pollens: olive, cypress and birch.

Authors/ year of publication	Pathologies	Allergens	Protocol	Patients	Staloral®				
					Sublingual form	Major allergen dose	Maintenance concentration	Cumulative dosage	Duration of Treatment
Vourdas 1998 [25]	Rhinoconjunctivitis and asthma	Olive tree	Pre- and coseasonal	Children	Drops	300 IR	Ole e1: 13.5 µg/ml of 100 IR	60,000 IR over 2 years	6 months each year, over 2 years
Khinchi 2004 [26]	Rhinoconjunctivitis and asthma	Birch tree	Pre- and coseasonal	Adults	Drops	300 IR	Bet v1: 49.2 µg (SLIT) 3.28 µg (SCIT)	11,182 µg Bet v1 over 2 years (SLIT) 51 µg Bet v1 over 2 years (SCIT)	24 months
Vervloet 2007 [27]	Rhinoconjunctivitis and asthma	Cypress tree	Coseasonal	Adults	Drops	300 IR	Jun a1: 76 µg/ml of 100 IR	n.a.	120 days

1. Vourdas D *et al.* Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollens extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. Allergy 1998;53:662-72.[25]

First study in allergic rhinoconjunctivitis combined with asthma induced by olive pollen in children

Vourdas *et al.*[25] conducted the first study in allergic rhinoconjunctivitis combined with asthma induced by olive pollen in children. This study was carried out in Greece.

Design

- Randomized, double-blind, placebo-controlled study
- Children 7 to 17 years old with rhinoconjunctivitis combined with moderate asthma, induced by olive pollen
- **Treatment:** Staloral® 300 IR Olive : n=34, Placebo: n=32

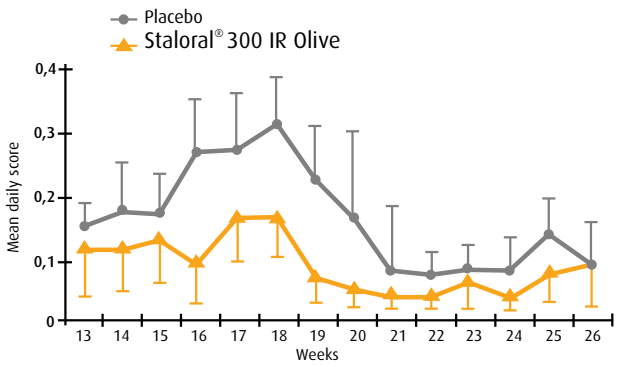
Protocol

- **Pre- and coseasonal** (from January to July)
- **Duration :** 2 pollen seasons (24 months)

RESULTS: EFFICACY

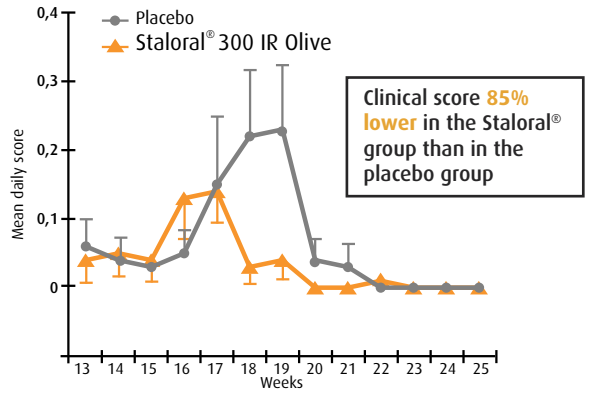
- **Significantly lower score of dyspnea (49%) in the Staloral® group than in the placebo group during the first year (p<0.04), sustained in the second year (p<0.03)**

Evaluation of the dyspnea score (first year)



- **Significant reduction in the symptoms of conjunctivitis during the pollen peak in the second year (p<0.05)**

Evaluation of the score of redness of the eyes (second year)



- Significant reduction in skin reactivity to cutaneous test (p<0.03)
- No significant difference between the two groups in the medication score, but the difference in oral corticosteroids use approached significance in favor of Staloral® (p=0.06)

RESULTS: SAFETY

- Staloral® was well-tolerated, with only few, minor adverse reactions

NOTE

The study by Vourdas *et al.* demonstrated the efficacy and safety of Staloral® in children allergic to olive pollen.
In this study, Staloral®:
- **Significantly improved dyspnea, conjunctivitis and skin reactivity**
- **Showed a good tolerability profile**

2. Khinchi MS *et al.* Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. Allergy 2004; 59:45-53.[26]

First study to compare SLIT with SCIT

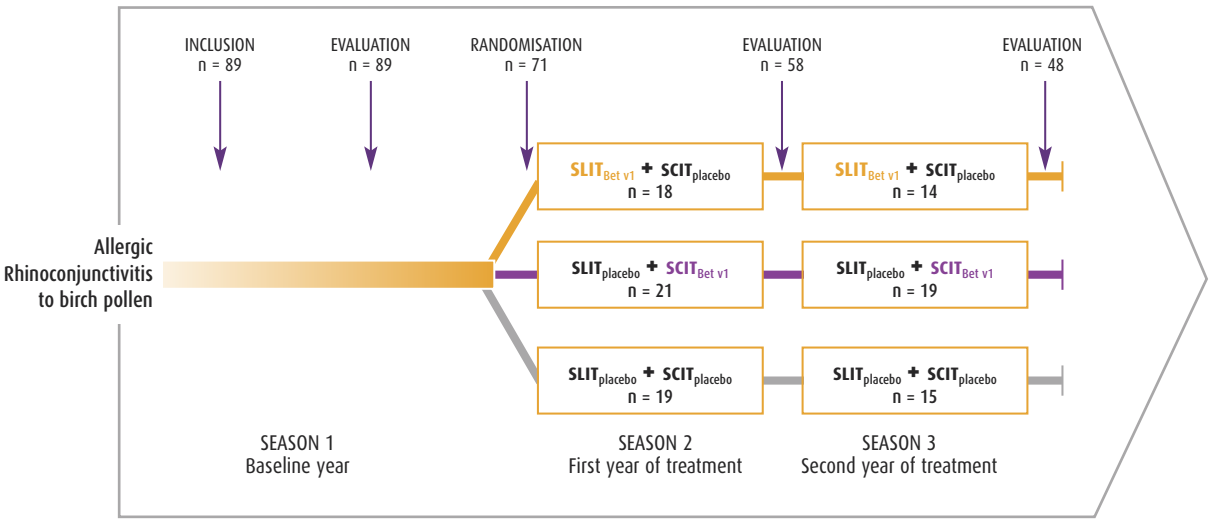
Khinchi *et al.*[26] conducted a study in patients with birch pollen allergy where high-dose Staloral® was compared to both placebo and subcutaneous immunotherapy.

Design

- Randomized, placebo-controlled, double-blind, double-dummy.
- 89 Adults from 20 to 58 years old with rhinoconjunctivitis symptoms induced by birch pollen
- **Treatment:** Staloral® 300 IR Birch, SCIT Birch, Placebo

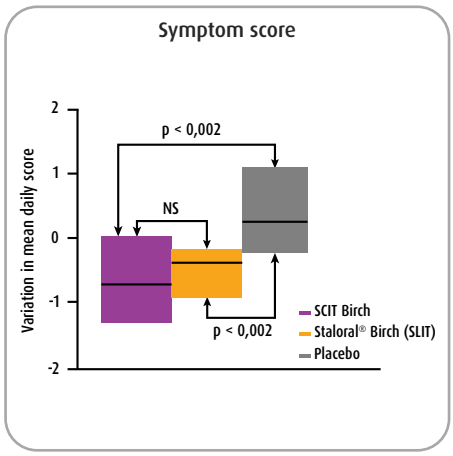
Protocol (SLIT)

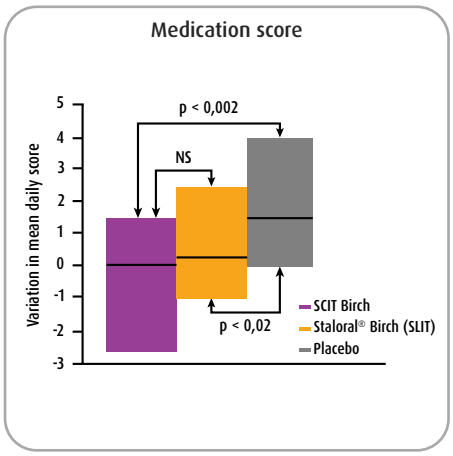
- **Pre- and coseasonal**
- **Duration**: 24 months

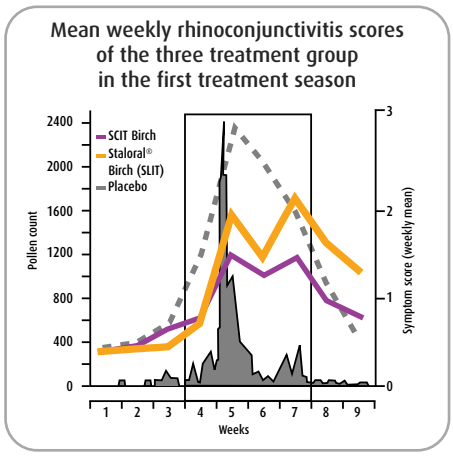


RESULTS: EFFICACY

- **Significant reduction of rhinoconjunctivitis symptoms**
  - Significant improvement in the median symptom score compared with the baseline value (-0.36 points, p<0.002)
  - Significant improvement in the symptom score by a factor 0.78 (p<0.01)
- **Significant reduction in drug consumption**
  - Slight increase in median medication score compared with the baseline value (0.29 points, p<0.02)
  - Improvement in the medication score by a factor 1.03 (p<0.05)
- Non-significant difference in efficacy between Staloral® (SLIT) and SCIT
- Due to paucity of pollen in the second treatment season all patients experienced few symptoms and used limited medications. Consequently, the second season is not included in the evaluation of efficacy







RESULTS: SAFETY

- SLIT treatment mainly resulted in local mild adverse reactions (itching or mild oedema in the mouth and/or throat)
- Systemic side-effects grade 2 (mostly rhinoconjunctivitis) occurred in all 3 groups
- 5 cases of systemic reaction grade 3 and 1 grade 4 were observed in the SCIT group and 1 grade 3 in placebo group. No grade 3 and 4 reactions occurred in the SLIT group

NOTE

- **The study by Khinchi *et al.* showed that Staloral® is effective on symptoms and drug consumption in allergic rhinoconjunctivitis due to birch pollen**
- **This study demonstrated that Staloral® is as effective as SCIT, but better tolerated**
- **The authors concluded that, due to its advantageous safety profile, SLIT may be favored over SCIT**

3. Vervloet D *et al.* Safety and efficacy of *Juniperus ashei* sublingual-swallow ultra-rush pollen immunotherapy in cypress rhinoconjunctivitis. Int Arch Allergy Immunol 2007;142:239-46.[27]

First efficacy and safety study with a coseasonal ultra-rush schedule in tree pollen rhinoconjunctivitis

The objective of the study by Vervloet *et al.*[27] was to evaluate for the first time the efficacy and safety of Staloral® when initiated at the beginning of tree pollen allergy responsible for rhinoconjunctivitis with an ultra-rush titration.
One characteristic of this study is that it was done with a purified, standardized cypress (*Juniperus ashei*) extract.

