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1. Algemene gegevens

Programma / Programme
Doelmatigheidsonderzoek: deelprogramma Effecten & Kosten

Subsidieronde/Subsidy round

E&K - round 09 - subsidieaanvraag

Projecttitel / Project title

Cost-effectiveness of subcutaneous immunotherapy in allergic rhinitis

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1.1. Goedgekeurd budget

€ 497.744,00

1.2. Looptijd project*

Data door ZonMw goedgekeurd op basis van de subsidieaanvraag/voortgangsverslag

Van startdatum: 1-1-2009 tot en met einddatum: 1-1-2013[1]

2. Result reporting

2.1. Background

Burden
Allergic rhinitis is one of the most prevalent chronic diseases and its prevalence has increased during the last decades. In several European countries a mean prevalence of 22.7% (95%CI: 21.1-24.2) has been reported.(1) The "Tweede Nationale Studie" reports an incidence of 8.8 /1000 patient-years in general practices in The Netherlands. Allergic rhinitis can significantly alter the social life of a patient.(2) Although not associated with severe morbidity and mortality, the high prevalence may yield a significant burden to society due to its impact on daily life, school- and work performance(3, 4) and the costs of treatment. In spite of the high prevalence and the awareness of the impact of allergic rhinitis, cost-effectiveness studies of interventions to reduce allergic nasal symptoms have not been done in the Dutch setting.

[1] Data door ZonMw goedgekeurd op basis van de subsidieaanvraag/voortgangsverslag

Treatment

The usual care of allergic rhinitis consists of allergen avoidance and pharmacotherapy, measures that can only suppress symptoms.
Subcutaneous immunotherapy or SCIT (repetitive subcutaneous injections with allergen extract leading to immune tolerance and blunting of the allergic reaction) targets the cause of the disease. More recently, a more convenient method of administering allergen extracts, i.e. in the form of sublingual drops or tablets (SLIT) has made its entry into clinical practice, though doubts have risen in the past regarding the effectiveness of some of the extracts.(5) The clinical efficacy of both SCIT and SLIT has already been established.(6-8) Sublingual immunotherapy, however, has been registered for grass pollen only.

Costs and cost-effectiveness

Annual costs of allergic rhinitis in different countries vary from €1,543 (seasonal rhinitis; Germany(9) to €4,260 (persistent rhinitis; France(10)) per adult. The economic burden in the Netherlands is not known. Although cost-effectiveness studies of SCIT have already been carried out in an international context (ref), country-specific evidence supporting its reimbursement from the basic benefits package of the Dutch Health Insurance Act (ZVW) is still lacking. The year 2012 saw 20,620 users of subcutaneous allergen extracts excluding those aimed at wasps, and with a total cost per user of €1,514 (not counting physician fees) SCIT constituted a burden on the collective ZVW-budget worth more than €31.2 million that same year.(11) Although the use and cost of SCIT have seen a downward trend for several years, the question remains whether the health gains of SCIT outweigh the total costs of treatment. It is expected that SCIT reduces the need for symptomatic medication, however, the costs of immunotherapy are unlikely to be fully offset by savings in symptomatic medications during the years of treatment. Rather, because effects of SCIT persist after completion of therapy(12) the costs probably precede the savings.

Clinical effectiveness in multi-sensitized patients

In daily clinical practice patients are often treated with a combination of 2 or 3 allergens (grass pollen, birch pollen and/or house dust mites). Although, the clinical efficacy of SCIT with these 3 allergens separately already has been proven in randomized placebo-controlled trials, effectiveness has never been evaluated in multi-sensitized patients using more than one allergen.

Adherence to immunotherapy

Both clinical effectiveness and cost-effectiveness will be influenced by the level of adherence to this long-lasting treatment. Several studies suggest that adherence to subcutaneous but also to sublingual immunotherapy is limited. Subcutaneous (SCIT) and sublingual (SLIT) allergen immunotherapy is a safe and effective treatment of allergic rhinitis, but high levels of compliance and persistence are crucial to achieving the desired clinical effects. The objective was therefore to assess levels and predictors of compliance and persistence among grass pollen, tree pollen and house dust mite immunotherapy users in real-life, and estimate costs of premature discontinuation.

Research questions

The study aims to address the following questions:

Primary

Clinical effectiveness
Is subcutaneous immunotherapy (SCIT) with tree pollen (TP), grass pollen (GP), house dust mites (HDM) or combinations effective compared to usual care (UC) only?

Cost-effectiveness

Is subcutaneous immunotherapy (SCIT) with tree pollen (TP), grass pollen (GP), house dust mites (HDM) or combinations cost-effective compared to usual care (UC) only?

Secondary
What is the adherence to SCIT using retrospective data from the project group, trial based data and data obtained from the PHARMO database?

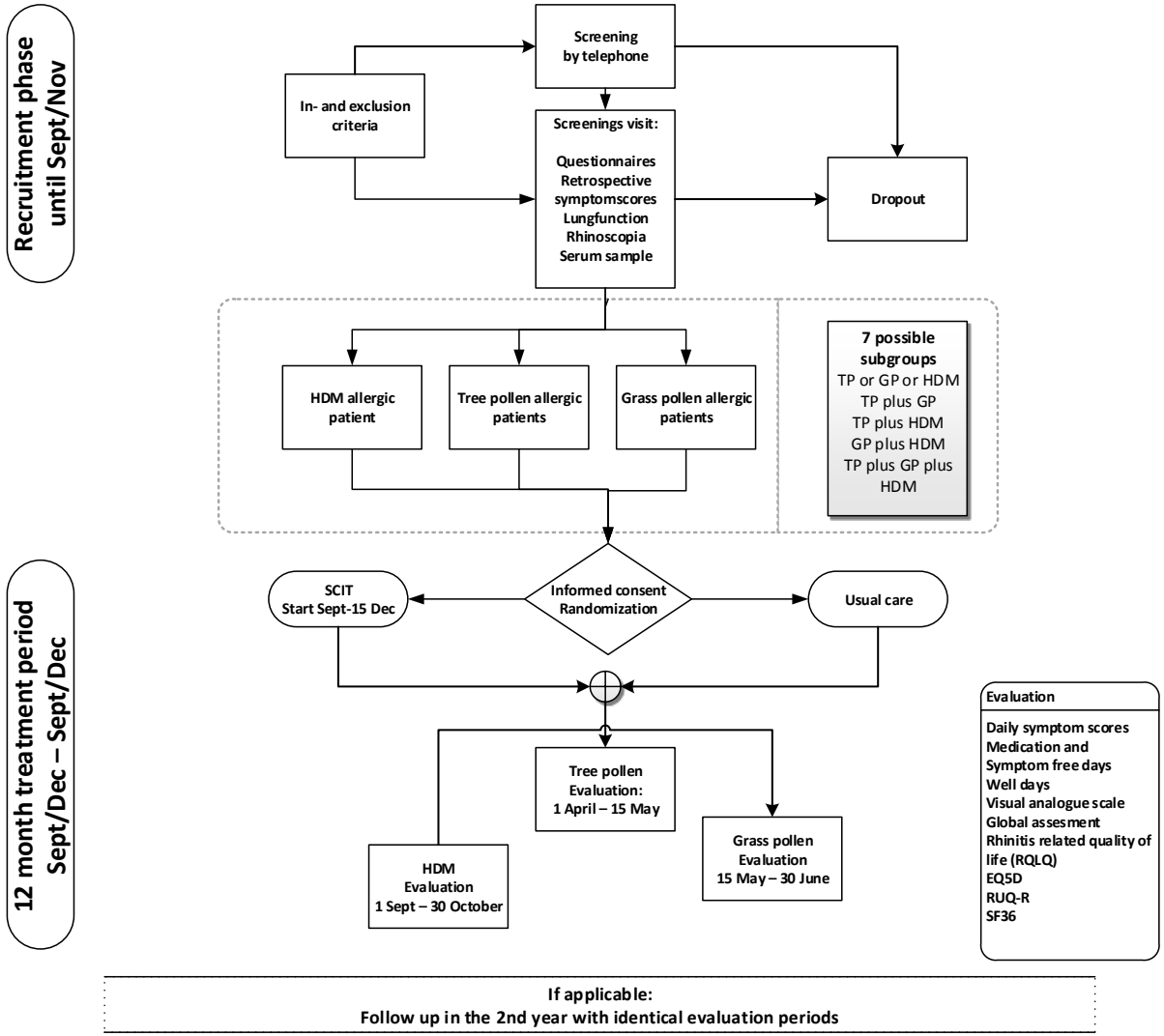
2.2. Realisation study objective and goals

To address the research questions a multicentre randomized trial (called the AIRFORCE study) was set up. AIRFORCE is an acronym for “Allergen Immunotherapy in Rhinitis, Focus on Outcomes, Resources and Cost-Effectiveness”. Nine hospitals and one Allergy Centre participated in the trial. Patients with allergic rhinitis undergoing subcutaneous immunotherapy (SCIT) as an add-on to usual care (UC) were compared with subjects receiving usual care only.

2.3. Methods

Design
The AIRFORCE study was designed as a prospective multicentre randomized controlled open clinical trial with two parallel treatment groups: SCIT plus UC versus UC only. Basically, patients were recruited for 1 year of treatment. Treatment was extended to a second year if this year could be included in the time frame of the study. As the symptoms of patients are affected by seasonal effects of house dust mite and pollen exposure patients should start treatment in the same period (September-December). Because of logistics (it is not feasible to enrol all patients at the same time in the same year) patients have been recruited in different years. Consequently, the 12-month efficacy could be estimated after pooling the data from the different years. Figure 1 gives an overview of the study design.

Figure 1 Study design



Patients

Patients with moderate/severe allergic rhinitis based on a sensitisation for tree pollen, grass pollen and/or house dust mite were recruited from outpatient hospital clinics, one non-hospital based allergy centre and general practices. In all cases screening and inclusion was performed by the investigators.

Inclusion criteria

- 18-45 years
- Clinically relevant moderate to severe allergic rhinitis due to a sensitization for one, two or three of the following allergens: tree pollen (TP), grass pollen (GP) and/or house dust mite (HDM). For each allergen (TP, GP, HDM) the following 3 criteria are evaluated. A sensitization for an allergen is considered clinically relevant and the rhinitis moderate/severe if:
    1. specific IgE ≥0.7 kU/l (Phadia)
    2. retrospective total symptom score (RSS) ≥4: participants will score 4 nose symptoms (sneezing, itching nose, watery running nose, nasal blockage) during the previous peak exposure period season (TP April 1-May 15; GP May 15-June 30; HDM September 1-October 31) on a 0-3 scale (0=none, 1=mild, 2=moderate, 3=severe; maximum total score =12)(5, 13).
    3. the presence of ≥1 of the following complaints due to rhinitis during the previous season (quality of life score or QOLs): sleep disturbance; impairment of daily activities; leisure and/or sport; impairment of school or work; troublesome symptoms.(6) Also, patients with a RSS = 3 and a QOLs ≥ 3 or RSS ≥ 9 with a QOLs=0 were eligible for inclusion.
- Signed informed consent

Exclusion criteria

- Severe/instable asthma
    - FEV1 <70% or FEV1/FVC < 70%
    - Asthma exacerbation requiring prednisolon treatment, visit to a first aid station (SEH/HAP) and/or hospitalization in the preceding 12 months.
- Specific IgE > 0.7 kU/l to animals the patient is in daily contact with
- Immunotherapy in preceding 5 years
- Anatomical disorders of the nose
- Language barrier
- No daily access to internet (because of web based questionnaires)
- Contraindications to immunotherapy (according to international guidelines; i.e. history of anaphylaxis; immunosuppressive treatment etc).(6)

With these in- and exclusion criteria we selected patients characterised by a relevant sensitization and a history of moderate to severe rhinitis. Hence, the study population was not restricted to patients with severe rhinitis, uncontrolled by pharmacotherapy. In this respect, the AIRFORCE study might represent daily clinical practice somewhat better than previously published double blind placebo controlled studies as the indications for immunotherapy in the international guidelines are broader (for instance unwillingness to be on constant or long-term pharmacotherapy) than in these trials.

Randomization

Computer generated randomization lists were created by the Department of Biostatistics of the ErasmusMC. Stratification was performed according to the referring physician (general practitioner / specialist) and sensitizations (TP only / GP only / HDM only / TP+GP / TP+ HDM / GP+HDM / TP+GP+HDM).

Treatment protocol and intervention

All patients – irrespective of the treatment group they were assigned to - were treated according to internationally accepted guidelines (i.e. antihistamine tablets, nasal steroids).(6)

Subjects allocated to the SCIT group started with immunotherapy between September 15 and December 15. Specialists started treatment (SCIT+UC or UC only). Patients in the UC group could be referred to the general practitioner in case of symptom control. With respect to the SCIT group, general practitioners could take over after the updosing phase.(14) Patients with concomitant asthma were mainly treated by specialists. The up dosing phase comprised 14 weekly administrations (one or more injections) of the relevant allergen(s). An adjusted up dosing scheme of 10 weeks was applied if patients allergic to tree pollen were randomized between 21 November and 15 December. With this scheme patients were able to finalize the up dosing phase before the start of the pollen season. The maintenance phase consisted of monthly injections with the top dose of the allergen extract(s).

Outcome measures

An overview of all outcome measures and the time points of assessment are shown in Table 1.