Design

- Randomized, double-blind, placebo-controlled study
- 76 patients 19 to 60 years old with rhinoconjunctivitis (with or without asthma) to cypress pollen
- **Treatment:** Staloral® 300 IR *Juniperus ashei:* n=38, Placebo: n=38

Protocol

- **Coseasonal**
- Titration was done in 90 min
- **Duration :** 120 days

RESULTS: EFFICACY

- **Staloral® resulted in a marked and significant reduction in medication score by about 50% (p<0.03) and the nasal steroid consumption by about 75% at the peak of the tree pollen season (the first 3 weeks after the ultra-rush protocol).**
- As in a previous study on grass pollen rhinitis, the efficacy of SLIT is demonstrated by the medication score, which was considerably and significantly decreased in terms of both the global score and nasal steroid consumption.

Rhinitis, conjunctivitis and medication scores during pollen peak (mean ± SD with median values in parentheses)

Symptom score	Staloral® *Juniperus*	Placebo	P value
Rhinitis total score (0-12) 2001 2002	3.06 ± 1.69 (2.88) 2.68 ± 1.64 (2.32)	2.58 ± 0.91 (2.43) 2.44 ± 2.06 (2.25)	0.43 NS* 0.68 NS*
Conjunctivitis total score (0-9) 2001 2002	1.58 ± 1.58 (1.53) 1.14 ± 1.14 (0.84)	0.89 ± 0.76 (1.11) 1.24 ± 1.40 (0.57)	0.23 NS** 0.95 NS**
Total medication score 2001 2002	4.76 ± 10.15 (1.72) 3.39 ± 3.94 (2.00)	5.09 ± 2.86 (4.35) 4.71 ± 5.00 (3.50)	0.04** 0.03**

RESULTS: SAFETY

- An ultra-rush protocol based on high-dose Staloral® is safe:
  - The only adverse reactions reported were minor and local (notably pruritus)
  - No serious adverse reactions occurred

* Student's test.
** Wilcoxon 2 sample test.
NS: Not Significant.

NOTE

- **The study by Vervloet *et al.* showed that Staloral® administered in an ultra-rush schedule to patients with tree pollen rhinoconjunctivitis reduces the medication score and is well-tolerated**
- **The authors concluded that SLIT can be started in patients who present shortly before or even at the beginning of a pollen season, while standard practice in this situation is to defer immunotherapy until the following year**

IV

Staloral®

Sublingual solution of allergen extracts for immunotherapy

Clinical Evidence in Allergic Rhinitis and Asthma Due to Mites

Five years after Staloral® was demonstrated to be effective in the treatment of hay fever, STALLERGENES undertook to investigate its potential in a more delicate allergenic model, namely allergy to mites. It is more difficult to design and conduct double-blind trials with this form of allergy and relevant parameters are less easy to analyze.

Staloral® has been studied in the treatment of various pathologies resulting from allergy to mites.

Authors/ year of publication	Pathologies	Patients	Staloral®				
			Sublingual form	Maintenance concentration	Major allergen dose	Cumulative dosage	Duration of treatment
Bousquet 1999 [28]	Asthma	Children Adults	Drops	300 IR	Der p 1: 4.2 mg (cumulative dose) Der f 1: 7.3 mg (cumulative dose)	104,000 IR	25 months
Guez 2000[29]	Rhinoconjunctivitis and asthma	Children Adults	Drops	300 IR	Der p 1: 2.2 mg (cumulative dose) Der f 1: 1.7 mg (cumulative dose)	90,000 IR	24 months
Mortemousque 2003[30]	Conjunctivitis	Children Adults	Drops	300 IR	Der p 1: 2.2 mg (cumulative dose) Der f 1: 1.7 mg (cumulative dose)	90,000 IR	24 months
Tonnel 2004[31]	Rhinitis and asthma	Children Adults	Drops + tablets	100 IR	Der p 1: 1.28 mg (mean cumulative dose) Der f 1: 1.47 mg (mean cumulative dose)	47,500 IR	24 months

1. Bousquet J *et al.* Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. Allergy 1999;54:249-60.[28]

First Staloral® study in the treatment of asthma due to mite allergy

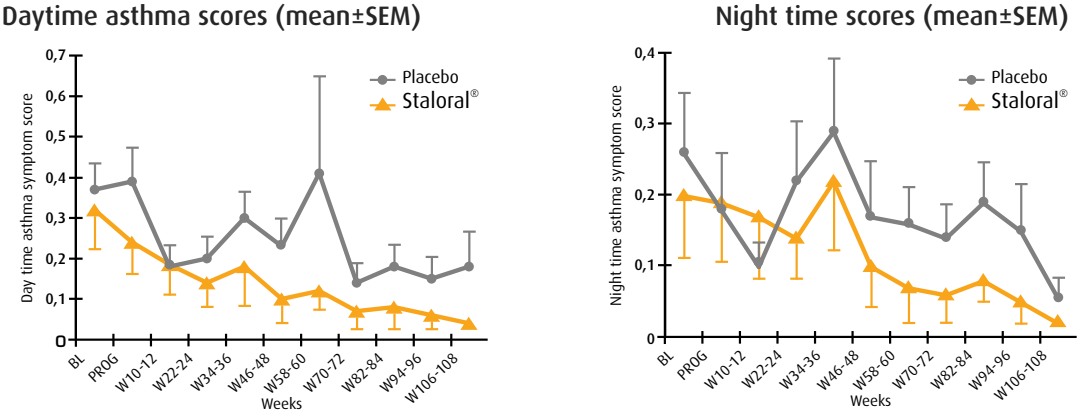
Design

- Randomized, double-blind, placebo-controlled study
- Adults and children 7 to 42 years old with at least on year history of confirmed moderate to moderately severe asthma due to house-dust mites (*D. pteronyssinus* or *D. farinae*)
- **Treatment:** StaloraL® 300 IR Mites: n=42, Placebo: n=43

Protocol

- **Perennial**
- **Duration:** 25 months

RESULTS: EFFICACY



Staloral® group: n=23 at week 108 (25 months); placebo group: n=26 at week 108 (25 months) - BL: baseline; PROG: progression; W: week

Changes in outcome measures from baseline to last diary card or last follow-up visit (end point of SLIT)

Means ± SD	Staloral® Mites			Placebo		
	Baseline	Last diary card	P	Baseline	Last diary card	P
Morning PEFR* (l/min)	404.1 ± 134.1	426.3 ± 136.7	0.01	415.7 ± 100.6	424.3 ± 114.5	NS
Evening PEFR* (l/min)	414.1 ± 137.3	433.2 ± 139.1	0.03	429.6 ± 100.5	437.7 ± 117.4	NS
Use of inhaled ß2-agonist (µg salbutamol/day)	181 ± 192	122 ± 235	0.01	168 ± 172	79 ± 136	0.02
Use of inhalated corticosteroids (µg beclomethasone/day)	555 ± 455	348 ± 410	0.01	495 ± 430	308 ± 408	0.02

* PEFR : Peak Expiratory Flow Rate

- Significant improvement in patients' quality of life:
  - The changes from baseline to end point showed significant differences in favour of SLIT group compared with the placebo for social functioning (+12.2 and -2.1, respectively; p=0.04, Wilcoxon T test) and bodily pain (+20.0 and -4.2, respectively; p=0.01).
- Significant increase in the levels of IgE and IgG4

RESULTS: SAFETY

- Good safety profile: the overall incidence of adverse events was similar in the SLIT and placebo groups

NOTE

- This was the first Staloral® study in patients with allergic asthma. The results have demonstrated the good tolerability of Staloral® in asthma and the favourable effects of Staloral® on both symptoms and medication use, although the difference versus placebo was not significant. This was a pilot study in patients with allergic asthma

2. Guez S *et al.* House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. Allergy 2000;55:369-75.[29]

Guez *et al.*[29] conducted a study in children and adults suffering from rhinitis induced by mites.

Design

- Randomized, placebo-controlled, double-blind study
- Adults and children 6 to 51 years old with a history of confirmed perennial rhinitis with or without asthma due to house-dust mite *(D. pteronyssinus and D. farinae)*.
- **Treatment:** Staloral® 300 IR Mites: n=36, Placebo: n=36

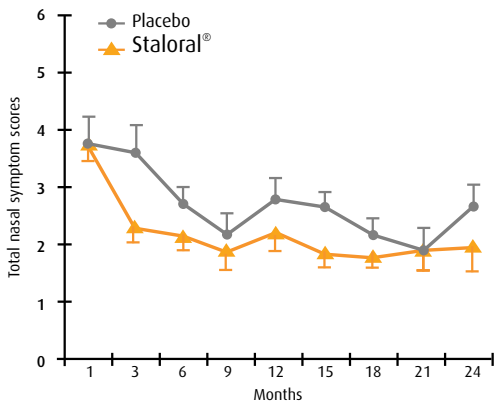
Protocol

- **Perennial**
- **Duration:** 24 months

RESULTS: EFFICACY

- **Total symptom and medication scores decreased significantly after 12 and 24 months (p<0.05) in both groups,** but no significant difference was observed between the active and placebo groups

Mean (±SEM) total nasal symptoms scores in active treatment (n = 24) and placebo (n=18) groups of patients who completed trial



Cumulative symptoms-medication score (mean weekly scores ± SD)		
Symptoms-medication score	Active (n=36)	Placebo (n=36)
1 month	13.0 ± 11.5	14.3 ± 11.6
12 months	7.2 ± 1.0*	9.5 ± 6.8*
24 months	6.4 ± 6.3**	9.2 ± 8.0**

* Level of significance for intragroup difference between 1 month and 12 months, p<0.01

** Level of significance for intragroup between 1 month and 24 months, p<0.01

- Significant increased level of specific IgE in the active group after 12 and 24 months

RESULTS: SAFETY

- No severe adverse effects were reported

NOTE

The study by Guez *et al.* showed that SLIT in rhinitis due to house-dust mite was safe, but there was a lack of consistent clinical benefit compared to placebo probably due to the impact of the allergen avoidance measures that lowered the allergen bad

In the course of the study, patients were encouraged to implement strict allergen avoidance measures, which they did so assiduously that neither group experienced many symptoms

3. Mortemousque B *et al.* House-dust mite sublingual-swallow immunotherapy in perennial conjunctivitis: a double-blind, placebo-controlled study. Clin Exp Allergy 2003;33:464-9.[30]

Mortemousque *et al.*[30] conducted a study with high-dose Staloral® in perennial conjunctivitis due to mites.

Design

- Randomized, double-blind, placebo-controlled study
- Adults and children 6-60 years old with a history of confirmed perennial conjunctivitis due to house-dust mite (*D. pteronyssinus and D. farinae*)
- **Treatment:** Staloral® 300 IR Mites: n=30 (26 of whom completed the study), Placebo: n=30 (19 of whom completed the study)

Protocol

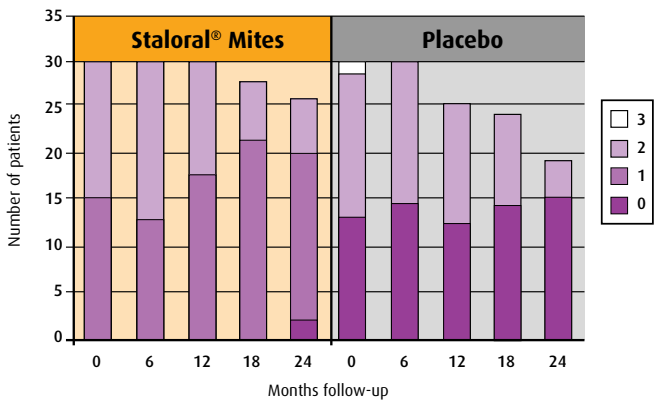
- **Perennial**
- **Duration:** 24 months

RESULTS: EFFICACY

- This study showed that Staloral®:
  - Significantly increased the allergenic threshold necessary to induce a positive reaction to conjunctival challenge testing (p=0.04)
  - Significantly improved the conjunctivitis symptom score following conjunctival challenge testing at 18 and 24 months (p<0.01 and p<0.0007, respectively)

- The number of dropouts was significantly greater in the placebo group than in the Staloral® group (11 patients and 4 patients, respectively; p<0.05)
  - 6.6% of patients dropped out because of insufficient efficacy in the Staloral® group compared to 26.6% of patients in the placebo group (p< 0.05)

Clinical scores at each study time/number of patients



Clinical score: 0, no symptoms since the last consultation; **1,** mild symptoms; **2,** moderate symptoms; **3,** severe symptoms

RESULTS: SAFETY

- No general adverse reactions were observed

NOTE

The study by Mortemousque *et al.* showed that high-dose Staloral® can be indicated in the treatment of perennial conjunctivitis due to mites

4. Tonnel AB *et al.* Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. Allergy 2004; 59:491-7.[31]

Tonnel *et al.*[31] assessed the efficacy of Staloral® drop formulation during the titration phase and tablet formulation during the maintenance phase in patients' suffering from rhinitis induced by mites.

Design

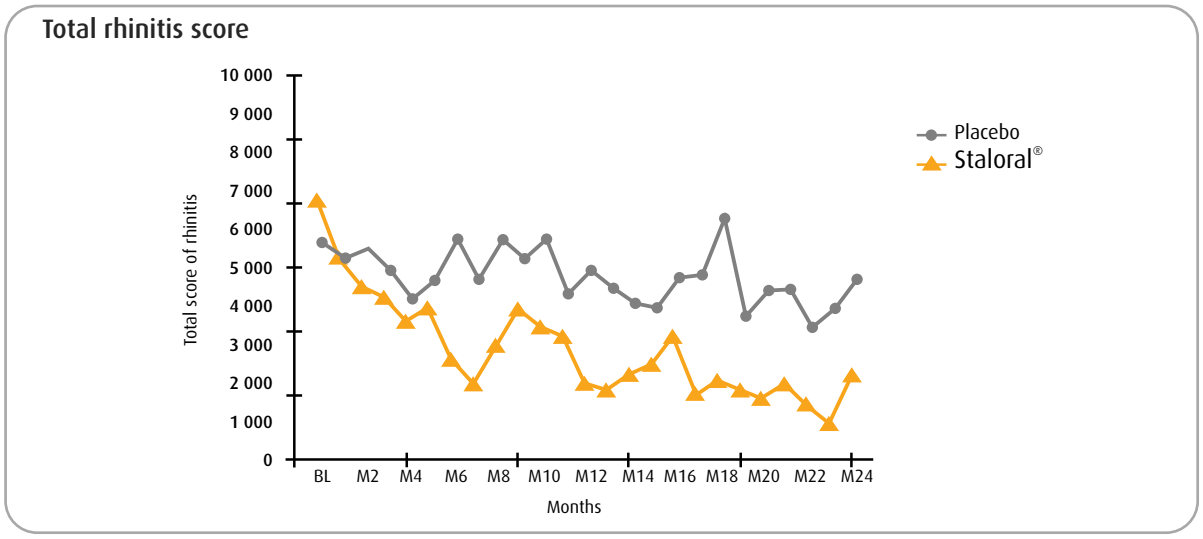
- Randomized, double-blind, placebo-controlled study
- Patients 9 to 38 years old with allergic rhinitis with or without moderate asthma (GINA 2) proven to be hypersensitive to mites (*D. pteronyssinus or D. farinae*)
- **Treatment:** Staloral® 100 IR Mites and mites extract tablets: n=15, Placebo: n=17

Protocol

- **Perennial**
- **Duration:** 24 months

RESULTS: EFFICACY

- **Significant reduction in the global rhinitis symptom score from the first year through the end of the second year (p<0.02)**
  - **↘ Significant decrease in nasal obstruction (p=0.01)**
  - **↘ Significant reduction in nasal pruritus (p=0.01)**



- Significant reduction in skin reactivity (p<0.04)
- Drug consumption was generally low, but no significant difference between the two groups was observed

RESULTS: SAFETY

- One adverse reaction of buccal pruritus was reported in one patient on Staloral®.

NOTE The study by Tonnel *et al.* showed that Staloral® is effective on symptoms of allergic rhinitis to mites and well-tolerated

V

Staloral®

Sublingual solution of allergen extracts for immunotherapy

Safety Profile

The results of clinical trials together with extensive drug safety reports covering thousands of patients in Europe show that Staloral® is safe.

Safety studies

GRASS POLLEN

Authors/year of publication	Number of subjects in the active/ placebo	Protocol Duration	Safety data
Sabbah A *et al*, 1994[12] • Randomized, double-blind, placebo-controlled study • 58 patients between 13 to 51 years old with grass pollen rhinoconjunctivitis	29/29	• **Pre- and coseasonal protocol** • **Duration:** 4 months	**Minor adverse reactions reported** (buccopharyngeal pruritus, rhinitis and digestive signs)
Clavel R *et al*, 1998[18] • Randomized, double-blind, placebo-controlled study • 120 patients between 8 to 55 years old with grass pollen rhinoconjunctivitis with or without asthma	62/58	• **Pre- and coseasonal protocol** • **Duration:** 7 months	• **Minor adverse reactions with similar frequencies in the Staloral® and placebo groups** (buccopharyngeal pruritus and wheezing were the main adverse reactions) • **No severe systemic adverse reactions**
Pradalier A *et al*, 1999[19] • Randomized, double-blind, placebo-controlled study • 123 patients between 7 to 58 years old with grass pollen rhinoconjunctivitis with or without asthma	62/61	• **Pre- and coseasonal protocol** • **Duration:** 4 months	• Numbers of patients with at least one adverse event were **not significantly different between the two groups** (27% in the active treatment group and 19% in the placebo group). • Most adverse reactions were minor mouth and throat disorders
Smith H *et al*, 2004[20] • Randomized, double-blind, placebo-controlled study • 136 patients between 18 to 58 years old with grass pollen rhinoconjunctivitis with or without asthma	44 (A for 2 years) 47 (A for 1 year) /45	• **Pre- and coseasonal protocol** • **Duration:** 24 months	• **In year 1,** minor adverse reactions were reported by 70% of patients receiving active SLIT and 44% of placebo-treated patients. Buccal and nasal side effects were more frequent in SLIT- treated subjects. • **In year 2,** fewer adverse reactions occurred: 15% placebo-treated subjects and 35% actively treated subjects reported 1 or more adverse reactions ($P<0.05$), mainly in mouth or nose.
Ott H *et al*, 2009[21] • Randomized, double-blind, placebo-controlled study • 145 patients between 8 to 65 years old with grass pollen rhinoconjunctivitis	99/46	• **Coseasonal protocol** • **Maintenance phase:** 36 months (3 pollen seasons)	• **No serious systemic or anaphylactic reactions** • **Numbers of patients with adverse event were not significantly different between the two groups** (69.0% in the active treatment group and 62.7% in the placebo group).