Table 1

Outcome measure	Description	Time points or periods
Daily symptom score(5, 13, 15)	The intensity of 4 rhinitis symptoms (nasal blockage, watery runny nose, sneezing, itching nose) were subjectively assessed by the patient on a scale grading from 0 = no complaints to 3 = serious complaints	TP: 1-4/15-5 GP: 15-5/30-6 HDM: 1-9/31-10
Daily medication use(5, 13)	Patients record all medication used for their nose, eye and lower airway daily Calculation of: The percentage of days with rescue medication use The percentage of 'well days', i.e. days without rescue medication and a symptom score ≤2 (range 0-12).	See daily symptom score
VAS (Visual analogue scale)(15)	Scores range from 0 (no symptoms) to 100 (very severe symptoms). The VAS refers to the overall nose-/and eye symptoms 7 days before measurement	TP allergy: mid-January (before season), April 1-May 15 (3x in season) and mid-June (after

		season). GP allergy: mid-April (before season), May 15-June 30 (3x in season) and mid-August (after season). HDM allergy: mid-June (before season), September 1-October 30 (3x in season) and mid-February (after season).
Rhinitis related quality of life (mini RQLQ)(16)	The mini-RQLQ has 14 items in 5 domains, each scored on a 7-point scale (0 - no impairment; 6 - maximum impairment). The mini-RQLQ measures quality of life one week before measurement	See VAS
EQ-5D-VAS and EQ-5D utilities(17, 18)	The EQ-5D is a self-administered questionnaire that contains a descriptive section and a valuation section. The descriptive section is a health status classification instrument with five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and three response options per dimension ranging from no problems to very severe problems. The second section of the EQ-5D is a visual analogue rating scale (EQ-5D-VAS) asking respondent to rate their overall health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). An EQ-5D utility was calculated by applying the Dutch preference weights (19) to the scores of the descriptive section. EQ-5D utilities range between –0.33 and 1 (full health).	See VAS
SF36v2	Short-form generic quality of life questionnaire with 36 questions that yields an eight-domain profile of functional health and well-being, as well as a physical and mental health summary score. Scores range from 0 to 100 (best health).(20)	See VAS
SF-6D	A selection of the SF-36 questions was used to describe a patient's health status on the SF-6D. Combined with a set of UK preference weights (21, 22), the SF-6D utility is	

	calculated. SF-6D utilities range between 0.296 and 1 (full health).	
Global assessment (GA)(23)	The global assessment of efficacy is based on a rating of general improvement in allergic symptoms on a 6-point ordinal scale (much worse, a little worse, no change, a little better, much better, completely absent)(23)	After each peak period of relevant allergen exposure and after 1 respectively 2 years of treatment
Resource Utilisation Questionnaire-Rhinitis (RUQ-R)	The RUQ-Rhinitis aims to measure health care utilization associated with rhinitis. It consists of 3 sections, one on caregiver contacts, one on absenteeism and presenteeism (health and labour questionnaire) and one on medication use	
IgG_4(24)	To evaluate the specific immune response to allergens during SCIT. IgG assessment was discarded as IgG_4 is particularly responsive to IT(24)	At baseline and at least at 1 year of treatment
Adherence	The number of patients discontinuing immunotherapy	
Safety	Reported SAE	

Questionnaires were administered using a web-based system of gathering patient-reported outcomes. Upon receiving a notification email or sms text message, patients logged on to a secured trial website. All health-related quality-of-life questionnaires – both disease-specific and non-disease specific – as well as resource utilization questionnaires, diaries collecting daily symptom scores and the annual global assessment questionnaires were administered in this fashion. During active trial participation, patients were also informed regarding overdue (open questionnaires) and expired questionnaires. By request, questionnaire alerts could be supressed for a limited time, for example in the case of vacation. The questions in the RUQ-R had a recall period of two weeks. The questionnaire was administered every two weeks during the entire pollen season and every eight weeks in the rest of the year. Consequently, the data collected outside the pollen season were linearly extrapolated to cover the entire period outside the pollen season.(25)
The main outcome for clinical effectiveness was the mean daily total rhinitis symptom score during the peak season in the first year.

Sample size calculation

The sample size calculation was based on the clinical effectiveness component of the study. The primary efficacy endpoint concerned the group of patients with presence of more than one clinically relevant sensitization for TP, GP or HDM. This has been the first study where such multi-sensitized patients are studied. Consequently, no comparable studies were available to form a basis for power calculations. We included 120 patients per treatment group, which we expected to be a feasible number. From retrospective records (Department of Allergology, ErasmusMC) we estimated that 78% of these patients would be multi-sensitized. This leaves 94 multi-sensitized patients per group. Estimating that about 20 percent would dropout (26, 27), it was expected that about 75 multi-sensitized patients would be evaluable. We considered this number as sufficient to detect clinically relevant differences. Furthermore, these numbers compared favourably to studies that have been done in this field, where patients were treated with only one allergen.(28) The detectable effect-size (difference of means/standard deviation) with 75 patients per group equals 0.46 at two-sided testing with 80% power, which can be considered a moderate effect- size.

Further, we aimed at a relatively large treatment effect: a difference in primary outcome (mean daily total rhinitis symptom score in the first year for multi-sensitized patients) between treatment groups of at least 30% was considered to be the minimal clinically important difference.(29)

Analyses of Clinical effectiveness

Patients with a pollen allergy were analysed without or with selection of pollen relevant days (see further). No selection of days was made for the analysis of house dust mite allergic subjects. In addition, all analysis were done according to an ITT (Intention to treat) and PP (Per protocol) analysis.

Selection of pollen relevant days

When selection of pollen relevant days was carried out for patients allergic to tree or grass pollen, only days with sufficient exposure to tree or grass pollen have been analysed. Pollen counts have been used to define eligible tree and grass pollen days.(5, 30) If the mean daily pollen count was less than 25 pollen grains/m^3 during the period of April 1st-May 15 for tree pollen or May 15-June 30 for grass pollen of a particular year, that year was considered a lost season and would not be evaluated. Second, only those days that exceeded the median pollen count of that year were considered as pollen- relevant days and consequently evaluated. Pollen counts have been obtained from two pollen- monitoring stations: University Medical Centre Leiden, Elkerliek Ziekenhuis Helmond and Delmerhorst (Germany).

Only days on which all 4 symptoms are recorded have been analysed. Only sufficiently complete diary cards, i.e. per season >50% of relevant days filled out, have been analysed.

Primary outcome

For each allergen the mean daily total rhinitis and eye symptom score in the relevant peak exposure periods (depending on the type of sensitization) was calculated.

Secondary outcomes

Univariable analysis (per allergen) has been carried out for the following secondary outcomes:

Eye symptoms, pulmonary symptoms, percentage symptom free days, percentage medication free days, percentage well-days, RQLQ, VAS and GA after the season and GA after the end of the study.

IgG_4 levels at baseline and at the end of the study have been compared.

Statistical analysis

Univariable analysis of the primary outcome and all secondary outcomes was done by the t-test or $\chi 2$ test in case of percentages.

The main evaluation of the primary end point was done using multiple linear regression (MLR) with the a priori defined independent variables "Treatment SCIT", ‘‘age’’ ,‘‘gender", "specialist", "year of inclusion", "allergy/treatment for 1 other allergen", "allergy/treatment for 2 other allergens" and "retrospective symptom score".

Linear mixed modelling

To utilize all available data (all individual total symptom scores for each day and each patient and all available pollen counts for each day; ITT without selection for pollen relevant days) the analysis was extended using linear mixed models with total symptom score (nose, eye, lung) as dependent variable,

log-transformed grass and birch pollen count, subgroup (mono-allergy and combinations of allergies) and treatment with SCIT as fixed effect and individual patient and date of assessment as random effect. P-values < 0.05 were considered as statistically significant.

Cost-effectiveness analysis

Type of study and perspective
A cost-effectiveness and cost-utility analysis was performed alongside the clinical trial. These analyses were performed from a healthcare perspective and a societal perspective. The latter analysis included direct healthcare costs, travel and parking costs, costs of productivity loss and costs of paid and unpaid household support. The latter three categories were excluded when adopting the healthcare perspective. For both perspectives we calculated the costs per QALY, the costs per successfully treated patient, the costs per unit of difference in the mini-RQLQ and the costs per symptom-free day gained. A patient was successfully treated when he reported that the allergic symptoms were “much better” or “completely absent” compared to the allergy season in the previous year.

Collection of resource use data
Data on rhinitis-related healthcare utilization, productivity loss, paid and unpaid household support and other costs were collected using the Resource Utilization Questionnaire for rhinitis (RUQ-Rhinitis). This questionnaire contains 3 parts. Part one contains questions about contacts with or visits to general practitioners, medical specialists, paramedical caregivers, emergency departments, and hospital admissions. It also asks patients to report the travel distance to these caregivers and institutions. Part two mirrors the Health and Labour Questionnaire(31), with questions on absenteeism and presenteeism. Absenteeism refers to absence from paid work due to rhinitis. Presenteeism refers to reduced productivity while at work, in this study because of rhinitis-related symptoms and complaints. Part three contains questions on prescribed as well as over-the-counter medication use.

The questions in the RUQ-Rhinitis had a recall period of two weeks. The questionnaire was administered every two weeks during the entire pollen season and every eight weeks in the rest of the year. Consequently, the data collected outside the pollen season were linearly extrapolated to cover the entire period outside the pollen season.(25) Like the other questionnaires the RUQ-Rhinitis was placed on the secured AIRFORCE website at the time that it should be submitted. Every time a questionnaire was put on the website for submission, the patients received a text message to remind them. When necessary, reminder text messages were sent.

Unit costs
To calculate costs, all health care utilization and other resource use was multiplied with 2012 unit costs. Most unit costs were obtained from the CVZ cost manual.(32) They were corrected for inflation to 2012 price levels, using consumer price indices. Medication costs were obtained from the website medicijnkosten.nl, which gives the pharmacy purchase price minus 6.82% clawback (with a maximum of €6.80 per prescription) plus 6% VAT. We added a dispensing charge of on average €7.65 per delivery, except for medicines that are available on an over-the-counter (OTC) basis. Productivity loss due to absence from paid work was estimated using the Friction Cost Method using a friction period of 23 weeks.(32, 33) The costs of presenteeism were based on the response to the question of how many hours the patient should have worked extra to compensate for a lower productivity caused by allergic rhinitis. This number was multiplied with the costs of productivity loss per hour.

On top of the costs that were calculated with the information collected by the RUQ-Rhinitis, we calculated the costs of study medication and the costs of administering the study medication, based on the desensitization scheme used in this study. Study medication was Alutard SQ®, which contains an extract of either grass pollen (SQ 293 or Grassen-5), tree pollen (SQ 197 or Bomen-3) or house dust mite (SQ 503 or D. pteronyssinus). Immunotherapy starts with an updosing phase of 14 weeks with weekly injections. This is followed by a maintenance phase with monthly injections during the remainder of the study. The updosing phase requires four bottles of 5 ml desensitization fluid of increasing strength, sold as one package. One bottle of 5 ml maintenance immunotherapy extract can be used for 25 weeks (i.e. 5-weekly injections of 1 ml each). Patients who were randomized between November 21st and December 15th, followed an accelerated updosing scheme (4 weeks shorter), in order to adequately prepare them for the arriving main tree pollen allergy season, i.e. birch pollen, which starts in April. Unit costs of study medication do not differ between allergens.

When patients have two or three allergies, the immunotherapy injections were administered during the same visit, i.e. the costs per drug-administration visit were the same regardless of the number of injections. Six percent of all drug-administration visits were carried out in the presence of a medical specialist and 94% of all drug-administration visits were done by the doctor's assistant alone. The average duration of a contact with the assistant who administers the injections was 15 minutes, not including the time that a patient needs to stay in the waiting room to ensure no serious side-effects occur. Beside personnel costs, the price per visit also includes costs of materials, housing and overhead & equipment. In case of premature withdrawal from the trial (dropout), the costs of study medication and administering the study medication were calculated until and including the week that patients discontinued the trial. provides an overview of all unit costs.

Table 2 Unit costs (2012 euros)

Resource use	Unit	Unit costs (€)	Source
Regular provider contact costs			
GP telephone consultation	Per consultation	14.90	1
GP practice visit	Per visit	29.70	1
GP visit at home	Per visit	45.70	1
Specialist#, outpatient clinic visit	Per visit	76.50	1
Other provider contact costs			
Physical therapist	Per visit	38.20	1
Other paramedical caregiver	Per visit	31.90	1
Alternative healthcare provider	Per visit	55.00	1
Institutional admission & clinical consultation costs			
Hospital admission academic hospital	Per day	610.50	1
Hospital admission general hospital	Per day	462.10	1
Hospital admission asthma center	Per day	485.44	1
Emergency department visit	Per visit	159.90	1
Clinical consultation during admission	Per visit	76.50	1

(Un)paid household assistant & home care costs			
Paid household help	Per hour	13.30	1
Unpaid household support	Per hour	13.30	1
Professional homecare: housekeeping assistance	Per hour	25,50	1
Professional homecare: nursing care	Per hour	46.50	1
Travel & parking costs			
Travel costs	Per km	0.22	1
Parking costs	Per visit to hospital or per day[$]	3.20	1
Medication costs			
Symptomatic medication	Various (e.g. tablets, puffs)	various	2
Study medication updosing phase (4 bottles of 5 ml)	Entire updosing phase	425.80	3
Study medication maintenance phase (1 bottle of 5 ml)	Per 5ml bottle	385.30	3
Study drug-administration visit (doctor's assistant only)	Per visit	15.20	4
Study drug-administration visit (doctor's assistant and specialist present)	Per visit	62.70	4
Productivity costs			
Productivity loss due to absenteeism or presenteeism	Per hour	31.21	1

Cost reference sources: 1) CVZ cost manual; 2) medicijnkosten.nl; 3) ALK-Albelló The Netherlands BV; 4) own calculation according to CVZ cost manual methodology; [#]Allergologist, ENT physician or pulmonologist; [$]Not applicable to GP visits

Cost-effectiveness ratios

The point estimates of the costs per QALY, the costs per successfully treated patient, the costs per unit of difference in the mini-RQLQ and the costs per symptom-free day gained were calculated as the difference in costs between SCIT and UC divided by the difference in the measure of effectiveness. When calculating these ratios the adjusted costs and effects were used (see statistical analysis).

Statistical analysis

All randomized patients who completed at least one RUQ-Rhinitis were included in the cost analysis. Costs were analysed using a Generalized Estimation Equation (GEE) model.(34) A modified Parker test was used to choose the distribution (Gaussian, Poisson, Gamma or Inverse Gaussian).(35) To select the model specification with the best fit, we compared the "quasi-likelihood under the independence model criterion" (QIC), and choose the model with the lowest QIC.(36) The model with the best fit assumed a gamma distribution, logarithmic link and a compound symmetry covariance structure.

The dependent variable was the mean two-week cost in each time interval; two-week costs because the recall period of the RUQ-Rhinitis was two weeks. Depending on the allergen group to which a patient belonged, there were up to 8 different time intervals (zero through seven), where the uneven numbers indicate that the interval falls within an allergy season and the even numbers refer to intervals outside the allergy season. As an example the figure below shows the time intervals for a patient with a mono-allergy, in this case a tree pollen allergy.

Figure 2 Time intervals for a patient with a tree pollen allergy (example)

Year	2010		2011											2012							
Week that RUQ was completed	49		5	13	21	23	25	27	35	43	50	5	13	21	23	25	27	35		43	
Number of weeks to cover	24				8				44			8						20			
Time interval	Interval 0				Interval 1*				Interval 2			Interval 3*						Interval 4			

** Time intervals in allergy season*

The following independent variables were always included in the GEE model:

- time interval (time interval 0, i.e. the first time interval before the first allergy season is included in the constant);
- type of allergy (perennial (=HDM) versus seasonal (=TP or GP)) (if a patient is allergic to HDM he was classified as perennial regardless of whether he also had a seasonal allergy);
- interaction between treatment group and time interval
- interaction between treatment group and allergy

In a backward elimination process the following independent variables were investigated for inclusion in the model:

- age (years);
- educational level (high versus low as reference);
- marital status (having a partner versus being single as reference);
- current smoking status (non-smoking versus smoking as reference);
- gender (male versus female as reference);
- referring doctor (medical specialist versus general practitioner as reference);
- presence of respiratory comorbidity (yes versus no as reference);
- history of skin disease (yes versus no as reference)

Variables with a p-value below 0.2 were included in the model. The final model results were used to predict the adjusted costs per treatment group, first for each combination of time interval and allergy, and then for year 1 and year 2, thereby assuming the same distribution across the sensitizations in both treatment groups (52.7% seasonal and 47.3% perennial, which was the actual distribution in the trial).
The dependent variable did not include the costs of study medication and the costs of administering the study medication. To calculate the total costs these costs were added to the adjusted costs estimated from the GEE model.