WEED POLLEN ALLERGY

Authors/year of publication	Number of subjects in the active/ placebo	Protocol Duration	Safety data
La Rosa M *et al*, 1999[22] • Randomized, double-blind, placebo-controlled study • 41 children 6 to 14 years old with rhinoconjunctivitis with or without asthma induced by wall pellitory	20/21	• **Duration:** 24 months	• **The most common adverse events were gastrointestinal complaints**
André C *et al*, 2003[23] • Randomized, double-blind, placebo-controlled study • 110 adults and children 8 to 62 years old with rhinoconjunctivitis with or without asthma induced wall by ragweed pollen	55/55	• **Pre- and coseasonal** • **Duration:** 7 months	• **No serious adverse events reported during the study** • **Most adverse events were mild or moderate and reported at the beginning of the study and did not persist in the maintenance phase.** Adverse reactions were more frequent in SLIT (70%) than placebo (13%)
Bowen T *et al*, 2004[24] • Randomized, double-blind, placebo-controlled study • 76 adults and children 6 to 58 years old with rhinoconjunctivitis and asthma induced by ragweed pollen	37/39	• **Pre- and coseasonal** • **Duration:** 2 ½ months	• 70% of patients in SLIT group and 40% of patients in placebo group reported at least 1 adverse event • **No adverse reactions were serious** • **No systemic adverse reactions were recorded** Most adverse reactions in SLIT group were related to local tolerance
TREE POLLEN ALLERGIES			
Vourdas D *et al*, 1998[25] • Randomized, double-blind, placebo-controlled study • 66 children 7 to 17 years old with rhinoconjunctivitis with moderate asthma induced by olive pollen	34/32	• **Pre and coseasonal** • **Duration:** 2 pollen seasons (24 months)	• **A few minor adverse events were reported only during the titration** (buccal itching, oropharyngeal pruritus, labial swelling and conjunctivitis symptoms)
Khinchi MS *et al*, 2004[26] • Randomized, double-blind, placebo-controlled, double-dummy study • 58 adults 20 to 58 years old with rhinoconjunctivitis and asthma induced by birch pollen	18(SLIT) 21(SCIT) 19 (Placebo)	• **Pre and coseasonal protocol** • **Duration:** 24 months	• **SLIT treatment mainly resulted in local mild adverse reactions** (itching or mild oedema in the mouth and/or throat) • Systemic side-effects grade 2 (mostly rhinoconjunctivitis) occurred in all 3 groups • 5 cases of systemic reaction grade 3 and 1 grade 4 were observed in the SCIT group and 1 grade 3 in placebo group. No grade 3 and 4 reactions occurred in the SLIT group
Vervloet D *et al*, 2007[27] • Randomized, double-blind, placebo-controlled study • 76 patients 19 to 60 years old with rhinoconjunctivitis and asthma to cypress pollen	38/38	• **Coseasonal** • **Duration:** 4 months	• **No serious adverse reactions** • **Adverse reactions were infrequent, local and of short duration**

HOUSE-DUST MITES ALLERGY

Authors/year of publication	Number of subjects in the active/ placebo	Protocol Duration	Safety data
Bousquet J *et al*, 1999[28] • Randomized, double-blind, placebo-controlled study • 85 adults and children 7 to 42 years old with moderate or moderately severe asthma due to house-dust mite	42/43	• **Perennial** • **Duration:** 25 months	• **The overall incidence of adverse reactions was similar in both groups** (SLIT group 35.7%, placebo group 32.6%)
Guez S *et al*, 2000[29] • Randomized, double-blind, placebo-controlled study • 72 adults 6 to 51 years old with perennial rhinitis with or without asthma due to house-dust mite	36/36	• **Perennial** • **Duration:** 24 months	• **No severe adverse reactions** • 2 patients receiving SLIT treatment reported local adverse reactions (mouth itching and burning) and 2 patients in the placebo group reported episode of mild asthma and episode of rhinosinusitis
Mortemousque B *et al*, 2003[30] • Randomized, double-blind, placebo-controlled study • 60 adults and children 6 to 60 years old with perennial conjunctivitis due to house-dust mite	30/30	• **Perennial** • **Duration:** 24 months	• **No general adverse reactions** • 2 patients in the active group reported more marked episodes of ocular pruritis in the first month • 1 of these two patients reported local effects (swelling, reddening and tingling of the tongue and gingiva) within less than 30 min of application during the first month
Tonnel AB *et al*, 2004[31] • Randomized, double-blind, placebo-controlled study • 32 patients 9 to 38 years old with allergic rhinitis and asthma due to house-dust mite	15/17	• **Perennial** • **Duration:** 24 months	• The only adverse reaction was a single case of buccal pruritus in one patient (receiving SLIT).
André C *et al*, 2000[33] • Data collected from 8 randomised, double-blind, placebo-controlled study • 690 patients (472 adults and 218 children) with allergic rhino-conjunctivitis and/or asthma induced by various allergens	347/343	Different courses of treatment between 4 months and 2 years	• **No significant difference was detected between children and adults with respect to the incidence of adverse reactions** (39% vs. 48%, respectively) • High doses of Staloral® were as well-tolerated as low doses

Authors/year of publication	Number of subjects in the active/ placebo	Protocol Duration	Safety data
Grosclaude M *et al*, 2002 [34] • Randomized, double-blind, placebo controlled study • 63 patients between 5 and 46 years with grass pollen rhinoconjunctivitis	15-16-16/16	• **Titration** (18 days), 3 dosage regimens: starting with 3 IR, 10 IR or 30 IR (until achieving 100 IR tablets) • **Maintenance phase:** use of solution of 300 IR during 8 months	• During the titration, 70 adverse reactions (67 SLIT, 3 Placebo) were reported by 27 patients • No cases of urticaria, angioedema or any other potentially life-threatening reactions were reported • No significant difference in the incidence of adverse reactions in the 3 SLIT treatment groups with different titration doses • **The study demonstrated that a dose of 10 IR to 30 IR is suitable for beginning the titration with Staloral®**
Seidenberg J *et al*, 2009 [35] • Observational study • 193 patients between 5 to 17 years of age with allergic rhinitis with or without mild to moderate asthma	193/---	• **Ultra-rush titration:** 30-90-150-300 IR within 90 minutes • **Maintenance phase:** 4 months	• **During ultra-rush titration:** - 60 patients (31%) reported 117 predominantly mild and local adverse reactions - All adverse reactions resolved within 30 to 150 minutes - No severe adverse reactions occurred during ultra-rush titration • **During the maintenance phase:** - 139 patients reported 562 adverse reactions - Nearly all the events has resolved by the end-of-study visit • The most frequent local adverse reactions were: oral pruritus, burning sensation, lip or tongue swelling, and gastrointestinal symptoms • The most frequent systemic adverse reactions were: mild rhinoconjunctivitis, urticaria and asthma
Gidaro G.B. *et al*, 2005 [37] • Safety of SLIT: analysis of published studies • 2 groups of studies: 13 Low allergen dose (LAD) studies and 12 High allergen dose (HAD) studies	**LAD:** 587 patients (302 actively treated and 285 with placebo) **HAD:** 850 patients (445 actively treated and 405 assuming placebo)		**There is evidence that adverse reactions occurrence is substantially not dose-dependent.** The analysis of these trials demonstrates that local reactions are quite common, with higher rate for low allergen dose, but mild and self-resolving, and that systemic adverse reactions occur more rarely and are not dose-dependent
Linda S. Cox *et al*, 2005 [38] • Summary of safety with SLIT: a comprehensive review	All studies, including retrospective DBPC and observational studies were considered		SLIT is associated with adverse reactions. By far **the most common are local symptoms in the oral cavity;** However, abdominal complaints, urticaria, and asthma have been reported, although all are uncommon

VI Staloral®

Sublingual solution of allergen extracts for immunotherapy

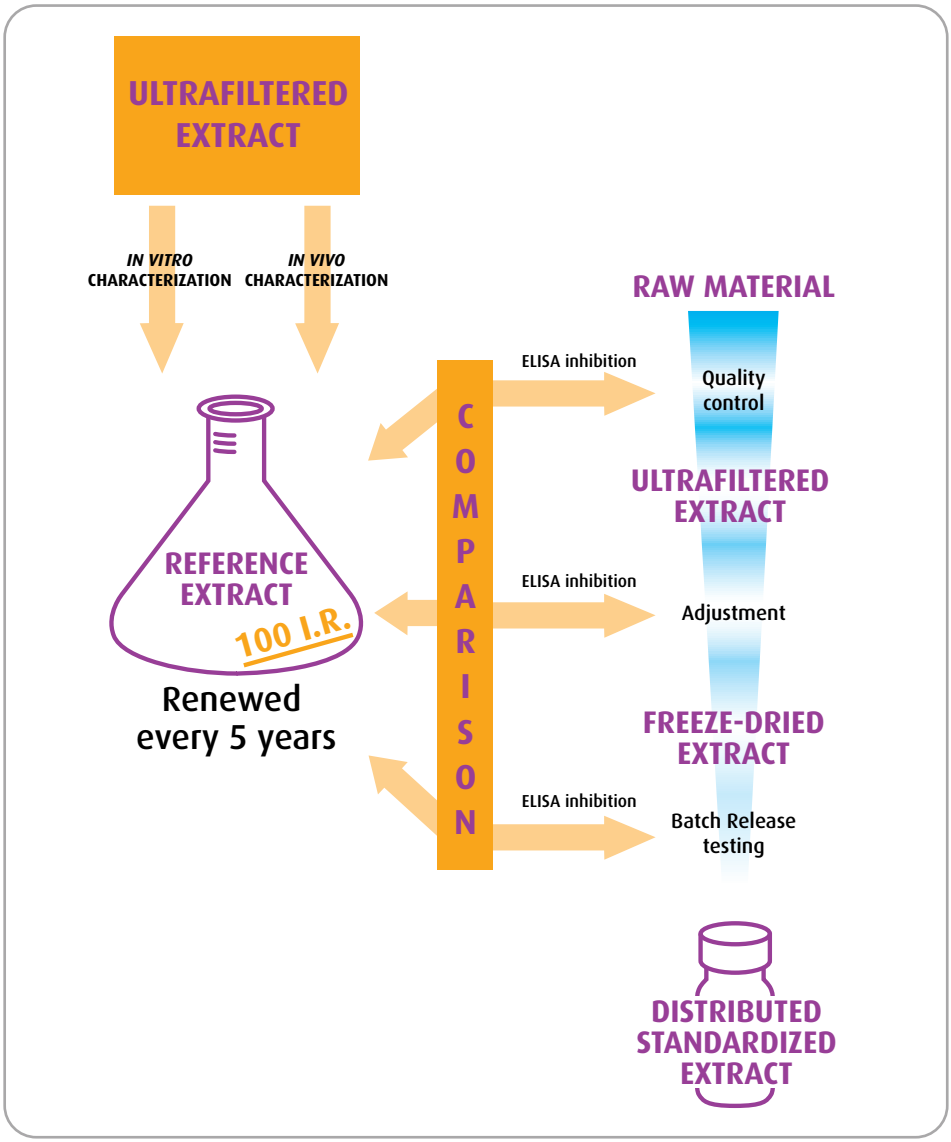
The product

Pharmaceutical Form[36]

Staloral® is a sublingual solution of allergens extracts for the curative treatment of IgE-dependent allergic disease.

Allergens extracts are purified, standardized and formulated into an easy to use pharmaceutical product.

Every standardized extract supplied has a corresponding reference extract. Qualitative and quantitative comparisons of marketed extracts with the reference extracts ensure consistency from batch to batch.



Allergen standardization

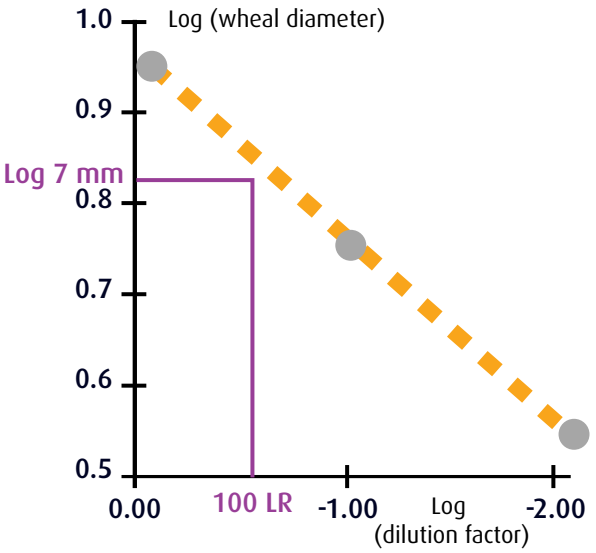
In order to ensure reproducible, safe treatment, STALLERGENES developed a reliable allergen standardization system in the 1980s.

The aim of allergen extracts' standardization is to guarantee the consistency from batch to batch by adjusting inherent variations in biological activity between batches of raw materials due to differences in:

- Geographical origins
- Cultivation conditions
- Extraction processes
- Seasonal or annual variations

A standardized allergen extract presents consistent allergen activity from one batch to another of the mother solution.

The allergen activity of an extract quantifies its capacity to induce an allergic reaction in a skin test practiced on a subject who is allergic to the relevant substance.



100 IR STALLERGENES= wheal diameter 7mm

Concentrations are expressed in logarithm form, in function of the concentration of the considered solution.

The value log (wheal diameter)= 7 mm corresponds to 100 IR

IR or Index of Reactivity

An allergen extract is attribuated a value of 100 IR/ml when it induces a mean 7 mm wheal diameter in a skin prick test using a Stallerpoint® needle in 30 subjects sensitized to the allergen in question. The reactivity of the subjects is also demonstrated by a positive response to a skin prick test with Codeine Phosphate (9%) or Histamine dihydrochloride (10 mg/ml)

It is not possible to standardise all allergen extracts, especially rare allergens for which it is difficult to find enough patients.

The standardization procedure is repeated every 3 to 5 years for every allergen.

Standardization is essential to conduct clinical trials. In its guidelines, the WHO ruled that the use of standardized extracts constitutes a prerequisite for effective allergen immunotherapy.[1,2,7]

Pharmacological properties

Staloral® efficacy has been conclusively demonstrated in clinical trials.

Mechanism of action

The mechanism of action underlying the efficacy of sublingual allergy immunotherapy has not been fully elucidated although certain physiological phenomena have been observed.

The mechanism of action appears to be similar at least in part to that of subcutaneous allergen immunotherapy which is believed to induce the following phenomena:[39]

- Possible reduction of the levels of specific IgE antibodies in the blood
- Modification of the behaviour of cells involved in the allergic reaction
- Modulation of the activities of Th1 and Th2 lymphocytes, leading to changes in the levels of cytokines which regulate IgE production (inhibition of IL-4 and stimulation of IFN-γ)

Allergen immunotherapy is known to induce a long-lasting immune response, sustained by a specific immunological memory.

There is convincing evidence for the hypothesis that dendritic cells – which are particularly dense in the buccal mucosa – play a major role in the mechanism of action of sublingual allergy immunotherapy.[40]
In fact, dendritic cells:

- Act as potent antigen-presenting cells
- Produce IL-12 which promotes the development of Th1 lymphocytes
- Carry a high density of high-affinity IgE receptors (FcεRI) on their surface and are therefore able to stimulate the large numbers of T cells present in the buccal mucosa
- Internalize allergenic molecules when exposed to them in tissue culture in a very rapid, dose-dependent fashion

Taken together, these observations strongly suggest that dendritic cells in the buccal mucosa could play a key role in the mechanism of action of sublingual allergen immunotherapy.

Composition

One vial of Staloral® contains 10 ml of solution at a concentration of:

- 10 or 300 IR/ml standardized allergen extracts
- 10 or 100 IC/ml non-standardized allergen extracts

A list of all the allergens available is presented in the appendix A. Lower concentrations can be supplied for particularly reactive patients.

VII Staloral®

Sublingual solution of allergen extracts for immunotherapy

in Practice

1. Indications[36]

Staloral® is indicated in adults and children over 5 years of age with type I allergic disease according to Gell & Coombs classification, mainly involving:

- Rhinitis
- Conjunctivitis
- Rhino-conjunctivitis
- Asthma (mild to moderate) of a seasonal or perennial nature

The role of allergen immunotherapy is to prevent the clinical consequences of contact between sensitised subjects and the allergen, when etiological factors have been clearly identified.

Indication of recommendations [1,5]

ALLERGIC RHINITIS	ALLERGEN IMMUNOTHERAPY Sublingual route	ALLERGIC ASTHMA	ALLERGEN IMMUNOTHERAPY Sublingual route
Mild, intermittent	Not recommended	Intermittent	Not recommended
Moderate/severe, intermittent	**Indicated**	Mild, intermittent	**Indicated**
Mild, persistent		Moderate, persistent	
Moderate/severe, persistent		Severe, persistent	Not indicated

2. Contraindications[36]

Staloral® is contraindicated in the following circumstances:

- Hypersensitivity to any of the excipients
- Autoimmune diseases, immune complex diseases or immunodeficiency diseases,
- Malignancies
- Treatment with ß-blocker (even when administered topically, such as eye drops)
- Severe or uncontrolled asthma (Forced Expiratory Volume - FEV_1 < 70%)
- Inflammatory oral disease associated with severe symptoms, such as ulcerated oral lichen planus or severe oral mycosis

3. Pregnancy and Breastfeeding

No adverse data on the clinical experience for the use of SIT in pregnant women have been reported.
Treatment with Staloral® should not be initiated during pregnancy.
If pregnancy occurs during treatment, the doctor should have to assess benefit of treatment continuation after evaluation of the general condition. The posology (dose and frequency) should never be increased in pregnant women to minimize the risk of systemic allergic reaction (anaphylactic shock).

No clinical data are available for the use of Staloral® during breastfeeding.

4. Initiation[36]

Allergen immunotherapy should be initiated:

- As soon as it has been established that it is indicated
- As early as possible, because the earlier the treatment, the greater its efficacy

Allergen immunotherapy should be initiated in association with symptomatic treatments in children and young adults, as soon as warranted by the severity of symptoms.

5. Administration[36]

Staloral® doses should be administered in the morning before breakfast.
Doses of the solution are delivered by exerting pressure on the pump:

- 1 pressure corresponds to 1 dose *i.e.* 100 µl
- The pump is calibrated and consistently delivers the same exact volume

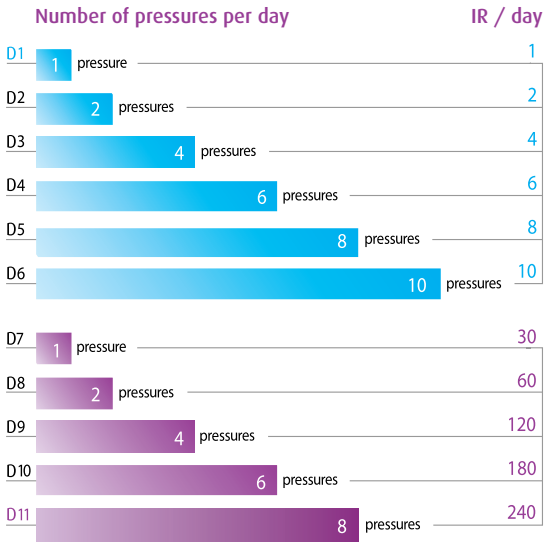
The solution should be deposited directly under the tongue and left there for about 2 minutes before swallowing.

Before use, always check that the extract being administered corresponds to the prescription and that the expiry date is still valid.