The EQ-5D utilities were also analyzed using a GEE model. The model with the best fit had a Gaussian distribution, identity link function and a compound symmetry covariance structure. The same variables as in the cost model were investigated for inclusion into the utility model. The final models were used to predict mean utilities at each time interval for each treatment group, again assuming that 52.7% and 47.3% of the patients in both SCIT and Usual Care have a seasonal and perennial allergy, respectively. QALYs were calculated using the area under the curve method using the adjusted utilities.

To calculate the adjusted RQLQ scores the same type of model as for the EQ-5D was estimated. When calculating the costs per unit of difference in RQLQ for the first year, the first-year difference in costs was divided by the difference in the RLQL score during the first allergy season. When calculating this ICER for the second year, the two-year difference in costs divided by 2 (denominator) was divided by the average difference in RQLQ score across all allergy seasons.

To calculate the symptom-free days a two-part model was estimated, where in part one the probability to have more than zero symptom-free days was estimated and in part two the number of symptom -free days given they were greater than zero. In the first part GEE model the link function was logit and the distribution binomial; in the second part GEE model the best fit was reached when using a link function power(-1) and a gamma distribution.

Uncertainty around the estimates of costs and health outcomes was addressed by bootstrapping the data.(37) The GEE models mentioned above were estimated for each of 1000 bootstrap replications. The mean values of incremental costs and effects from the bootstrap replications were used as the point estimates. The 95% confidence interval around the difference in mean total costs and health outcomes was determined by taking the 2.5th percentile and the 97.5th percentile of these bootstrap replications. The bootstrap replicates for the adjusted outcomes and costs after 1-year and 2-year were plotted in cost-effectiveness planes (CE planes). The information from the CE planes on incremental costs per QALY was summarized in cost-effectiveness acceptability curves, which represent the likelihood that SCIT is the most cost-effective option at different values of the maximum acceptable willingness to pay for a QALY.(38, 39)

Sensitivity analysis

In the sensitivity analysis we investigated how sensitive the results were to the choice of the utility measure. Instead of using EQ-5D utilities, we used SF-6D utilities, to investigate whether the SF-36 may be more sensitive to changes in health-related quality of life in this patient population. A second sensitivity analysis relates to the definition of the allergy season. The first RUQ-Rhinitis questionnaire that was administered during the allergy season was administered in the first week that the season was expected to start. Given a recall period of two weeks, this measurement of the RUQ-Rhinitis might have measured resource utilization outside the allergy season. Therefore, we investigated the impact of assigning that measurement to the previous time interval outside the allergy season instead of to the allergy season.

Subgroup analysis

We performed a subgroup analysis by type of allergen: grass pollen, tree pollen and house dust mite. Because the number of patient was too low to include only patients with a mono-allergy into these subgroups we included the patients that had the allergy of interest with or without another allergy. This means for example that the grass pollen group included patients who only had grass pollen allergy and patients who had both grass pollen and tree pollen allergy.

Analysis of adherence to immunotherapy

A retrospective analysis of a Dutch community-pharmacy database from the PHARMO® institute containing data from 6486 patients starting immunotherapy for one or more of the allergens of interest between 1994 and 2009. 2796 patients received SCIT and 3690 received SLIT. Time-to-treatment discontinuation was analysed and included Cox proportional Hazard models with time-dependent covariates, where appropriate.

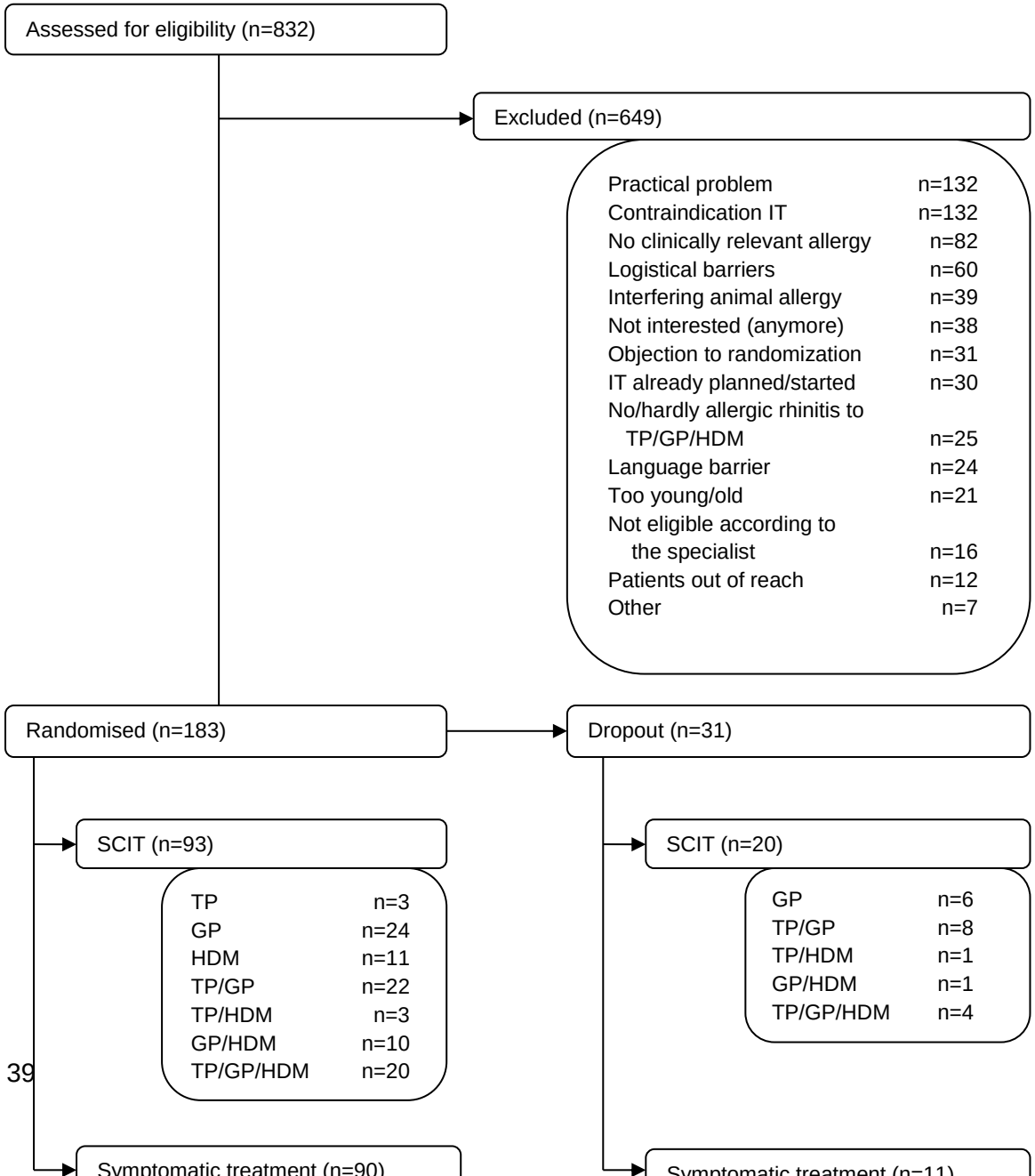
2.4. Results/new insights

Recruitment

The recruitment of participants was severely hampered in 2009. Most importantly, the pandemic Influenza A (H1N1) infection and the subsequent vaccination program rolled out over the Netherlands made involvement of general practitioners impossible. In addition, delays in medical ethical committee procedures delayed the recruitment process beyond the appropriate time period for recruitment. Only 4 patients could be randomised in 2009 and it was decided to extend the study with one year. Consequently, patients entering the trial in 2009 and 2010 participated for two years and those starting in 2011 for one year.

Approximately 6300 patients were invited by their specialist or general practitioner, of which 2083 responded. 1251 were not interested in participating, mainly because of no or hardly any allergic rhinitis to BP, GP and/or HDM (n=347) and practical problems (e.g. no time, distance to the hospital, no computer/internet; n=253). 832 patients entered the screening procedure (Fig 3). 649 (78%) were excluded, mainly because of practical problems (n=132), contra-indications to immunotherapy (n=132) and absence of a clinically relevant allergy (n=82). Finally, 183 patients were randomly assigned to SCIT (n=93) or symptomatic treatment only (n=90).

Figure 3 Recruitment flowchart


Assessed for eligibility (n=832)
Excluded (n=649)
Practical problem n=132
Contraindication IT n=132
No clinically relevant allergy n=82
Logistical barriers n=60
Interfering animal allergy n=39
Not interested (anymore) n=38
Objection to randomization n=31
IT already planned/started n=30
No/hardly allergic rhinitis to TP/GP/HDM n=25
Language barrier n=24
Too young/old n=21
Not eligible according to the specialist n=16
Patients out of reach n=12
Other n=7
Randomised (n=183)
Dropout (n=31)
SCIT (n=93)
TP n=3
GP n=24
HDM n=11
TP/GP n=22
TP/HDM n=3
GP/HDM n=10
TP/GP/HDM n=20
SCIT (n=20)
GP n=6
TP/GP n=8
TP/HDM n=1
GP/HDM n=1
TP/GP/HDM n=4
Symptomatic treatment (n=90)
Symptomatic treatment (n=11)

TP, tree pollen (birch); GP, grass pollen; HDM, house dust mite; IT immunotherapy; SCIT, Subcutaneous immunotherapy

The baseline characteristics of the randomised population are shown in Table 3. The treatment groups are comparable for gender, specific IgE TP/GP/HDM, multisensitization, and lower airway symptoms. The average age in the symptomatic treatment group was slightly higher (p=0.042).

Table 3 Baseline characteristics of the randomized population

	SCIT n=93	**Usual Care n=90**	**Total N=183**
Age (y)			
Mean (SD)	33.0 (8.1)	35.4 (7.8)	34.1 (8.0)
Gender			
Male participants, n (%)	47 (51)	42 (47)	89 (49)
Sensitization pattern, n (%)			
Tree pollen	3 (3.2)	6 (6.7)	9 (4.9)
Grass pollen	24 (25.8)	22 (24.4)	46 (25.1)
House dust mite	11 (11.8)	13 (14.4)	24 (13.1)
Tree pollen + grass pollen	22 (23.7)	17 (18.9)	39 (21.3)
Tree pollen + house dust mite	3 (3.2)	4 (4.4)	7 (3.8)
Grass pollen + house dust mite	10 (10.8)	10 (11.1)	20 (10.9)
All three allergens	20 (21.5)	18 (20.0)	38 (20.8)
No. of participants with multisensitization[#] (%)	55 (59%)	49 (54%)	104 (57%)
Specific IgE (kU/L) [median (range)]			
Tree pollen (birch)	2.0 (0.1 to >100)	1.2 (0.1 to >100)	1.6 (0.1 to >100)
Grass pollen	10.3 (0.1 to >100)	11.8 (0.1 to >100)	11.1 (0.1 to >100)
House dust mite	0.91 (0.1 to >100)	1.2 (0.1 to >100)	1.2 (0.1 to >100)
Lower airway symptoms[$], n (%)	63 (68)	58 (64)	121 (66)
Recent comorbidities, n (%)			
Skin disease	14 (19.4)	6 (7.8)	20 (13.4)
Asthma	12 (16.7)	12 (15.6)	24 (16.1)
COPD	3 (4.2)	3 (3.9)	6 (4.0)
Current smoker, n (%)	8 (11.1)	10 (13.0)	18 (12.1)
Education level			
High level of education, n (%)	34 (48.6)	42 (55.3)	76 (52.1)
Health insurance, n (%)			
Basic benefits only	12 (16.7)	11 (14.3)	23 (15.4)
Extended coverage	60 (83.3)	66 (85.7)	126 (84.6)

[#] *A clinically relevant sensitization to >1 allergen (birch pollen/grass pollen/house dust mite)*
[$] *Dyspnea, wheezing and/or dry cough at night in the last 12 months*

Dropout

A total of 152 participants completed the study. 31 subjects dropped out (20 SCIT; 11 UC). Reasons for dropout are shown in table 4. Dropouts were seen in the group starting autumn 2010: 14 during the first year and 12 during the second year and the group starting autumn 2011: 5 during their first (and only) year. The mean duration patients participated before dropout was 20.9 months for SCIT and 21.8 months for UC in the 2010 cohort and 10.8 months for SCIT and 11.5 months for UC in the 2011 cohort. The Kaplan Meier curves for the 2 cohorts are shown in Figure 4 and Figure 5.

Table 4 Dropout: stated reasons and numbers by trial group

	SCIT	UC	Total
No time/motivation to complete questionnaires/diary card	4	5	9
Personal circumstances	3	3	6
Patient's request after protocol violation (qua SCIT) by specialist	4	0	4
SCIT toot time-consuming and/or "too much of a burden"	5	0	5
Patient's request to be treated with allergen not allowed according to trial protocol	1	0	1
Unknown	3	3	6
Total	20	11	31

Figure 4 Kaplan Meier curve of patient dropout in first year over all patients, 2009-2010-2011 trial groups (SCIT vs. Control). No significant differences in dropout exist (p<0.05) between SCIT and usual care ("Control")

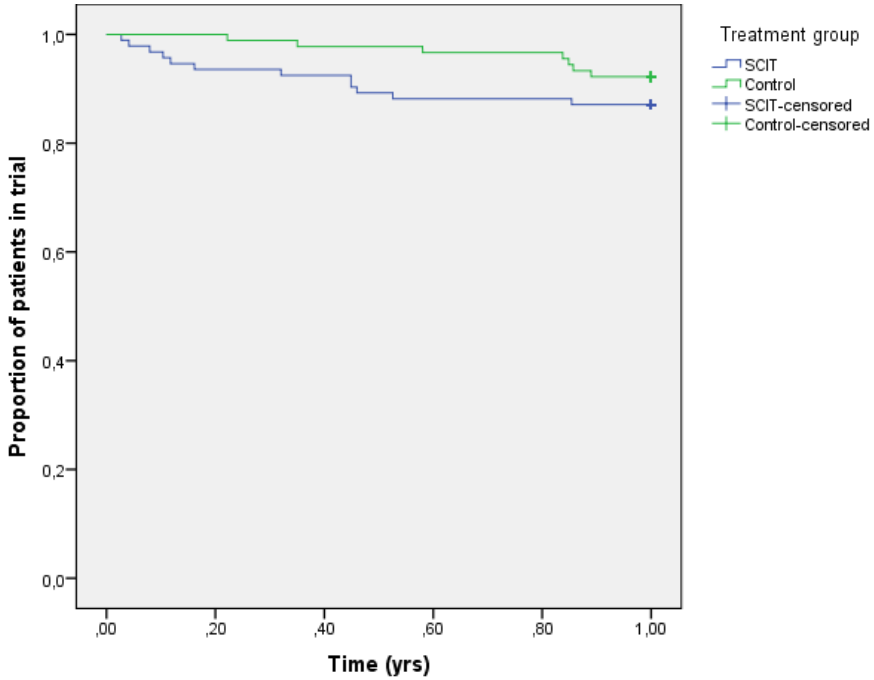
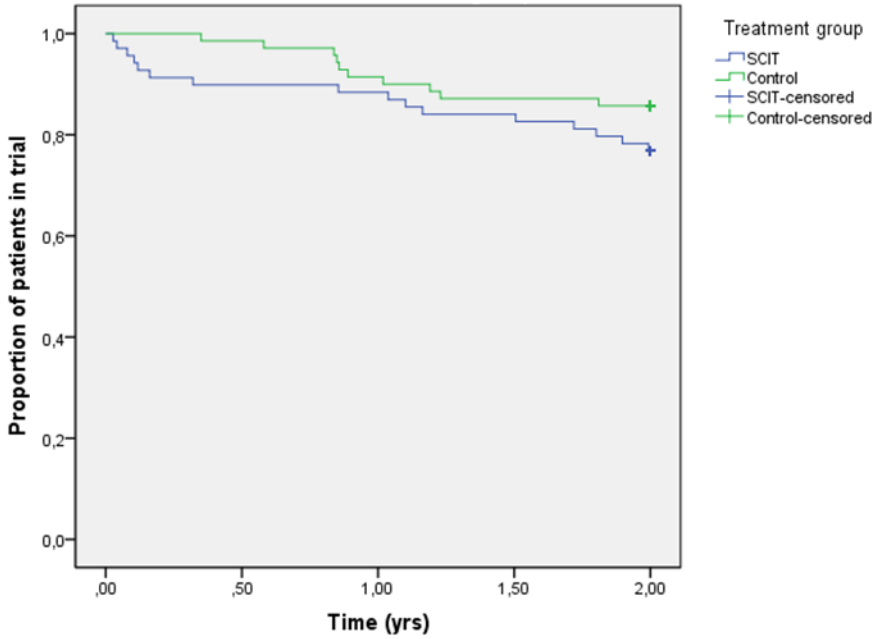


Figure 5 Kaplan Meier curve for two years for the 2009 and 2010 trial groups (SCIT vs. Control)



127 patients out of the 183 randomised subjects were included in the Per Protocol (PP) analysis. Reasons for exclusion are shown in Table 5.

Table 5 Per Protocol (PP) selection

	SCIT	UC	Total
Total	93	90	183
PP-selection			
unknown	2	0	2
included in PP	53	74	127
Not included in PP	38	16	54
Reasons for exclusion PP			
Dropouts	20	11	31
Switched from UC to SLIT*	0	5	5
Ended SCIT before end of study	16	0	16
Randomised to SCIT, but never started	2	0	2

**SLIT: sublingual immunotherapy*

Pollen

Pollen counts were obtained from three pollen-monitoring stations: University Medical Center Leiden, Elkerliek Ziekenhuis Helmond and Delmenhorst (Germany). Depending on their address, the participants were assigned to one of the pollen-monitoring stations.

A pollen season could be analysed if the mean daily pollen count was at least 25 pollen grains/m^3 during the peak period of April 1st-May 15 for tree pollen (birch) or May 15-June 30 for grass pollen of a particular year. In 2010 the pollen-monitoring stations in Leiden and Helmond recorded less than 25 grass pollen grains/m^3 in the peak season. The same applies to the tree pollen exposure measured in Leiden in 2012. Consequently, those seasons could not be analyzed.

Clinical efficacy per allergen

Tree pollen

Forty-eight patients allergic to tree pollen were randomised to SCIT whereas 45 were randomised to the UC group. These patients were included in the ITT analysis. Thirty-five and 39 patients remained in the PP analysis, respectively.

Univariable analysis

Analysis was performed for all patients without (A) and with correction (B) for sufficiently complete diaries (i.e. per diaries completed on >50% of the days with sufficient pollen counts). The latter selection yielded too much missing in the analysis of VAS, RQLQ and GA. Therefore, data without correction were analysed.

In addition, as in 2012 the mean daily pollen count was less than 25 pollen grains/m^3 during the period of April 1st-May 15 for tree pollen that year was considered a lost season. Therefore the second year could not be evaluated.

The ITT analysis did not demonstrate significant differences in symptom scores apart from a difference in lung symptoms (Table 6), percentage of symptom free days, medication free days or well days (Table 7) and VAS, RQLQ (Table 8).
GA was significant higher in the SCIT group for both 1st and 2nd year (Table 8). Although not significant the percentage of symptom free days was higher in the SCIT group. This was not the case for medication free days and well days.
MLR did not reveal an effect of SCIT on the mean total nasal symptom score either without or with pollen selection (Table 9).

ITT analysis

Table 6 Total daily symptom scores (TP)

a. Without selection for complete diaries and pollen relevant days

Year	Organ	SCIT	UC	Delta	p-value
1	Eye	1.1	1.7	-0.5	0.079
	Nose	2.6	3.4	-0.8	0.054
	Lung	0.4	0.8	-0.5	0.013
2	Eye	1.0	1.3	-0.3	0.438
	Nose	2.5	2.8	-0.4	0.715
	Lung	0.4	0.5	-0.1	0.453
b. With selection for complete diaries and pollen relevant days					
1	Eye	1.8	2.3	-0.5	0.438
	Nose	2.8	4.3	-1.4	0.453
	Lung	0.4	1.1	-0.7	0.715

Table 7 Percentage symptom free days, medication free days and well days (TP)

a. Without selection for complete diaries and pollen relevant days

	Year	SCIT%	UC%	p-value
Symptom free days	1	59.0	45.4	0.071
	2	59.4	47.5	0.310
Medication free days	1	75.7	78.2	0.768
	2	88.0	92.9	0.569
Well days	1	75.7	78.2	0.768
	2	88.0	92.9	0.569
b. With selection for complete diaries and pollen relevant days				
Symptom free days	1	42.7	45.4	0.213
Medication free days	1	71.9	75.9	0.731

Well days	1		71.9	75.9	0.731

Table 8 Mean VAS scores, RQLQ and Global assessment (GA) per season without selection for complete diaries and pollen relevant days (TP)

	Year	SCIT	UC	Delta	t-stat	p-value
VAS	1	41.3	45.2	-4.0	-0.65	0.519
	2	33.3	37.4	-10.7	-1.19	0.244
RQLQ	1	1.7	1.9	-0.2	-0.86	0.391
	2	1.3	1.8	-0.6	-1.94	0.059
GA	1	2.9	2.4	0.5	2.13	0.038
	2	3.1	2.4	0.7	2.17	0.036

Table 9 MLR of mean daily total nasal and eye symptom score (TP)

a. Without selection for complete diaries and pollen relevant days 1st year

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	1.019	1.506	0.677	0.501
Treatment SCIT	-0.245	0.483	-0.508	0.613
Age	0.008	0.036	0.234	0.816
Gender (female)	1.070	0.528	2.025	0.047
Specialist	0.650	0.540	1.204	0.233
Year of inclusion (2011)	-1.178	0.619	-1.902	0.061
Patients with 1 allergy	1.006	0.628	1.604	0.113
Patients with > 1 allergy	-0.646	0.515	-1.253	0.214
Retrospective score	0.087	0.099	0.880	0.382
b. Without selection for complete diaries and pollen relevant days 2nd year				
(not available)				
c. With selection for complete diaries and pollen relevant days 1st year				
(Intercept)	2.150	2.351	0.914	0.365
Treatment SCIT	-0.854	0.705	-1.212	0.231
Age	0.013	0.054	0.245	0.807
Gender (female)	0.924	0.756	1.222	0.227
Specialist	0.892	0.825	1.080	0.285
Year of inclusion (2011)	-1.0317	1.296	-0.796	0.430
Patients with 1 allergy	0.559	0.999	0.559	0.578
Patients with > 1 allergy	-0.535	0.742	-0.721	0.474
Retrospective score	0.008	0.150	0.054	0.957
d. With selection for complete diaries and pollen relevant days 2nd year				
(not available)				

PP analysis

The PP demonstrated significantly lower nasal and lung symptom scores after selection for pollen relevant days (Table 10b.). However, the difference is very small. No significant differences was seen in percentage of symptom free days, medication free days or well days (Table 11) and VAS, RQLQ (Table 12). GA was significant higher in the SCIT group for the 2nd year (Table 12) Again, although not significant the percentage of symptom free days was higher in the SCIT group. This was not the case for medication free days and well days. MLR did not reveal an effect of SCIT on the mean total nasal symptom score either without or with pollen selection (

Table 13).

Table 10 Total daily symptom scores (TP)

a. Without selection for complete diaries and pollen relevant days

Year	Organ	SCIT	UC	Delta	p-value
1	Eye	1.2	1.5	-0.3	0.421
	Nose	2.5	3.1	-0.6	0.197
	Lung	0.3	0.7	-0.4	0.050
2	Eye	1.0	1.3	-0.3	0.387
	Nose	2.5	2.8	-0.4	0.618
	Lung	0.4	0.5	-0.1	0.698

b. With selection for complete diaries and pollen relevant days					
Year	**Organ**	**SCIT**	**UC**	**Delta**	**p-value**
1	Eye	1.0	1.3	-0.3	0.365
	Lung	0.4	0.5	-0.1	0.006

Table 11 Percentage symptom free days, medication free days and well days (TP)

a. Without selection for complete diaries and pollen relevant days

	Year	**SCIT%**	**UC%**	**p-value**
Symptom free days	1	57.5	50.5	0.420
	2	59.5	49.5	0.421
Medication free days	1	69.7	77.5	0.455
	2	84.8	92.4	0.455
Well days	1	69.7	77.5	0.445
	2	84.8	92.4	0.445
b. With selection for complete diaries and pollen relevant days				
Symptom free days	1	42.5	50.5	0.533
Medication free days	1	63.9	75.1	0.419
Well days	1	63.9	75.1	0.419

Table 12 Mean VAS scores, RQLQ and Global assessment (GA) per season

Without selection for complete diaries and pollen relevant days (TP)

	Year	**SCIT**	**UC**	**Delta**	**t-stat**	**p-value**
VAS	1	37.5	43.4	-5.9	-0.89	0.3764
	2	34.7	45.8	-11.1	-1.16	0.2557
RQLQ	1	1.7	1.9	-0.2	-1.02	0.3132
	2	1.3	1.9	-0.5	-1.69	0.1009
GA	1	3.0	2.4	0.5	1.96	0.0556
	2	3.1	2.4	0.8	2.17	0.0370

Table 13 MLR of mean daily total nasal and eye symptom score (TP)

	Estimate	Std. Error	t value	Pr(>|t|)
a. Without selection for complete diaries and pollen relevant days 1st year				
(Intercept)	1.403	1.498	0.936	0.354
Treatment SCIT	-0.044	0.506	-0.087	0.931
age	0.006	0.039	0.145	0.885
Gender (female)	0.821	0.537	1.529	0.132
Specialist	0.669	0.582	1.151	0.255
Year of inclusion (2011)	-1.339	0.626	-2.139	0.037
Patients with 1 allergy	1.577	0.648	2.432	0.018
Patients with > 1 allergy	-0.436	0.542	-0.805	0.425
Retrospective score	0.023	0.113	0.199	0.843
b. Without selection for complete diaries and pollen relevant days 2nd year				
(not available)				
c. With selection for complete diaries and pollen relevant days 1st year				
(Intercept)	1.362	2.454	0.555	0.582
Treatment SCIT	-0.573	0.768	-0.746	0.460
age	0.033	0.064	0.511	0.612
Gender (female)	0.770	0.785	0.981	0.333
Specialist	1.054	0.982	1.074	0.290
Year of inclusion (2011)	-2.601	1.367	-1.902	0.065
Patients with 1 allergy	0.747	1.080	0.692	0.493
Patients with > 1 allergy	-0.834	0.792	-1.056	0.297
Retrospective score	0.025	0.174	0.143	0.887
d. With selection for complete diaries and pollen relevant days 2nd year				
(not available)				

Grass pollen

Seventy-six patients allergic to grass pollen were randomised to SCIT whereas 45 were randomised to the UC group. These patients were included in the ITT analysis. Fifty-seven and 37 patients remained in the PP analysis, respectively.

Univariable analysis
Analysis was performed for all patients without (A) and with correction (B) for sufficiently complete diaries (i.e. per season >50% of the relevant pollen days). The latter selection yielded too much missing in the analysis of VAS, RQLQ and GA. Therefore, data without correction were analysed

ITT analysis
The ITT analysis did not demonstrate significant differences in symptom scores apart from a difference in lung symptoms in the 1st year and lower eye symptoms in the 1st and 2nd year in the SCIT group (Table 14), percentage of symptom free days, medication free days or well days (Table 15) and VAS, RQLQ (Table 16). GA was significant higher in the SCIT group for both 1st and 2nd year (Table 16). Although not significant the percentage of symptom free days, medication free days and well days was higher in the SCIT group.
MLR did not reveal an effect of SCIT on the mean total nasal symptom score either without or with pollen selection (Table 17).