- Perennial protocol: Staloral® should be administered perennially for allergies to mites
- Pre- and coseasonal protocol: Staloral® should be administered pre- and coseasonally for allergies to pollen: grasses, weeds, and trees.

Staloral® posology does not vary according to age, but must be adjusted on the basis of each patient's reactivity.

Titration phase *



10 IR/ml
1 pressure = 1 IR

300 IR/ml
1 pressure = 30 IR

- **Progressive daily increase of the doses till the optimal maintenance dose is reached.**

Maintenance Phase *

- **Concentration:**
  300 IR/ml
- **Recommended dose:**
  4 to 8 pressures/day
  i.e. 120 to 240 IR
  (with 300 IR/ml concentration)

- **Some Staloral® clinical studies have confirmed that dose of 10 pressures daily with the 300 IR/ml concentration (300 IR/day) are well tolerated.[36]**

This protocol is indicative only and may be adapted to the reactivity of each individual. For very sensitive patients, treatment could be initiated with a lower concentration.
* For non standardized allergens or for allergens available at 100 IR/ml, please refer to the corresponding protocol mentioned in the SmPC.

NOTE

Pre- and coseasonal: treatment started 2 to 3 months before the pollen season and stopped at the end of the pollen season for 3 consecutives seasons.

Perennial: treatment is maintained year long for 3 years.

6. Treatment duration[36]

According to guidelines, the overall recommended treatment duration is 3 years on average when improvement is noticed.

Lack of improvement is an indication for treatment reassessment:

- After the first year for perennial allergy
- After the first pollen season for seasonal allergy

7. Precautions of use

Before starting an allergen immunotherapy, symptoms of allergy should be stabilised with an appropriate symptomatic therapy if necessary.

Patients with a prescription for a sublingual allergen immunotherapy should also always have medications for the treatment of allergen-mediated symptoms available such as corticoids, H_1-antihistamines and $ß_2$-sympathomimetics.

In case of onset of symptoms following treatment administration such as intensive itching in palms of hand and soles of the feet, urticaria reaction, mouth edema, pharyngeal edema leading to difficulty in swallowing, in breathing, or voice modification, a physician has to be consulted immediately and the treatment should be discontinued.

In case of severe allergic reactions, use of epinephrine may be necessary.

In patients treated with tricyclic antidepressants and mono amine oxidase inhibitors (MAOIs), risk of undesirable effects of epinephrine can be increased with possible fatal consequences. This risk would have to be considered prior to initiating allergen immunotherapy.

In case of inflammatory conditions in the oral cavity such as mycosis, aphtha, lesions, dental loss or extraction or buccal surgery, treatment should be discontinued until complete healing (at least 7 days).

Clinical experience in relation to simultaneous vaccination and treatment with Staloral® is missing. Vaccination may be given without interrupting treatment with Staloral® after medical evaluation of the general condition of the patient.

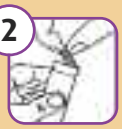
Staloral® contains 590 mg of sodium chloride per vial (in a 10 ml solution). Take it into account for patients following a strict low sodium diet, particularly for children.

Patients should inform doctors of any recent intercurrent disease or increase in the severity of allergic disease.

8. Instructions to patients before first administration[36]

Instructions for first use are the following:

NOTE If Staloral® is presented with pump already pre-assembled on the vial, patients go directly to Step 5

1 	• Remove the plastic colored part of the capsule
2 	• Pull on the metal tab and completely remove the aluminum capsule
3 	• Remove the grey stopper
4 	• Remove the pump from its plastic protector • Place the vial on a flat surface and, holding it firmly with one hand, fit the pump into place by applying a firm pressure
5 	• Remove the orange security ring
6 	• Prime the pump by successive pressures • After 5 pressures, the pump delivers a complete dose
7 	• Place the tip in the mouth, underneath the tongue • Press firmly to obtain the recommended dose • Repeat to administer the number of doses prescribed by your doctor • Keep the solution under the tongue for 2 minutes
8	• Clean the mouthpiece after use and re-install the security ring

For subsequent uses, after removing the security ring, patients only need to go through steps 7 and 8.

9. Adverse reactions - Description and Management

Adverse reactions

Allergen immunotherapy is a treatment that may induce undesirable allergic effects which can be local and/or systemic.

A given dose is not necessarily always tolerated. It may vary in time as a function of specific reactivity of the individual and the environment, in this case the dose schedule should be re-considered.

In any case, patient should inform his doctor on the occurrence of undesirable effect while receiving allergen immunotherapy.

Common undesirable effects are local:

- Oral: pruritus, edema, oropharyngeal discomfort, salivary glands disorders
- Gastrointestinal: nausea, abdominal pain, vomiting, diarrhea

Most of the time, these effects are mild to moderate and do not necessarily require any change to the dosing regimen.

Uncommon undesirable effects are systemic:

- Systemic effects such as rhinitis, conjunctivitis, asthma or urticaria, are uncommon and may require a symptomatic treatment with an H_1 antihistamines, beta-$_2$ mimetic or possibly oral corticosteroid. In any event, the prescribing physician must reassess the dose schedule or the benefits of continuing allergen immunotherapy.
- In very uncommon cases, severe systemic undesirable effects such as generalized urticaria, angioedema, oropharyngeal edema, laryngeal edema, severe asthma or anaphylactic shocks have been reported.

Rare undesirable effects are non IgE mediated reactions:

- Asthenia, cephalgia
- Pre-existing atopic eczema aggravation
- A delayed reaction of the "serum sickness" type may follow, with arthralgia myalgia, urticaria, nausea, adenopathy, fever. Such occurrence should terminate the treatment with Staloral®.

If doses higher than the recommended daily dose are taken, the risk of undesirable effects may be increased, including severe systemic or local allergic reactions.

In case of treatment interruption for reasons not related to adverse reactions

In case of treatment interruption of less than one week, it is recommended to continue the treatment the next morning at the usual dosage.

In case of treatment interruption of more than one week, whatever the initiation or the maintenance period is concerned, it is recommended to bring in the treatment again from one single dose while using the same vial concentration (as the one at the interruption) and then re-increase the doses according to the initiation scheme till the optimal well-tolerated dose.

10. Shelf-life and storage precautions[36]

Shelf-life

Refer to the local SmPC of Staloral®.

Special storage precautions

- Staloral® solutions should be kept at a temperature between +2 and +8°C
- When travelling, vials must be maintained in an upright position and must be packed in their box fitted with the security ring
- In the case of plane travel, the assembled Staloral® vial should not be checked in the luggage compartment, but taken on board into the cabin of the plane
- The vials must be replaced in the refrigerator as soon as possible

- **Staloral®'s efficacy depends on compliance and respect of treatment duration**
- **Giving clear instructions to the patient and explaining the importance of taking the right dosage at the correct time can help to foster adherence**

11. Staloral® - Available concentrations and the dosing pump[36]

Available concentrations

Concentration	10 IR/ml	300 IR/ml
Cap color	Blue	Violet
		

For particularly reactive patients, lower concentrations can be supplied.

Dosing pump

The dosing pump makes the administration of Staloral® simple and practical, and may thereby improve patient's adherence.

The exclusive calibrated dispensing system guarantees:

- precise dosing
- reproducible extraction volume

- Security ring to avoid loss of product when unused
- This security ring must be removed at each use

The dosing pump is convenient for the patient:

- Easy to use
- Allows rapid extraction

VIII Staloral®

Sublingual solution of allergen extracts for immunotherapy

List and references of mite and pollen allergens available for Staloral® at 300 IR/ml

Mites

335 *Blomia tropicalis*
314 *Dermatophagoides farinae*
315 *Dermatophagoides pteronyssinus*
350 *D.pteronyssinus + D.farinae* (50/50)

Grass pollen

705 Bermuda grass *(Cynodon dactylon)*
627 Cocksfoot *(Dactylis glomerata)*
658 Meadow grass *(Poa pratensis)*
671 Rye *(Secale cereale)*
638 Rye-grass *(Lolium perenne)*
631 Sweet vernal grass *(Anthoxantum odoratum)*
661 Timothy *(Phleum pratense)*
701 3 grasses
687 4 cereals
688 5 grasses
690 5 grasses / 4 cereals (50/50)
689 12 grasses

Weed pollen

605 Mugwort *(Artemisia vulgaris)*
604 Ragweed *(Ambrosia elatior)*
710 Russian thistle *(Salsola kali)*
657 Wall pellitory *(Parietaria officinalis)*

Tree pollen

609 Alder *(Alnus glutinosa)*
632 Ash *(Fraxinus Excelsior)*
615 Birch *(Betula alba)*
716 *Cupressaceae (Juniperus ashei)*
649 Hazel *(Corylus avellana)*
619 Hornbeam *(Carpinus betulus)*
651 Olive *(Olea europaea)*
702 *Betulaceae*

Bibliography

1. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5 Suppl):S147-S334.
2. Bousquet J, Khaltaev N, Cruz AA, *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63(Suppl 86):8-160.
3. Bauchau E *et al.*. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005; 60: 350-353.
4. White P *et al.* Symptom control in patients with hay fever in UK general practice: how well are we doing and is there a need for allergen immunotherapy? *Clinical and Experimental Allergy* 1998; 28: 266-270
5. World Allergy Organization. Sub-Lingual Immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009; 64(s91):1-59.
6. Rachelefsky GS. National guidelines needed to manage rhinitis and prevent complications. *Ann Allergy Asthma Immunol* 1999;82:296-305.
7. Bousquet J, Lockey R, Malling HJ and the WHO panel members. Allergen immunotherapy : therapeutic vaccines for allergic disease. A WHO position paper. *J Allergy Clin Immunol* 1998;102:558-62.
8. Committee on the safety of medicines. CSM update. Desensitising vaccines. *BMJ* 1986;293:948.
9. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;177:1572-3.
10. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to dust mite. *Clin Allergy* 1986; 16:483-91.
11. Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite: a double-blind study. *Allergol Immunopathol (Madr)* 1990;18:277-84.
12. Sabbah A, Hassoun S, Le Sellin J, *et al.* A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollens extract. *Allergy* 1994;49:309-13.
13. Wilson DR, Torres-Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2003; 2:CD002893.
14. Calamita Z, Saconato H, Pelá AB, *et al.* Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 2006:61:1162-72.
15. Penagos M, Compalati E, Tarantini F, *et al.* Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006;97:141-8.
16. Penagos M, Passalacqua G, Compalati E, *et al.* Meta-analysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 2008;133:599-609.
17. Compalati E, Passalacqua G, Bonini M, *et al.* The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA²LEN meta-analysis. *Allergy* 2009;64:1570-9.
18. Clavel R, Bousquet J, André C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. *Allergy* 1988;53:493-8.
19. Pradalier A, Basset D, Claudel A, *et al.* Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy* 1999;54:819-28.
20. Smith H, White P, Annila I, *et al.* Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004;114:831-7.
21. Ott H, Sieber J, Brehler R, *et al.* Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy* 2009;64:179-86.
22. La Rosa M, Ranno C, André C, *et al.* Double-blind placebo controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999; 104(2 Pt 1):425-32.

23. André C, Perrin-Fayolle M, Grosclaude M, *et al.* A double-blind placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. *Int Arch Allergy Immunol* 2003;131:111-8.
24. Bowen T, Greenbaum J, Charbonneau Y, *et al.* Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2004;93:425-30.
25. Vourdas D, Syrigou E, Potamianou P, *et al.* Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollens extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy* 1998;53:662-72.
26. Khinchi MS, Poulsen LK, Carat F, *et al.* Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004;59:45-53.
27. Vervloet D, Birnbaum J, Laurent P, *et al.* Safety and efficacy of Juniperus ashei sublingual-swallow ultra-rush pollen immunotherapy in cypress rhinoconjunctivitis. *Int Arch Allergy Immunol* 2007;142:239-46.
28. Bousquet J, Scheinmann P, Guinnepain MT, *et al.* Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. *Allergy* 1999;54:249-60.
29. Guez S, Vatrinet C, Fadel R, *et al.* House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy* 2000;55:369-75.
30. Mortemousque B, Bertel F, De Casamayor J, *et al.* Housedust mite sublingual-swallow immunotherapy in perennial conjunctivitis: a double-blind, placebo-controlled study. *Clin Exp Allergy* 2003;33:464-9.
31. Tonnel AB, Scherpereel A, Douay B, *et al.* Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004;59:491-7.
32. Pham-Thi N, Scheinmann P, Fadel R, *et al.* Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite avoidance measures. *Pediatr Allergy Immunol* 2007;18:47-57.
33. André C, Vatrinet C, Galvain S, *et al.* Safety of sublingual-swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000;121:229-34.
34. Grosclaude M, Bouillot P, Alt R, *et al.* Safety of various dosage regimens during induction of sublingual immunotherapy. A preliminary study. *Int Arch Allergy Immunol* 2002;129:248-53.
35. Seidenberg J, Pajno GB, Bauer CP, *et al.* Safety and tolerability of seasonal ultra-rush, high-dose sublingual-swallow immunotherapy in allergic rhinitis to grass and tree pollens: an observational study in 193 children and adolescents. *J Investig Allergol Clin Immunol* 2009;19:125-31.
36. Staloral® Summary of Product Characteristics
37. Gidaro GB, Marcucci F, Sensi L, *et al.* The safety of sublingual-swallow immunotherapy: an analysis of published studies. *Clin Exp Allergy* 2005;35:565-71.
38. Cox LS, Larenas Linnemann D, Nolte H, *et al.* Sublingual immunotherapy: A comprehensive review. *J Allergy Clin Immunol* 2006;117:1021-35.
39. James LK, Durham S. Update on mechanisms of allergen injection immunotherapy. *Clin Exp Allergy* 2008;38:1074-188.
40. Moingeon P *et al.* Immune mechanisms of allergen-specific sublingual immunotherapy. *Allergy* 2006;61:151-165.

Summary of Product Characteristics*

1. NAME OF THE MEDICINAL PRODUCT: Staloral®, sublingual solution of allergen extracts for specific immunotherapy. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION:** One10 ml vial contains: • 0.1, 1, 10 100 or 300 IR/mL (standardized allergen extract), or • 0.1, 1 ,10 or 100 IC/mL (non standardized allergen extract) of one allergen extract or a mixture of several allergen extracts (for the list of allergens, please refer to the local dossier). • *IR (Index of Reactivity): An allergen extract is said to have a titre of 100 IR/ml if in a prick-test performed using a Stallerpoint® in 30 subjects sensitised to the allergen in question, it produces a wheal of 7 mm in diameter (geometric mean). Skin reactivity in these subjects is simultaneously demonstrated by a positive response to a prick-test with codeine phosphate 9% or 10 mg/ml histamine dihydrochloride.* • *IC (Index of Concentration): An allergen extract is said to have an Index of Concentration of 100 IC/ml if its manufacturing parameters correspond to the same dilution ratio than those of standardized extracts at 100 IR/ml from the same family, extracts taken as a reference. When the family does not contain any standardized reference extract, the value 100 IC/ml corresponds to an extract dilution ratio established according to the medical experience.* The active substance corresponds to a mannitoled freeze-dried allergen extract, or to a glycerinated mannitoled allergen extract solution. For excipients, refer to section 6.1 "List of excipients". **3. PHARMACEUTICAL FORM:** Sublingual solution. **4. CLINICAL PARTICULARS: 4.1 Therapeutic Indications:** Type I allergies (Gell and Coombs classification) mainly involving rhinitis, conjunctivitis, rhino-conjunctivitis or asthma (mild to moderate) of a seasonal or perennial nature. **4.2 Posology and method of administration:** • Conditions for use Specific immunotherapy should be considered both for adults and children, when indicated. Treatment is particularly effective when started early. Specific immunotherapy is not recommended before the age of 5. • Posology and therapeutic schedule Dosage does not vary with age, but it should take into consideration individual parameters such as: sensitivity profile, tolerance and response to the treatment. The following therapeutic schemes are only indicative, and should be adjusted to the evolution of the patient's condition and to any occurrence of adverse reactions, in order to maintain a favourable benefit/risk balance. The medicine should be preferably taken in the morning before breakfast. The solution is placed directly under the tongue and kept under the tongue for two minutes before being swallowed. Young children will need the help of an adult when taking this medicine. For seasonal allergies, it is recommended to start the treatment 2 to 3 months before the pollen season and pursuing along the season. For perennial allergies, it is recommended to maintain the treatment along the entire year. The treatment is performed in two periods: • an initiation treatment with a progression of doses; • a maintenance treatment with constant dosage. ***Initial treatment: dose increase:*** The medicine is taken daily in rising doses from 1 to 10 IR (or IC) per day until the most favourable benefit/risk balance is attained. In average, the titration phase lasts between 9 to 21 days.

Possible therapeutic scheme using the Staloral® pump system:

Days	Vial concentration	Number of pressures	Dose (IR or IC)
D1	10 IR/ml or 10 IC/ml	1	1
D2		2	2
D3		4	4
D4	(Blue cap)	6	6
D5	100 IR/ml or 100 IC/ml	1	10
D6		2	20
D7		4	40
D8	(Red cap)	6	60
D9	300 IR/ml	1	30
D10	(only for standardized extracts)	2	60
D11		4	120
D12		6	180
D13	(Violet cap)	8	240

Or (only for standardized allergens):

Days	Vial concentration	Number of pressures	Dose (IR)
D1	10 IR/ml	1	1
D2		2	2
D3	(Blue cap)	4	4
D4		6	6
D5		8	8
D6		10	10
D7	300 IR/ml	1	30
D8		2	60
D9	(Violet cap)	4	120
D10		6	180
D11		8	240

In particular cases such as patients hypersensitive to allergen, the treatment with Staloral® can start with the vial concentration of 1 IR/ml or 1 IC/ml or with the vial concentration of 0.1 IR/ml or 0.1 IC/ml. ***Maintenance treatment: constant dose:*** Once the initiation period achieved, the maintenance dose corresponds to the optimal dose to maintain a favourable benefit/risk balance. The therapeutic scheme is: • daily dose: 120 to 240 IR (standardized allergens extract) corresponding to 4 to 8 pressures with the 300 IR/ml vial concentration or 100 IC (non standardized allergen extract) corresponding to 10 pressures with the 100 IC/ml vial concentration or • 3 times/week doses: 240 IR (standardized allergens extract) corresponding to 8 pressures with the 300 IR/ml vial concentration or 100 IC (non standardized allergen extract) corresponding to 10 pressures with the 100 IC/ml vial concentration. Some Staloral® clinical studies have confirmed that dose of 10 pressures daily with the 300 IR/ml vial concentration (300 IR per day) are well tolerated. • **Length of treatment:** According to International consensus (WHO position paper 1998), specific immunotherapy should continue for 3 to 5 years. If there is no improvement of symptoms after 1 year for perennial allergy or after the first season for pollen allergy, the indication of SIT should be re-assessed. • **Interruption of the treatment:** In case of treatment interruption of less than one week, it is recommended to continue the treatment the next morning at the usual dosage. In case of treatment interruption of more than one week, whatever the initiation or the maintenance period is concerned, it is recommended to bring in the treatment again from one single dose while using the same vial concentration (as the one at the interruption) and then re-increase the doses according to the initiation scheme till the optimal well tolerated dose. • **Method of administration:** Before each treatment, check: • the expiry date; • that the vial to be used matches the prescription (composition, name of the patient (in case of Named Patient Product), concentration, schedule) Place the solution inside the mouth, underneath the tongue, wait for 2 minutes before swallow. Clean the mouthpiece after use. **4.3 Contraindications:** • Hypersensitivity to one of excipients (see list of excipients); • Autoimmune diseases, immune complex diseases or immune deficiency diseases; • Malignant disease, malignant tumour; • Patients with uncontrolled or severe asthma (FEV1 < 70%); • Ongoing treatment with beta-blockers (including ocular topics); • Inflammatory conditions in the oral cavity with severe symptoms such as oral lichen planus with ulcerations or severe oral mycosis. **4.4 Special warnings and precautions for use:** Before starting a specific immunotherapy, symptoms of allergy should be stabilised with an appropriate symptomatic therapy if necessary. Patients with a prescription for a sublingual specific immunotherapy should also always have medications for the treatment of allergen-mediated symptoms available such as corticoids, H1-antihistamines and ß2-sympathomimetics. In case of onset of symptoms following treatment administration such as intensive itching in palms of hand and soles of the feet, urticaria reaction, mouth edema, pharyngeal edema leading to difficulty in swallowing, in breathing, or voice modification, a physician has to be consulted immediately and the treatment should be discontinued. In case of severe allergic reactions, use of epinephrine may be necessary. In patients treated with tricyclic antidepressants and mono