Table 14 Total daily symptom scores (ITT)
a. Without selection for complete diaries and pollen relevant days (GP)

Year	Organ	SCIT	UC	Delta	p-value
1	Eye	1.3	1.7	-0.4	0.129
	Nose	2.7	3.1	-0.4	0.214
	Lung	0.4	0.7	-0.3	0.038
2	Eye	1.0	1.3	-0.3	0.210
	Nose	2.5	2.8	-0.4	0.453
	Lung	0.4	0.5	-0.1	0.715
b. With selection for complete diaries and pollen relevant days					
1	Eye	1.6	2.4	-0.9	0.017
	Nose	3.1	3.2	-0.1	0.821
	Lung	0.5	0.7	-0.2	0.276
2	Eye	1.3	2.1	-0.8	0.024
	Nose	2.8	3.3	-0.5	0.250
	Lung	0.4	0.6	-0.2	0.227

Table 15 Percentage symptom free days, medication free days and well days (GP)
a. Without selection for complete diaries and pollen relevant days

	Year	SCIT%	UC%	p-value
Symptom free days	1	54.0	45.9	0.187
	2	54.3	43.6	0.200
Medication free days	1	77.5	75.0	0.727
	2	90.5	80.1	0.181
Well days	1	77.5	75.0	0.727
	2	90.5	80.1	0.181
b. With selection for complete diaries and pollen relevant days				
Symptom free days	1	47.3	35.9	0.088
	2	47.7	35.9	0.170
Medication free days	1	77.7	70.7	0.488
	2	94.7	77.6	0.084
Well days	1	77.7	70.7	0.488
	2	94.7	77.6	0.084

Table 16 Mean VAS scores, RQLQ and Global assessment (GA) per season (GP)
Without selection for complete diaries and pollen relevant days

	Year	SCIT	UC	Delta	t-stat	p-value
VAS	1	36.2	38.8	-2.7	-0.67	0.505
	2	33.0	34.6	-1.6	-0.33	0.739
RQLQ	1	1.6	1.8	-0.2	-1.22	0.225
	2	1.5	1.7	-0.3	-1.28	0.206
GA	1	3.0	2.6	0.4	2.15	0.034
	2	3.0	2.4	0.5	2.09	0.041

Table 17 MLR of mean daily total nasal and eye symptom score (GP)

	Estimate	Std. Error	t-stat	Pr(>|t|)
a. Without selection for complete diaries and pollen relevant days 1st year				
(Intercept)	-1.587	2.303	-0.689	0.492
Treatment SCIT	-0.294	0.389	-0.757	0.451
age	-0.012	0.027	-0.456	0.649
Gender (female)	0.913	0.398	2.296	0.024
Specialist	1.082	0.503	2.152	0.034
Year of inclusion (2010)	2.747	2.165	1.269	0.207
Year of inclusion (2011)	1.940	2.209	0.878	0.382
Patients with 1 allergy	0.709	0.409	1.734	0.086
Patients with > 1 allergy	-0.036	0.398	-0.090	0.928
Retrospective score	0.097	0.085	1.145	0.255
b. Without selection for complete diaries and pollen relevant days 2nd year				
(Intercept)	-0.129	1.902	-0.068	0.946
Treatment SCIT	-0.303	0.457	-0.662	0.510
age	-0.019	0.034	-0.556	0.580
Gender (female)	0.352	0.466	0.755	0.453
Specialist	0.747	0.629	1.185	0.240
Year of inclusion (2010)	1.231	1.187	1.037	0.303
Patients with 1 allergy	0.446	0.485	0.920	0.361
Patients with > 1 allergy	0.567	0.463	1.224	0.225
Retrospective score	0.131	0.110	1.191	0.238

c. With selection for complete diaries and pollen relevant days 1st year

	Estimate	Std. Error	t-stat	Pr(>|t|)
(Intercept)	-1.001	1.898	-0.528	0.599
Treatment SCIT	-0.659	0.537	-1.227	0.223
Age	0.036	0.039	0.918	0.361
Gender (female)	0.625	0.546	1.145	0.255
Specialist	1.607	0.726	2.213	0.030
Year of inclusion (2010)	-0.587	0.720	-0.815	0.418
Year of inclusion (2011)	1.639	0.569	2.882	0.005
Patients with 1 allergy	-0.631	0.553	-1.140	0.257
Patients with > 1 allergy	0.203	0.123	1.657	0.101
Retrospective score	-1.001	1.898	-0.528	0.599
d. With selection for complete diaries and pollen relevant days 2nd year				
(Intercept)	-1.157	2.241	-0.516	0.607
Treatment SCIT	-0.718	0.527	-1.361	0.179
Age	0.013	0.040	0.347	0.730
Gender (female)	0.437	0.547	0.799	0.428
Specialist	0.140	0.747	0.188	0.852
Year of inclusion (2010)	1.278	1.274	1.002	0.320
Patients with 1 allergy	0.588	0.544	1.081	0.284
Patients with > 1 allergy	0.424	0.529	0.801	0.426
Retrospective score	0.155	0.132	1.170	0.247

Per protocol analysis

The PP analysis did not demonstrate significant differences in symptom scores (Table 18), percentage of symptom free days, medication free days or well days (Table 19) and VAS, RQLQ and GA (Table 20).

MLR did not reveal an effect of SCIT on the mean total nasal symptom score either without or with pollen selection (Table 21).

Table 18 Total daily symptom scores (GP)

a. Without selection for complete diaries and pollen relevant days

Year	Organ	SCIT	UC	Delta	p-value
1	Eye	1.3	1.5	-0.2	0.575
	Nose	2.6	2.9	-0.3	0.414
	Lung	0.4	0.6	-0.2	0.259
2	Eye	1.2	1.5	-0.3	0.310
	Nose	2.6	2.7	-0.1	0.894
	Lung	0.5	0.4	0.0	0.939
b. With selection for complete diaries and pollen relevant days					
1	Eye	1.6	2.2	-0.6	0.129
	Nose	3.0	2.9	0.1	0.856
	Lung	0.6	0.6	-0.1	0.741
2	Eye	1.4	2.1	-0.7	0.059
	Nose	2.9	3.4	-0.5	0.311
	Lung	0.4	0.5	-0.1	0.410

Table 19 Percentage symptom free days, medication free days and well days (GP)

a. Without selection for complete diaries and pollen relevant days				
	Year	**SCIT%**	**UC%**	**p-value**
Symptom free days	1	53.8	50.5	0.637
	2	54.2	45.8	0.236
Medication free days	1	73.1	76.5	0.679
	2	88.3	83.2	0.524
Well days	1	73.1	76.5	0.679
	2	88.3	83.2	0.524
b. With selection for complete diaries and pollen relevant days				
Symptom free days	1	47.6	50.5	0.236
	2	45.0	45.8	0.443
Medication free days	1	74.0	72.9	0.921

	2	93.5	80.9	0.228
Well days	1	74.0	72.9	0.921
	2	93.5	80.9	0.228

Table 20 Mean VAS scores, RQLQ and Global assessment (GA) per season (GP)

	Year	SCIT	UC	Delta	t-stat	p-value
VAS	1	32.6	42.7	-10.1	-1.70	0.093
	2	38.3	38.1	0.2	0.03	0.979
RQLQ	1	1.5	1.8	-0.3	-1.38	0.170
	2	1.4	1.7	-0.3	-1.20	0.235
GA	1	1.5	1.8	-0.3	-1.38	0.170
	2	1.4	1.7	-0.3	-1.20	0.235

Table 21 MLR of mean daily total nasal and eye symptom score (GP)
a. Without selection for complete diaries and pollen relevant days 1st year

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	-1.141	2.188	-0.521	0.604
Treatment SCIT	-0.164	0.413	-0.397	0.693
Age	-0.030	0.029	-1.037	0.303
Gender (female)	0.814	0.412	1.977	0.051
Specialist	0.897	0.571	1.572	0.120
Year of inclusion (2010)	2.876	1.999	1.439	0.154
Year of inclusion (2011)	2.034	2.047	0.994	0.323
Patients with 1 allergy	0.922	0.447	2.060	0.043
Patients with > 1 allergy	0.269	0.426	0.632	0.529
Retrospective score	0.069	0.090	0.770	0.444

b. Without selection for complete diaries and pollen relevant days 2nd year				
	Estimate	**Std. Error**	**t value**	**Pr(>|t|)**
(Intercept)	-1.316	2.059	-0.639	0.525
Treatment SCIT	-0.045	0.502	-0.090	0.929
Age	-0.012	0.038	-0.326	0.746
Gender (female)	0.523	0.504	1.037	0.304
Specialist	1.321	0.772	1.710	0.092
Year of inclusion (2010)	1.446	1.215	1.190	0.239
Patients with 1 allergy	0.911	0.556	1.639	0.106
Patients with > 1 allergy	0.190	0.533	0.356	0.723
Retrospective score	0.194	0.126	1.535	0.130
c. With selection for complete diaries and pollen relevant days 1st year				
(Intercept)	-1.172	2.112	-0.555	0.581
Treatment SCIT	-0.278	0.588	-0.472	0.638
Age	0.037	0.043	0.851	0.397
Gender (female)	0.709	0.588	1.205	0.232
Specialist	1.635	0.843	1.940	0.056
Year of inclusion (2010)	-0.886	0.773	-1.147	0.255
Year of inclusion (2011)	1.789	0.663	2.696	0.009
Patients with 1 allergy	-0.413	0.624	-0.662	0.510
Patients with > 1 allergy	0.171	0.139	1.227	0.224
Retrospective score	-1.172	2.112	-0.555	0.581
d. With selection for complete diaries and pollen relevant days 2nd year				
(Intercept)	-2.558	2.302	-1.111	0.272
Treatment SCIT	-0.520	0.552	-0.941	0.351
Age	0.024	0.042	0.583	0.562
Gender (female)	0.582	0.557	1.045	0.301
Specialist	0.884	0.884	1.000	0.322
Year of inclusion (2010)	1.444	1.257	1.149	0.256

Patients with 1 allergy	1.097	0.601	1.826	0.074
Patients with > 1 allergy	0.010	0.584	0.018	0.986
Retrospective score	0.230	0.142	1.617	0.112

House dust mites

Forty-four patients allergic to HDM were randomised to SCIT whereas 45 were randomised to the UC group. These patients were included in the ITT analysis. Thirty-eight and 37 patients remained in the PP analysis, respectively.

ITT analysis

The ITT demonstrated significantly lower eye symptom scores in the first year (Table 23). However, the difference is very small. This difference was not significant in the second year. A higher percentage of symptom free days, medication free days or well days was seen in the SCIT group. The difference in symptom free days in the 1st year only was significant (Table 23). No difference was seen in VAS, RQLQ and GA (Table 24). MLR did not reveal an effect of SCIT on the mean total nasal and eye symptom score either without or with pollen selection (Table 25).

Table 22 Total daily symptom scores (HM)

Year	Organ	SCIT	UC	Delta	p-value
1	Eye	1.1	1.8	-0.7	0.034
	Nose	2.8	3.4	-0.6	0.209
	Lung	0.4	0.7	-0.3	0.086
2	Eye	0.9	1.4	-0.5	0.132
	Nose	2.8	2.4	0.3	0.494
	Lung	0.7	0.4	0.2	0.357

Table 23 Percentage symptom free days, medication free days and well days (HM)

	Year	SCIT%	UC%	p-value
Symptom free days	1	59.3	42.2	0.028
	2	61.0	40.4	0.061
Medication free days	1	78.1	69.4	0.339
	2	87.6	74.0	0.205

Well days		1	78.1	69.4	0.339
		2	87.6	74.0	0.205

Table 24 Mean VAS scores, RQLQ and Global assessment (GA) per season (HM)

	Year	SCIT	UC	Delta	t-stat	p-value
VAS	1	35.7	33.5	2.3	0.38	0.707
	2	44.7	36.8	7.9	1.01	0.320
RQLQ	1	1.8	2.0	-0.2	-0.92	0.361
	2	1.7	1.8	-0.2	-0.55	0.585
GA	1	2.7	2.6	0.0	0.05	0.962
	2	2.7	2.4	0.3	0.79	0.438

Table 25
a. MLR of mean daily total nasal and eye symptom score 1st year (HM)

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	-3.135	2.234	-1.403	0.165
Treatment SCIT	-0.017	0.537	-0.032	0.974
Age	0.025	0.036	0.693	0.491
Gender (female)	1.772	0.560	3.164	0.002
Specialist	0.442	0.641	0.690	0.492
Year of inclusion (2010)	2.338	1.764	1.326	0.189
Year of inclusion (2011)	1.593	1.882	0.846	0.400
Patients with 1 allergy	-0.495	0.611	-0.810	0.421
Patients with > 1 allergy	0.462	0.663	0.696	0.489
Retrospective score	0.215	0.126	1.709	0.092
b. MLR of mean daily total nasal and eye symptom score 2nd year				
(Intercept)	-1.365	2.068	-0.660	0.513
Treatment SCIT	0.224	0.535	0.420	0.677
Age	-0.014	0.040	-0.358	0.722
Gender (female)	0.122	0.533	0.228	0.821
Specialist	-0.091	0.621	-0.147	0.884
Year of inclusion (2010)	1.884	1.369	1.377	0.177
Patients with 1 allergy	-0.136	0.579	-0.235	0.816
Patients with > 1 allergy	0.334	0.607	0.550	0.585
Retrospective score	0.237	0.115	2.058	0.046

Per protocol analysis

In general, the PP demonstrate lower symptom scores (Table 26) in the SCIT group, higher percentage of symptom free days, medication free days or well days in the SCIT group (Table 27) and lower RQLQ in the SCIT group (28). However statistical significance was not reached. GA was significant higher in the 2nd year. MLR did not reveal an effect of SCIT on the mean total nasal and eye symptom score (table 29).

Table 26 Total daily symptom scores (HM)

Year	Organ	SCIT	UC	Delta	p-value
1	Eye	1.1	1.5	-0.4	0.244
	Nose	2.6	3.0	-0.6	0.344
	Lung	0.4	0.6	-0.2	0.384
2	Eye	0.9	1.3	-0.4	0.132
	Nose	2.6	2.4	0.2	0.494
	Lung	0.6	0.4	0.3	0.357

Table 27 Percentage symptom free days, medication free days and well days (HM)

	Year	SCIT%	UC%	p-value
Symptom free days	1	58.5	46.8	0.206
	2	61.3	43.4	0.171
Medication free days	1	70.3	68.8	0.897
	2	84.9	76.8	0.524
Well days	1	70.3	68.8	0.897
	2	84.9	76.8	0.524

Table 28 Mean VAS scores, RQLQ and Global assessment (GA) per season (HM)

	Year	SCIT	UC	Delta	t-stat	p-value
VAS	1	33.1	31.3	1.9	0.32	0.749
	2	41.8	36.1	5.7	0.69	0.500
RQLQ	1	1.7	1.9	-0.3	-1.00	0.323
	2	1.7	1.9	-0.2	-0.48	0.634
GA	1	2.7	2.6	0.0	0.15	0.881
	2	3.0	2.4	0.7	2.53	0.014

Table 29
a. MLR of mean daily total nasal and eye symptom score 1st year (HM)

	Estimate	Std. Error	t value	Pr(>|t|)

(Intercept)	1.494	2.223	-0.672	0.505
Treatment SCIT	0.109	0.576	0.188	0.851
Age	0.001	0.038	-0.028	0.978
Gender (female)	1.125	0.608	1.847	0.071
Specialist	0.061	0.762	0.081	0.936
Year of inclusion (2010)	2.165	1.537	1.408	0.166
Year of inclusion (2011)	1.412	1.667	0.847	0.401
Patients with 1 allergy	-0.711	0.658	-1.080	0.286
Patients with > 1 allergy	0.759	0.731	1.039	0.304
Retrospective score	0.162	0.125	1.296	0.202

b. MLR of mean daily total nasal and eye symptom score 2nd year

	Estimate	**Std. Error**	**t value**	**Pr(>|t|)**
(Intercept)	-1.494	2.341	-0.620	0.540
Treatment SCIT	0.497	0.633	0.785	0.439
Age	-0.006	0.044	-0.133	0.895
Gender (female)	0.192	0.631	0.305	0.763
Specialist	0.612	0.796	0.769	0.448
Year of inclusion (2011)	1.525	1.361	1.121	0.272
Patients with 1 allergy	-0.218	0.685	-0.318	0.753
Patients with > 1 allergy	-0.227	0.723	-0.314	0.755
Retrospective score	0.242	0.133	1.825	0.078

Linear Mixed Models

Table 30 shows the results from linear mixed modelling. This approach enabled us to include all available patients, and to use all daily symptom scores and pollen counts. A significant effect from the birch or grass pollen count could be seen in patients allergic to tree pollen or grass pollen. Significant effects from the treatment with SCIT on the total daily score could not be demonstrated. Also, no interaction from concomitant allergies could be found.