amine oxidase inhibitors (MAOIs), risk of undesirable effects of epinephrine can be increased with possible fatal consequences. This risk would have to be considered prior to initiating specific immunotherapy. In case of inflammatory conditions in the oral cavity such as mycosis, aphtha, lesions, dental loss or extraction or buccal surgery, treatment should be discontinued until complete healing (at least 7 days). Clinical experience in relation to simultaneous vaccination and treatment with Staloral® is missing. Vaccination may be given without interrupting treatment with Staloral® after medical evaluation of the general condition of the patient. This medicine contains 590 mg of sodium chloride per vial (in a 10 ml solution). Take it into account for patients following a strict low sodium diet, particularly for children. Patient should inform doctors of any recent intercurrent disease or increase in the severity of allergic disease. **4.5 Interaction with other medicinal products and other forms of interactions:** No interaction with other drugs or medicines, have been reported at the moment. Concomitant administration of anti-allergic symptomatic drugs (H1 antihistamines, corticoids, mast cells degranulation inhibitors) may be used to improve the tolerance to specific immunotherapy. **4.6 Pregnancy and lactation:** *Pregnancy*: No adverse data on the clinical experience for the use of SIT in pregnant women have been reported. Treatment with Staloral® should not be initiated during pregnancy. If pregnancy occurs during treatment, the doctor should have to assess benefit of treatment continuation after evaluation of the general condition. The posology (dose and frequency) should never be increased in pregnant women to minimize the risk of systemic allergic reaction (anaphylactic shock). *Lactation*: No clinical data are available for the use of Staloral® during lactation. **4.7 Effects on ability to drive or to use machines:** Staloral® has no known effect on the ability to drive and use machines. **4.8 Undesirable effects:** Desensitization is an allergenic treatment that may induce undesirable allergic effects which can be local and / or systemic. A given dose is not necessarily always tolerated. It may vary in time as a function of specific reactivity of the individual and the environment, in this case the dose schedule should be reconsidered. • *Common undesirable effects are local*: • Oral: pruritus, edema, oropharyngeal discomfort, salivary glands disorders • Gastrointestinal: nausea, abdominal pain, vomiting, diarrhea. Most of the time, these effects are mild to moderate and do not necessarily require any change to the dosing regimen. • *Uncommon undesirable effects are systemic*: • Systemic effects such as rhinitis, conjunctivitis, asthma or urticaria, are uncommon and may require a symptomatic treatment with an H1 antihistamines, beta-2 mimetic or possibly oral corticosteroid. In any event, the prescribing physician must reassess the dose schedule or the benefits of continuing specific immunotherapy. • In very uncommon cases, severe systemic undesirable effects such as generalized urticaria, angioedema, oropharyngeal edema, laryngeal edema, severe asthma or anaphylactic shocks have been reported. • *Rare undesirable effects are non Ig-E mediated reactions*: • Asthenia, headache. • Pre-existing atopic eczema aggravation. • A delayed reaction of the "serum sickness" type may follow, with arthralgia myalgia, urticaria, nausea, adenopathy, fever. Such occurrence should terminate the SLIT. In any case, patient should inform his doctor on the occurrence of undesirable effect while receiving specific immunotherapy. **4.9 Overdose:** If doses higher than the recommended daily dose are taken, the risk of undesirable effects may be increased, including severe systemic or local allergic reactions. **5. PHARMACOLOGICAL PROPERTIES: 5.1. Pharmacodynamic properties:** Pharmacotherapeutic group: Allergen extracts. **ATC code: V01AA.** The precise mechanism of action of allergens administered during the course of specific immunotherapy (SIT) is not clearly understood. A number of changes can be demonstrated in laboratory parameters: • appearance of specific antibodies (IgG) that may act as "blocking antibodies", • possible decrease in plasma concentrations of specific IgEs, • change in behaviour of cells involved in allergic reaction, • favourable change in activities of Th2 and Th1 lymphocytes, resulting in production of cytokines (notably decrease in IL-4 and increase in IFN-γ) that regulate IgE production. In addition, SIT is known to reduce both immediate and late-phase allergen-induced symptoms. **5.2. Pharmacokinetic properties:** The greater part of allergens in Staloral® is a mixture of proteins and glycoproteins. There is no direct bioavailability of intact allergens to blood. Therefore, no pharmacokinetic studies in animals or in human have been carried out to investigate the pharmacokinetic profile and metabolism of Staloral®. **5.3. Preclinical safety data:** Genotoxicity, repeat dose toxicity, embryofetal development or juvenile toxicity studies were conducted with several allergen extracts contained in solutions for sublingual immunotherapy and revealed no special hazard for humans. **6. PHARMACEUTICAL PARTICULARS: 6.1. List of excipients:** • Sodium chloride, • Mannitol • Glycerol, • Purified

water. **6.2. Incompatibilities:** None. **6.3 Shelf life:** Refer to the local dossier. **6.4. Special precautions for storage:** Store in a refrigerator (+ 2°C and + 8°C). In any case when vials are transferred, keep them in an upright position. Staloral® vials to which the metered pump has already been adjusted may only be transferred in the packaging with the safety ring in place. Staloral® vials to which the metered pump has already been adjusted may not be transported in the cargo compartment. **6.5. Nature and contents of container:** Primary packaging is an amber glass vial type I, rubber stopper, aluminium "Tear-off" closure with colour differentiated plastic cover: Yellow for 0.1IR/ml or IC/ml, green for 1IR/ml or IC/ml, blue for 10 IR/ml or IC/ml, red for 100 IR/ml or IC/ml and violet for concentration 300 IR/ml, dosing pump, package leaflet, plastic box. Initiation treatment starts with a pack containing different vials of different concentrations The maintenance treatment is conducted with the optimal well tolerated dose/concentration. On medical prescription only. **6.6. Special precautions for disposal:** No special requirements. **7. DATE OF CREATION OF THE TEXT:** August 2009. **8. DATE OF REVISION OF THE TEXT:** October 2010.

SUMMARY

Staloral® has proven its efficacy and good safety profile in an extensive clinical trials programme

Staloral® has widely contributed to the recognition of the sublingual route

- On the basis of the results of many clinical trials conducted with Staloral®:
  - The ARIA guidelines[1,2] recognized the sublingual route as valid for the same indications as the subcutaneous route
  - Five meta-analyses, covering a large number of patients[13-17], showed SLIT to be effective and safe in the treatment of allergic rhinitis and allergic asthma in both adults and children

Staloral® has shown clear clinical Evidence in Allergic Rhinitis and Asthma Due to Pollen

- Staloral® has demonstrated its efficacy and good tolerability in both adults and children with allergic rhinoconjunctivitis with or without asthma
- Staloral® administered pre- and coseasonally has demonstrated its efficacy:
  - On all relevant clinical criteria: symptom and medication scores
    In a variety of pollen allergies (trees, weeds and grasses)
- The results of Staloral® trials have:
  - Demonstrated the similar efficacy of the sublingual and the subcutaneous routes of administration
  - Validated the "high-dose" pre- and coseasonal protocols
  - Investigated new protocols, both effective and safe, like the "ultra-rush" protocol

Staloral® Clinical Evidence in Allergic Rhinitis and Asthma Due to Mites

- The results of controlled studies have demonstrated that Staloral® can be indicated for the treatment of allergy to mites causing rhinitis, conjunctivitis or mild to moderate asthma
- "High-dose" protocols with Staloral® have been shown to be effective and safe in both adults and children
- Staloral® can help restore the quality of life of allergic patients

Staloral® Safety

The retrospective safety analyses conducted by André *et al.* and the studies by Grosclaude *et al.* and Seidenberg *et al.* established:

- The good safety profile of Staloral® in both children and adults with rhinitis or moderate asthma
- The good tolerability of both high-dose and low-dose Staloral® under various titration schedules
- The data from Grosclaude *et al.* suggest that a fast titration phase is possible
- The study by Seidenberg *et al.* supports the safety of an ultra-rush high-dose titration regimen

Staloral® – The Product

- Staloral® represents the perfect balance between each patient's specific needs and the treatment prepared
- Its efficacy is the result of techniques that have been developed to ensure the manufacturing of standardized allergens

Staloral® in Clinical Pratice

- Staloral® is indicated for the treatment of perennial or seasonal rhinitis, conjunctivitis, rhinoconjunctivitis and mild to moderate asthma in both children and adults.
- Staloral® administration is:

- Simple:

- Short-term, 11-day titration phase (followed by a maintenance phase), ensuring that effective cumulative dose, namely the 300 IR/ml concentration is reached fast.
- Adapted protocol pre- and coseasonal for seasonal allergens/perennial for perennial allergies

- Practical:

The calibrated dosing pump guarantees delivery of reproducible doses; it is easy to use for the patient, as the dose is measured in the number of pressures.

- Allergen immunotherapy with Staloral® is generally completed in 3 years.

SUBLINGUAL SOLUTION OF ALLERGEN EXTRACTS
FOR IMMUNOTHERAPY

Staloral®

Evidence is difference

Boz. 7268-3 - June 2011

STALLERGENES
Allergen vaccines worldwide