Table 30 Linear Mixed Models

Allergy	models	Fixed effects	Estimate	Std. Error	t-value
Tree pollen	Tree pollen only (R = 0.797)	Intercept	4.128	1.719	2.401
		Log (birch pollen)	0.768	0.259	2.968
		Log (grass pollen	1.312	0.417	3.147
		Treatment SCIT	0.171	2.919	0.058
	All tree pollen allergic subjects (R = 0.789)	Intercept	3.676	1.139	3.227
		Log (birch pollen)	1.318	0.070	18.746
		Log (grass pollen	0.941	0.078	12.047
		Treatment SCIT	-0.561	0.735	-0.764
		TP+GP	-0.787	1.262	-0.624
		TP+GP+HDM	0.453	1.251	0.362
		TP + HDM	2.190	1.681	1.303
Grass pollen	Grass pollen only (R = 0.729)	Intercept	4.020	0.795	5.059
		Log (grass pollen)	1.169	0.209	5.584
		Log (birch pollen)	0.562	0.409	1.374
		Treatment SCIT	0.135	1.091	0.123
	All grass pollen allergic subjects (R = 0.708)	Intercept	4.326	0.585	7.396
		Log (grass pollen)	0.962	0.071	13.627
		Log (birch pollen)	1.276	0.071	18.033
		Treatment SCIT	-0.324	0.572	-0.567
		GP+HM	-0.601	0.900	-0.668
		GP+TP	-1.542	0.763	-2.022
		GP+TP+HDM	0.297	0.745	-0.398
All groups	Without house dust mites (R = 0.694)	Intercept	4.309	0.616	7.000
		Log (grass pollen)	0.880	0.131	6.730
		Log (birch pollen)	1.159	0.120	9.656
		Treatment SCIT	0.173	0.690	0.250
		TP	-0.607	1.141	-0.532
		GP+TP	-1.573	0.733	-2.145

	With house dust mite (R = 0.743)	Intercept	3.621	1.065	3.401
		Log (grass pollen)	0.882	0.070	12.619
		Log (birch pollen)	1.294	0.072	18.082
		Treatment SCIT	0.082	0.917	0.089
		HM	1.557	1.335	1.166
		TP+HM	0.281	1.166	0.241
		GP+TP+HM	2.137	1.810	1.181

Dependent variable: Total daily score (eye/nose/lung); Random effects: Patient ID, Dates of assessment;
R: correlation between fitted and observed data

Separate linear mixed models for tree pollen, grass pollen and house dust mites with an interaction term for dropout and treatment did not reveal an effect modification (data not shown).

IgG4 levels

IgG4 was used as a marker of immunological response to SCIT. Ideally, IgG4 was expected to increase in the SCIT group, whereas the UC group should not be characterised by an increase in IgG4.

Table 31 shows the mean difference in IgG4 (mg/l) for SCIT and UC.

Table 31 IgG4

Allergen	**SCIT**			**UC**		
	baseline	end	difference	baseline	end	difference
Tree pollen	0.52	3.95	3.43	0.67	0.64	-0.03
Grass pollen	0.17	7.14	6.97	0.24	0.55	0.31
House dust mite	0.30	2.44	2.15	0.27	0.32	0.05

A global assessment score after the 1st and 2nd year evaluated improvement assessed by the patient. A significant higher score was seen after the 2nd year for both the ITT and PP analysis (Table 32).

Table 32 Global assessment after 1 and 2 years

a. ITT analysis

	Year	**SCIT**	**UC**	**Delta**	**t-stat**	**p-value**
GA	1	2.9	2.6	0.3	1.50	0.136
	2	2.9	2.4	0.5	2.33	0.022
b. PP analysis						
GA	1	3.0	2.6	0.3	1.91	0.059
	2	3.1	2.4	0.8	3.28	0.002

Results cost-effectiveness analysis

Patients included in the health economic data set

Of the 183 patients who were randomized, 170 patients completed at least one RUQ-Rhinitis, 84 in SCIT and 86 in UC. These patients were included in the cost analysis. Just as for the total group of randomized patients the two groups were comparable with respect to baseline characteristics, except for the fact that the proportion of patients with a skin disease was higher in SCIT (19.4%) than in UC (7.8%).

Resource utilization, absenteeism and presenteeism

Table 33 provides an overview of the percentage of patients that has used a particular healthcare service for allergic rhinitis at least once, had at least one spell of absence from paid work or reported at least one hour of presenteeism. Note that the visits to the clinic to get the SCIT injections were not included in this overview. There were no rhinitis-related hospital admissions, visits to paramedical caregivers, alternative healers or home care. There were no statistically significant differences. It is of interest that over 40% of patients in both groups reported that they felt less productive at work due to the rhinitis symptoms they experienced.

Table 33 Number and proportion of patients with healthcare utilization, absenteeism and presenteeism

	SCIT (n=84)		**Usual care (n=86)**		**P-value***
	N	%	N	%	
General practitioner	23	27	20	23	0.54
Specialist[#]	26	31	34	40	0.24
Other healthcare provider[$]	5	6	7	8	0.58
Emergency department	2	2	1	1	0.62
Absence from work	15	18	9	11	0.17
Presenteeism	37	44	38	44	0.99
(Un)paid household help	12	14	15	17	0.32

* *Differences in percentages were tested with Fisher's exact test or Chi-Square test;* [#]*Allergologist, ENT physician or pulmonologist;* [$]*Other healthcare provider: physical therapist, paramedical healthcare provider or provider of alternative medicine*

Table 34 presents the mean unadjusted health care utilization and other resource utilization during the first year and the second year of the study. There do not seem to be major differences, although the number of contacts with other healthcare providers in year 1, absenteeism in year 1 and presenteeism in year 2 is slightly higher in the SCIT group.

Table 34 Mean (SD) of health care utilization, absenteeism and presenteeism per patient

	Year 1	**Year 2**

	SCIT (n=84)	Control (n=86)	Diff.	SCIT (n=47)	Control (n=54)	Diff.
Number of GP contacts	0.88 (2.29)	0.65 (1.91)	0.23	0.36 (1.70)	0.37 (1.79)	-0.01
Number of specialist contacts	2.17 (5.09)	2.37 (5.28)	-0.20	0.46 (2.21)	0.33 (1.49)	0.12
Number of other healthcare provider contacts	0.95 (5.49)	0.23 (1.14)	0.71	0.21 (1.96)	0.28 (1.41)	-0.07
Number of emergency department visits	0.06 (0.51)	0.05 (0.43)	0.01	0.02 (0.22)	0	0.02
Hours of (un)paid household help	6.46 (29.25)	1.85 (9.20)	4.61	0.60 (3.55)	1.30 (6.78)	0.70
Days of absence from paid work	1.87 (7.21)	1.19 (5.12)	0.68	1.08 (4.02)	0.24 (1.23)	0.84
Number of hours required to compensate for lost productivity while at work	24.23 (62.20)	25.85 (60.14)	-1.62	18.24 (70.13)	11.31 (31.19)	6.93

Costs

Table 35 and Table 36 show the unadjusted costs from the healthcare and the societal perspective as calculated from the resource use in the RUQ-Rhinitis, before modelling. For patients who do not complete the trial, the costs up until the point of dropout are included. As expected in the SCIT group, the main cost driver was the immunotherapy including the costs of (administering) the study medication. For a monosensitized patient who completed the 2-year trial, the costs of SCIT study medication were €1735.82, i.e. €425.80 for the updosing phase and €1310.02 for the maintenance phase. Of note is the fact that the majority of trial participants had at least two sensitizations. The costs of administering SCIT during two trial years in this patient were €568.12, of which €252.50 was incurred during the updosing phase and €315.62 during the maintenance phase. Unlike SCIT study medication costs, costs of administering SCIT were the same for mono- and multi sensitised patients. SCIT study medication costs of a patient that was treated for one year were €934.40, including €425.80 for the updosing phase and €508.60 for the maintenance phase. Costs of administration in the one-year trial cohort were unchanged for the updosing phase (€252.50) but were lower during the maintenance phase (€126.25) due to the limited trial duration which decreases the length of the maintenance phase. Apart from the study medication costs, the healthcare costs of allergic rhinitis are relatively low. The costs of symptomatic medication were somewhat lower in SCIT and the costs of contact with other healthcare providers were somewhat higher in SCIT than in SLIT (Table 35).

When adopting a societal perspective (Table 36), the second major cost driver besides the cost of study medication was productivity loss, either due to absence from work or reduced productivity while at work. Productivity loss seemed to be higher in SCIT than in UC, which is probably due to the need to take time off work to visit the clinic to receive SCIT.

Table 35 Mean (SD) unadjusted costs per patient from the healthcare perspective during year 1 and year 2, 2012 euros

	Year 1			**Year 2**		
	SCIT (n=84)	usual care (n=86)	Diff.	SCIT (n=47)	usual care (n=54)	Diff.
GP	22.34 (64.64)	15.08 (44.46)	7.26	8.33 (32.07)	10.02 (46.60)	-1.69

Specialist	166.06 (389.33)	181.24 (403.89)	-15.18	35.03 (169.41)	25.62 (113.92)	9.41
Other healthcare provider	51.56 (297.81)	11.16 (52.67)	40.40	11.79 (108.02)	11.98 (56.65)	-0.19
Emergency department	8.88 (81.42)	7.44 (68.97)	1.45	3.81 (34.89)	0	3.81
Symptomatic medication*	121.88 (197.14)	150.14 (219.10)	-28.26	42.79 (98.78)	86.29 (212.00)	-43.50
Total costs excl. study medication	370.73 (668.64)	365.06 (504.06)	5.66	101.74 (245.26)	133.91 (271.85)	-32.16
Study medication[#]	1586.56 (747.18)	N/A	1586.56	873.23 (781.44)	N/A	873.23
Administering SCIT	362.41 (57.20)	N/A	362.41	123.51 (88.44)	N/A	123.51
Total costs incl. SCIT	2319.70 (961.42)	365.06 (504.06)	1954.64	1098.49 (930.38)	133.91 (271.85)	964.58

** Without study medication; [#] excluding costs of administering SCIT*

Table 36 Mean (SD) unadjusted costs per patient from the societal perspective during year 1 and year 2, 2012 euros

	Year 1			**Year 2**		
	SCIT (n=84)	Usual care (n=86)	Diff.	SCIT (n=47)	Usual Care (n=54)	Diff.
GP	22.34 (64.64)	15.08 (44.46)	7.26	8.33 (32.07)	10.02 (46.60)	-1.69
Specialist	166.06 (389.33)	181.24 (403.89)	-15.18	35.03 (169.41)	25.62 (113.92)	9.41
Other healthcare provider	51.56 (297.81)	11.16 (52.67)	40.40	11.79 (108.02)	11.98 (56.65)	-0.19
Emergency department	8.88 (81.42)	7.44 (68.97)	1.45	3.81 (34.89)	0	3.81
Symptomatic medication*	121.88 (197.14)	150.14 (219.10)	-28.26	42.79 (98.78)	86.29 (212.00)	-43.50
Informal care[#]	83.60 (378.80)	26.40 (140.50)	57.20	7.71 (45.98)	16.79 (87.78)	-9.09
Absenteeism	436.93 (1799.31)	250.00 (1156.99)	186.93	184.94 (669.82)	54.46 (294.25)	130.48
Presenteeism	726.63 (1931.35)	804.68 (1872.99)	-78.04	593.02 (2196.10)	353.01 (973.32)	240.01
Travel costs	25.17 (79.28)	21.43 (45.07)	3.74	8.90 (31.63)	6.34 (23.60)	2.56
Total costs excl. study medication	1643.06 (3020.25)	1467.57 (2922.75)	175.49	896.31 (2762.74)	564.51 (1203.20)	331.80
Study medication[$]	1586.56 (747.18)	N/A	1586.56	873.23 (781.44)	N/A	873.23
Administering SCIT	362.41 (57.20)	N/A	362.41	123.51 (88.44)	N/A	123.51
Total costs incl. study medication	3592.03 (2971.96)	1467.57 (2922.75)	2124.46	1893.06 (3092.54)	564.51 (1203.20)	1328.55

** without study medication; [$] excluding costs of administering SCIT; [#] including care provided by family members and (un)paid household help*

Table 35 Mean (SD) unadjusted costs per patient from the healthcare perspective during year 1 and year 2, 2012 euros

	Year 1			Year 2		
	SCIT (n=84)	usual care (n=86)	Diff.	SCIT (n=47)	usual care (n=54)	Diff.
GP	22.34 (64.64)	15.08 (44.46)	7.26	8.33 (32.07)	10.02 (46.60)	-1.69
Specialist	166.06 (389.33)	181.24 (403.89)	-15.18	35.03 (169.41)	25.62 (113.92)	9.41
Other healthcare provider	51.56 (297.81)	11.16 (52.67)	40.40	11.79 (108.02)	11.98 (56.65)	-0.19
Emergency department	8.88 (81.42)	7.44 (68.97)	1.45	3.81 (34.89)	0	3.81
Symptomatic medication*	121.88 (197.14)	150.14 (219.10)	-28.26	42.79 (98.78)	86.29 (212.00)	-43.50
Total costs excl. study medication	370.73 (668.64)	365.06 (504.06)	5.66	101.74 (245.26)	133.91 (271.85)	-32.16
Study medication[#]	1586.56 (747.18)	N/A	1586.56	873.23 (781.44)	N/A	873.23
Administering SCIT	362.41 (57.20)	N/A	362.41	123.51 (88.44)	N/A	123.51
Total costs incl. SCIT	2319.70 (961.42)	365.06 (504.06)	1954.64	1098.49 (930.38)	133.91 (271.85)	964.58

** Without study medication; [#] excluding costs of administering SCIT*

Table 36 Mean (SD) unadjusted costs per patient from the societal perspective during year 1 and year 2, 2012 euros

	Year 1			Year 2		
	SCIT (n=84)	Usual care (n=86)	Diff.	SCIT (n=47)	Usual Care (n=54)	Diff.
GP	22.34 (64.64)	15.08 (44.46)	7.26	8.33 (32.07)	10.02 (46.60)	-1.69
Specialist	166.06 (389.33)	181.24 (403.89)	-15.18	35.03 (169.41)	25.62 (113.92)	9.41
Other healthcare provider	51.56 (297.81)	11.16 (52.67)	40.40	11.79 (108.02)	11.98 (56.65)	-0.19
Emergency department	8.88 (81.42)	7.44 (68.97)	1.45	3.81 (34.89)	0	3.81
Symptomatic medication*	121.88 (197.14)	150.14 (219.10)	-28.26	42.79 (98.78)	86.29 (212.00)	-43.50
Informal care[#]	83.60 (378.80)	26.40 (140.50)	57.20	7.71 (45.98)	16.79 (87.78)	-9.09
Absenteeism	436.93 (1799.31)	250.00 (1156.99)	186.93	184.94 (669.82)	54.46 (294.25)	130.48
Presenteeism	726.63 (1931.35)	804.68 (1872.99)	-78.04	593.02 (2196.10)	353.01 (973.32)	240.01
Travel costs	25.17 (79.28)	21.43 (45.07)	3.74	8.90 (31.63)	6.34 (23.60)	2.56
Total costs excl. study medication	1643.06 (3020.25)	1467.57 (2922.75)	175.49	896.31 (2762.74)	564.51 (1203.20)	331.80
Study medication[$]	1586.56 (747.18)	N/A	1586.56	873.23 (781.44)	N/A	873.23
Administering SCIT	362.41 (57.20)	N/A	362.41	123.51 (88.44)	N/A	123.51
Total costs incl. study medication	3592.03 (2971.96)	1467.57 (2922.75)	2124.46	1893.06 (3092.54)	564.51 (1203.20)	1328.55

** without study medication; [$] excluding costs of administering SCIT; [#] including care provided by family members and (un)paid household help*

In Table 37 we grouped the costs by time period, where the uneven numbers indicate the allergy season and the even numbers the non-allergy periods. Time 0 is the time interval after randomization and before the first allergy season, time 1 is the first allergy season, time 2 is the period between the two allergy seasons and time 3 is the second allergy season etc. The first allergy season (time 1) is either the grass pollen season, tree pollen season or HDM season, depending on the sensitizations. Similarly, for the second allergy season (time 3). Only patients with a combination of sensitization that includes HDM (i.e. GP+HDM, TP+HDM, GP+TP+HDM) contribute to the estimates of time interval 5 to time 7. During the allergy season medication costs seem lower in the SCIT group than in the UC group.

Table 37 Mean unadjusted two-week costs from a societal perspective per time interval (uneven numbers are the allergen seasons), 2012 euros

	Time 0 SCIT N=82	**Time 0** UC N=84	**Time 1** SCIT N=76	**Time 1** Control N=75	**Time 2** SCIT N=57	**Time 2** Control N=66	**Time 3** SCIT N=50	**Time 3** Control N=54
GP	1.38	0.98	1.04	0.67	0.64	0.26	0.68	0.70
Specialist	11.33	10.20	7.71	9.33	1.34	2.74	1.63	2.20
Other healthcare provider	1.13	0.47	6.91	0.52	1.47	0.21	0.00	1.58
Emergency department	0.66	0.00	0.00	0.00	0.00	2.39	0.00	0.00
Symptomatic medication	5.19	5.85	6.66	9.40	3.77	6.46	3.81	8.31
Informal care	3.27	1.02	4.62	2.11	0.75	0.31	0	3.24
Absenteeism	30.34	18.26	20.62	6.43	4.94	17.33	15.16	3.27
Presenteeism	41.62	32.88	26.70	72.57	19.40	39.49	38.30	34.53
Travel costs	1.43	1.61	1.61	0.50	0.50	0.45	0.49	0.44
Total costs	75.75	72.14	74.57	101.51	32.82	69.63	54.27	67.65
	Time 4 SCIT N=37	**Time 4** UC N=36	**Time 5** SCIT N=16	**Time 5** UC N=17	**Time 6** SCIT N=11	**Time 6** UC N=16	**Time 7** SCIT N=10	**Time 7** UC N=16
GP	0.76	1.03	0.25	0.29	2.70	0.00	0.75	1.75
Specialist	0.98	0.00	19.50	4.88	0.00	0.00	0.00	1.50
Other healthcare provider	0.00	0.59	0.00	1.62	0.00	0.00	0.00	0.00
Emergency department	0.00	0.00	0.00	0.00	0.00	0.00	8.00	0.00
Symptomatic medication	1.97	3.88	3.20	8.59	1.60	7.87	3.83	5.88
Informal care	0.00	0.18	0..00	0.00	1.18	0.76	0.00	0.76
Absenteeism	10.11	0.00	13.22	0.00	0.00	0.00	22.47	14.69
Presenteeism	55.03	4.33	37.16	35.75	21.28	28.46	27.57	23.10
Travel costs	0.24	0.34	1.89	0.83	0.08	0.00	0.31	0.15
Total costs	67.65	10.35	75.22	51.96	26.84	37.09	62.92	47.83

The GEE models are given in Table 38. The dependent variable is the two-week cost per time interval. The coefficients should be interpreted as follows. During the first allergy season the two-week societal costs in patients with a seasonal allergy are 42% lower in SCIT than in UC (Exp (-0.5378)=0.58). In patients with a perennial allergy these costs are 37% lower in SCIT than in UC (Exp(0.0827 - 0.5378)=0.63). However, there is no statistically significant difference between SCIT and UC, neither during the allergy season (the uneven time intervals) or outside this season (the uneven time intervals). Only at time interval 4 and 7, there is a significant difference between SCIT and UC in favor of the latter, but these may be chance findings. There is a statistically significant difference in healthcare costs between patients with and without a perennial (=HDM) allergy, where the two-weeks costs are on average 2 Euros higher in patients with the perennial allergy (Exp(0.714)=2.03).

Table 38 GEE models of two-week costs from the health care and the societal perspective

	Health care perspective			**Societal perspective**		
	Coefficient	SE	P-value	Coefficient	SE	P-value
Constant	2.540	0.284	0.000	3.099	0.689	0.000
Time interval 1*	0.365	0.284	0.199	0.353	0.401	0.378
Time interval 2	-0.429	0.292	0.142	-0.289	0.412	0.482
Time interval 3*	-0.300	0.311	0.334	-0.277	0.437	0.527
Time interval 4	-1.394	0.359	0.000	-2.250	0.504	0.000
Time interval 5*	-0.508	0.487	0.297	-0.911	0.684	0.183
Time interval 6	-1.248	0.487	0.010	-1.079	0.684	0.115
Time interval 7*	-0.013	0.487	0.037	-1.016	0.685	0.138
Perennial allergy	0.710	0.292	0.015	0.643	0.382	0.092
Perennial allergy * Treatment	-0.634	0.421	0.133	0.083	0.548	0.880
	Health care perspective					**Societal perspective**
	Coefficient	SE	P-value	Coefficient	SE	P-value
Time 1 * Treatment	0.271	0.390	0.488	-0.538	0.521	0.302
Time 2 * Treatment	-0.098	0.412	0.812	-0.629	0.553	0.026
Time 3 * Treatment	-0.513	0.440	0.244	-0.013	0.593	0.983
Time 4 * Treatment	0.312	0.490	0.525	2.044	0.665	0.002
Time 5 * Treatment	0.972	0.709	0.170	0.527	0.981	0.591
Time 6 * Treatment	0.658	0.779	0.398	-0.147	1.081	0.892
Time 7 * Treatment	1.666	0.284	0.037	0.603	1.108	0.587
Gender	-0.452	0.209	0.030			
Skin disease	0.864	0.328	0.108			
Age				0.0256	0.0169	0.129

Perennial allergy: 1 = HDM with or without another allergy, 0 = seasonal allergy (GP and/or TP) only
Treatment: 1 = SCIT, 0 = UC; Gender: 1 = male, 0 = female; Skin disease: 1 = present, 0 = not present

From these models, the following cost differences were derived (Table 39).

Table 39 Adjusted difference in costs between SCIT and UC

	Costs from health care perspective (€)		
	SCIT	UC	Adjusted difference (95% CI)*
Excluding costs of study medication			
Year 1	402	452	- 50 (95%CI: -413;357)
Year 2	196	215	- 19 (95%CI: -227;275)
Year 1+2	598	667	- 69 (95%CI: -92;378)
Cost of study medication			
Year 1	1949	0	1949
Year 2	997	0	997
Year 1+2	2946	0	2946
Including costs of study medication			
Year 1	2351	452	1899 (95%CI: 128;3687)
Year 2	1193	215	978 (95%CI: 99;3214)
Year 1+2	3544	667	2877 (95%CI: 198;4178)
	Costs from societal perspective (€)		
	SCIT	UC	Difference (95% CI)*
Excluding costs of study medication			
Year 1	1915	2028	- 113 (95%CI: -3319;1722)
Year 2	1341	883	458 (95%CI: -970;2515)
Year 1+2	3256	2911	345 (95%CI: -1663;3538)
Cost of study medication			
Year 1	1949	0	1949
Year 2	997	0	997
Year 1+2	2946	0	2946
Including costs of study medication			
Year 1	3864	2028	1836 (95%CI: 219;3587)
Year 2	2338	883	1455 (95%CI: 355;4128)
Year 1+2	6202	2911	3291 (95%CI: 166;5986)

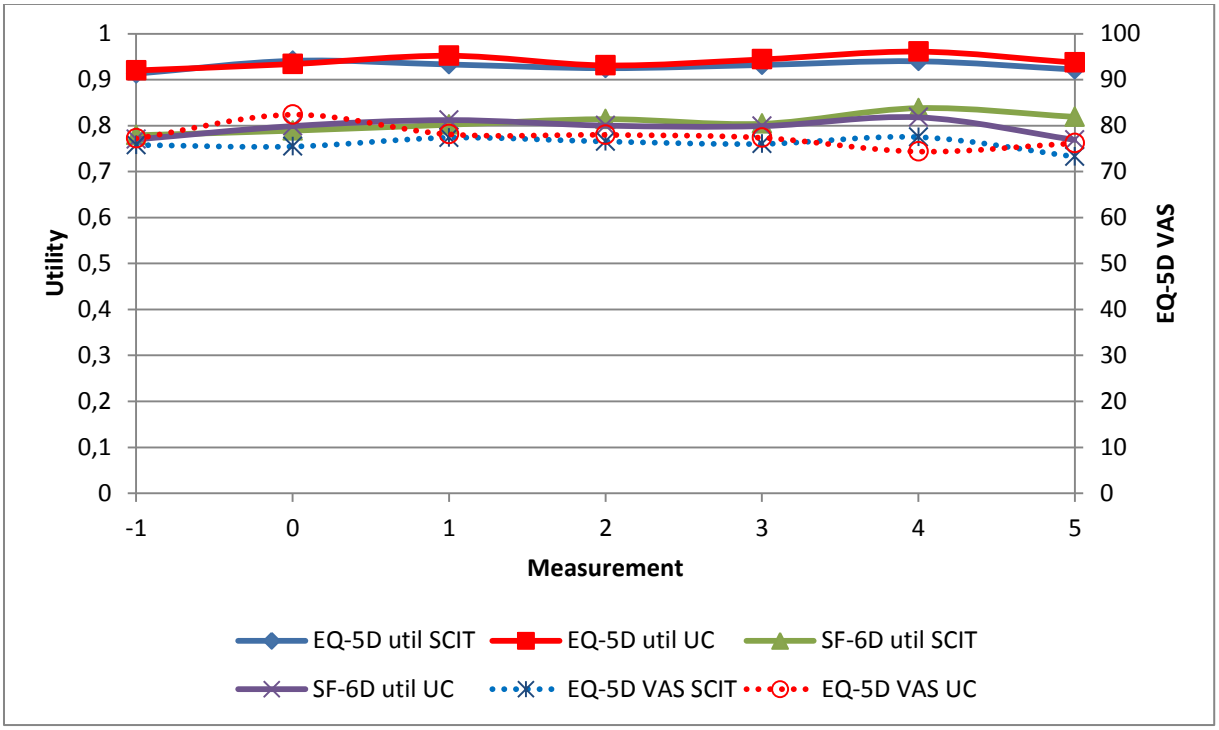
** 95% CI were based on bootstrapping*

Utilities and QALYs

Of the 183 trial participants, 156 completed at least one EQ-5D questionnaire (SCIT 76; UC 80). No significant differences in baseline characteristics between the two trial groups exist. The vast majority of patients in both treatment groups do not report any problems in any EQ-5D domain. About 10% of patients report some problems on the EQ-5D domains daily activities, pain and anxiety/depression. Similarly, the vast majority of patients do not report any limitations or problems on the SF-6D domains, except for the vitality domain where 10% scores problems all of the time, 25% most of the time and 20% some of the time. Also, on the SF-6D domain social functioning, 20-25% scores problems a little of the time.

Figure 6 shows the EQ-5D utility, EQ-5D VAS and SF-6D utilities over time. The EQ-5D utilities are consistently higher than the SF-6D utilities, but there is little difference between SCIT and UC over time.

Figure 6 EQ-5D VAS and utilities and SF-6D utilities



-1 refers to the baseline measurement; the uneven measurement numbers are measurements during the pollen season.

Table 40 shows the GEE models for EQ-5D and SF-6D utilities, respectively. There are no statistically significant differences between SCIT and UC on any of the time points. Patients with a perennial allergy (=HDM) have lower SF-6D utilities than patients without a perennial allergy.

Table 40 GEE models of EQ-5D and SF-6D utilities

	EQ-5D utility			**SF-6D utility**		
	Coefficient	SE	P-value	Coefficient	SE	P-value
Constant	0.997	0.038	0.000	0.826	0.037	0.000
Utility at screening	0.003	0.016	0.834	-0.011	0.012	0.343
Time interval 1*	0.013	0.017	0.457	0.004	0.013	0.752
Time interval 2	0.007	0.017	0.704	0.014	0.013	0.268
Time interval 3*	0.019	0.018	0.294	0.014	0.013	0.280
Time interval 4	0.038	0.0190	0.047	0.029	0.014	0.035
Time interval 5*	0.020	0.024	0.396	0.014	0.018	0.446
Perennial allergy	-0.017	0.020	0.403	-0.057	0.020	0.005
Perennial allergy * Treatment	-0.024	0.029	0.409	0.040	0.030	0.177
Screening utility * treatment	-0.001	0.023	0.957	-0.010	0.023	0.670
Time 0 * Treatment	0.010	0.025	0.681	-0.024	0.024	0.309
Time 1 * Treatment	-0.015	0.025	0.549	-0.029	0.025	0.234
Time 2 * Treatment	-0.008	0.025	0.746	-0.014	0.024	0.563
Time 3 * Treatment	-0.001	0.026	0.958	-0.023	0.024	0.347
Time 4 * Treatment	-0.023	0.027	0.397	-0.015	0.025	0.539
Time 5 * Treatment	-0.002	0.035	0.941	-0.012	0.030	0.690
Age	-0.002	0.001	0.021	-0.002	0.001	0.123
Gender	0.030	0.015	0.038	0.060	0.015	<0.001
Level of education	0.019	0.014	0.194	0.023	0.015	0.121
Referring doctor	-0.023	0.016	0.158			

Perennial allergy: 1 = HDM with or without another allergy, 0 = seasonal allergy (GP and/or TP) only
Treatment: 1 = SCIT, 0 = UC; Male: 1 = male, 0 = female; Level of education: 1 = high level of education, 0 = rest

From these models the following QALY estimates were derived. These were used when calculating ICERs.

Table 41 QALY estimates

			EQ-5D
	SCIT	UC	Adjusted difference (95% CI)*
Year 1	0.922	0.936	-0.014 (95%CI: -0.071;0.038)
Year 2	0.929	0.951	-0.022 (95%CI: -0.082;0.025)
Year 1+2	1.851	1.887	-0.036 (95%CI: -0.153;0.059)
			SF-6D
	SCIT	UC	Adjusted difference (95% CI)*
Year 1	0.790	0.792	-0.002 (95%CI: -0.055;0.062)
Year 2	0.803	0.832	-0.029 (95%CI: -0.073;0.017)
Year 1+2	1.593	1.624	-0.031 (95%CI: -0.127;0.075)

** 95% CI were based on bootstrapping*

Rhinitis Quality of Life Questionnaire

Table 42 shows the GEE model for the RQLQ. There was no statistically significant difference between the two groups during the allergy season not outside the season.

Table 42 GEE model of RQLQ

	RQLQ		
	Coefficient	SE	P-value
Constant	1.471	0.188	0.000
RQLQ at screening	0.417	0.162	0.010
Time interval 1*	0.645	0.173	0.000
Time interval 2	-0.293	0.174	0.092
Time interval 3*	0.321	0.176	0.068
Time interval 4	-0.226	0.188	0.230
Time interval 5*	-0.050	0.229	0.825
Perennial allergy	0.733	0.193	0.000
Perennial allergy * Treatment	-0.268	0.277	0.333
RQLQ at screening * treatment	0.257	0.222	0.247
Time 0 * Treatment	0.334	0.259	0.197
Time 1 * Treatment	-0.160	0.238	0.501
Time 2 * Treatment	0.440	0.247	0.074
Time 3 * Treatment	-0.109	0.248	0.661
Time 4 * Treatment	0.290	0.260	0.264
Time 5 * Treatment	0.104	0.326	0.749
Gender	-0.544	0.136	0.000

Perennial allergy: 1 = HDM with or without another allergy, 0 = seasonal allergy (GP and/or TP) only;
Treatment: 1 = SCIT, 0 = UC; Male: 1 = male, 0 = female; Level of education: 1 = high level of education, 0 = rest

Based on this model, the difference in RQLQ score between SCIT and UC during the first allergy season is -0.160 for patients with a GP and TP allergy and -0.418 for patients with a HDM allergy. Given that 52.7 percent of the patients had a seasonal allergy only and 0.473 had a HDM allergy (with or without a seasonal allergy), the weighted mean difference in RQLQ score was -0.287.

The difference in RQLQ score between SCIT and UC, averaged over all allergy seasons applicable to a particular allergy, was -0.134 for patients with a GP or TP allergy only and -0.323 for patients with a HDM allergy (with or without a seasonal allergy). The weighted mean was -0.223.

These estimates of the weighted mean difference in RQLQ score were used when calculating ICERs.

Number of successfully treated patients

Patients' responses to the global assessment of efficacy after one year and after two years of treatment are given in the table below. A successfully treated patient was a patient whose symptoms during the allergy season were "much better" or "completely absent" compared to the previous year. There was no difference in percentage of successfully treated patients between SCIT and UC after year 1. After the second year 36% of the patients continuing SCIT reported treatment was successful, compared to 19.6% of the patients in UC (Fisher's exact test p=0.061). See Table 43.

Table 43 Global assessment (GA) of efficacy: percentage of patients per response option

Questionnaire response options:	**Year 1**		**Year 2**	
	SCIT (n=73)	UC (n=76)	SCIT (n=50)	UC (n=56)
Much worse	3%	0%	2%	5%
A little worse	3%	13%	4%	13%
No change	39%	29%	22%	29%
A little better	42%	36%	36%	34%
Much better	22%	21%	34%	18%
No allergic symptoms anymore	1%	1%	2%	2%

Symptom-free days

The two-part model to estimate symptom-free days in presented below. Because of the link function used in the second part (i.e. 1/x), the number of symptom-free days should be calculated as 1 divided by the coefficient (e.g. for the constant 1/0.08566 = 11.67). T

Table 44 Two-part model for symptom-free days

	P (SFD>0)			**SFD conditional on P>0**		
	Coefficient	SE	P-value	Coefficient*	SE	P-value
Time interval 3	-0.294	0.257	0.253	0.001	0.012	0.905
Time interval 5	-2.240	0.370	0.000	-0.023	0.020	0.249
Time interval 7	-1.876	0.330	0.000	0.030	0.029	0.299
Gender	0.506	0.260	0.052	-0.032	0.015	0.038
Perennial allergy	-0.122	0.360	0.734	0.010	0.021	0.641
Perennial allergy * Treatment	0.276	0.516	0.594	-0.017	0.028	0.556
Time 1 * Treatment	-0.068	0.412	0.870	0.004	0.020	0.856
Time 2 * Treatment	-0.192	0.417	0.644	0.006	0.022	0.792
Time 3 * Treatment	-0.063	0.594	0.915	0.035	0.033	0.294
Time 4 * Treatment	-0.296	0.551	0.591	-0.015	0.039	0.702
Constant	-0.244	0.304	0.423	0.086	0.017	0.000

** Because the link function is 1/x the number of symptom-free days can be calculated as 1/(∑coefficients); a negative coefficient means a positive effect on number of symptom-free days; Perennial allergy: 1 = HDM with or without another allergy, 0 = seasonal allergy (GP and/or TP) only; Treatment: 1 = SCIT, 0 = UC; Male: 1 = male, 0 = female; Level of education: 1 = high level of education, 0 = rest*

Based on this model the difference in the number of symptom free days was estimated to be 0.767 during the first year and -1.040 during the second year. These differences were not statistically significant.

Cost-effectiveness ratios

The one-year and two-year cost-effectiveness ratios are presented in Table 45 and

Table 46, respectively. In terms of costs per QALY gained SCIT is dominated by UC because the costs of SCIT are higher and there is no gain in QALYs. In the first year, the costs per additional successfully treated patient are very high because of the very small difference in outcome. This ICER improves in the second year because of a greater difference in outcome.

Table 45 One-year cost-effectiveness from a healthcare and a societal perspective

	Year 1	
Healthcare perspective	Diff. SCIT-UC (95% CI)	ICER
Health care costs incl study medication	€1899 (95%CI: 128;3687)	
QALYs (based on EQ-5D utility)	-0.014 (95%CI: -0.071;0.038)	
QALYs (based on SF-6D utility)	-0.002 (95%CI: -0.055;0.062)	
RQLQ	-0.287	
Proportion of successfully treated patients	0.92%	
Symptom-free days	0.767	
Costs per QALY gained (EQ-5D)		Dominated
Costs per QALY gained (SF-6D)		Dominated
Costs per unit of difference in RQLQ		€6,621
Costs per additional successfully treated patient		€206,413
Costs per additional symptom-free day gained		€2,476
	Year 1	
Societal perspective	Diff. (95% CI)	ICER
Societal costs costs incl study medication	€1836 (95%CI: 219;3587)	
QALYs (based on EQ-5D utility)	-0.014 (95%CI: -0.071;0.038)	
QALYs (based on SF-6D utility)	-0.002 (95%CI: -0.055;0.062)	
RQLQ	-0.287	
Proportion of successfully treated patients	0.92%	
Symptom-free days	0.767	
Costs per QALY gained (EQ-5D)		Dominated
Costs per QALY gained (SF-6D)		Dominated
Costs per unit of difference in RQLQ		€6,401
Costs per additional successfully treated patient		€199,565
Costs per additional symptom-free day gained		€2,393

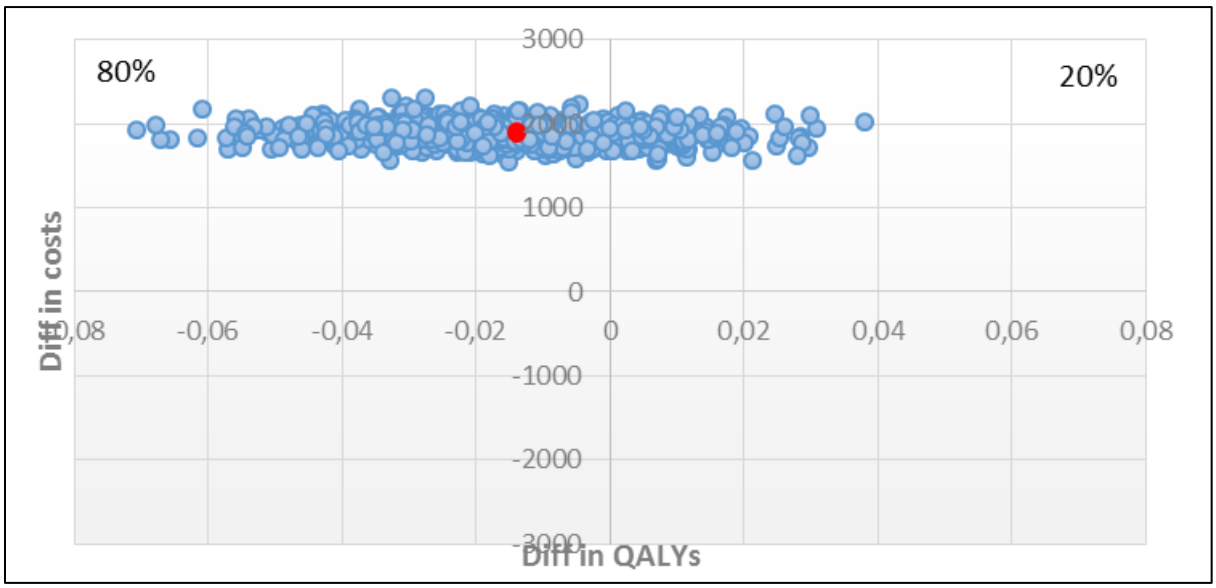
Table 46 Two-year cost-effectiveness from a healthcare and a societal perspective

	Year 2	
Healthcare perspective	Diff. SCIT-UC (95% CI)	ICER
Health care costs incl study medication	€2877 (95%CI: 198;4178)	
QALYs (based on EQ-5D utility)	-0.036 (95%CI: -0.153;0.059)	
QALYs (based on SF-6D utility)	-0.031 (95%CI-0.127;0.075)	
RQLQ	-0.223	
Proportion of successfully treated patients	19.92%	
Symptom-free days	-1.040	
Costs per QALY gained (EQ-5D)		Dominated
Costs per QALY gained (SF-6D)		Dominated
Costs per unit of difference in RQLQ*		€6,437
Costs per additional successfully treated patient		€14,984
Costs per symptom-free day gained		Dominated
Societal perspective	Diff. (95% CI)	ICER
Societal costs costs incl study medication	€3291 (95%CI: 166;5986)	
QALYs (based on EQ-5D utility)	-0.036 (95%CI: -0.153;0.059)	
QALYs (based on SF-6D utility)	-0.031 (95%CI-0.127;0.075)	
RQLQ	-0.223	
Proportion of successfully treated patients	19.92%	
Symptom-free days	-0.993	
Costs per QALY gained (EQ-5D)		Dominated
Costs per QALY gained (SF-6D)		Dominated
Costs per unit of difference in RQLQ*		€7,363
Costs per additional successfully treated patient		€17,141
Costs per symptom-free day gained		Dominated

** To calculate the costs per unit of difference in RQLQ the nominator (two-year costs) were divided by 2 to make the ICER comparable to the ICER from the first year*

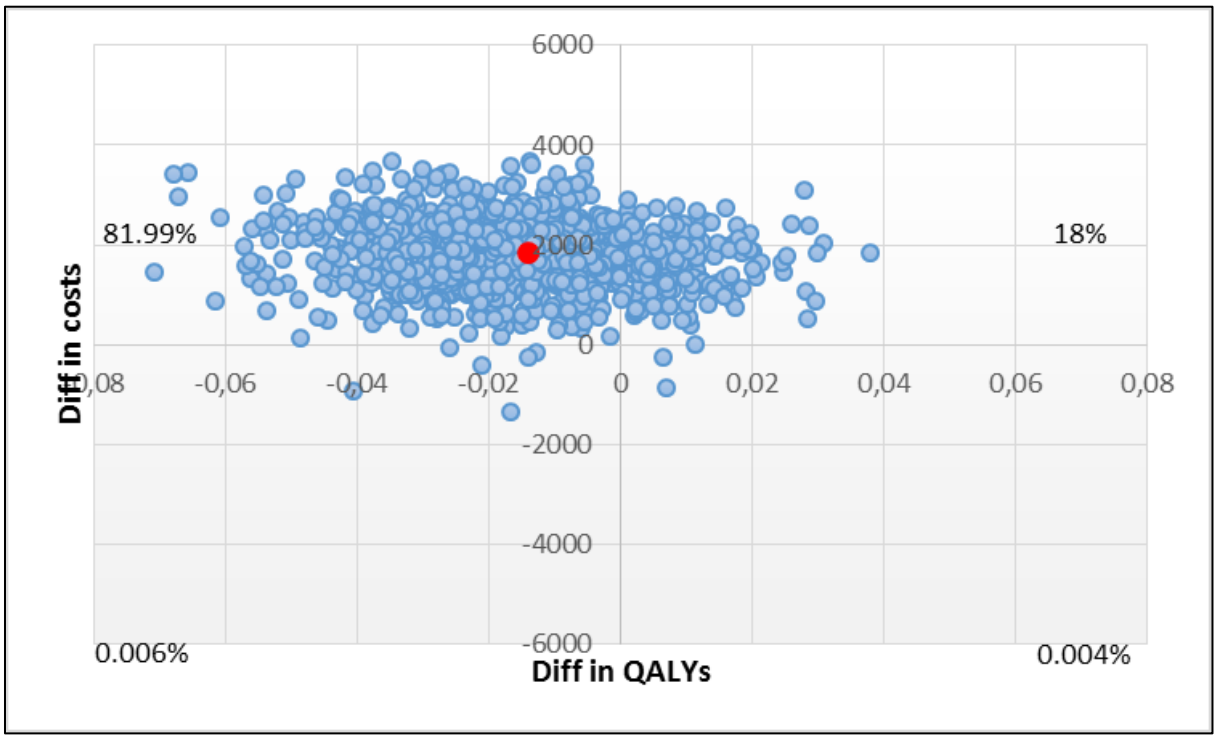
The one-year CE-planes of the costs per QALY, with QALYs based on EQ-5D utilities, are shown in Figure 7 for the healthcare perspective, and Figure 8, for the societal perspective. All bootstrap replications are located in the Northern quadrants, indicating higher costs. Only 20% of bootstrap replications point towards a QALY gain.

Figure 7 One-year CE-plane of costs per QALY (based on EQ-5D) from the healthcare perspective



The red dot is the point estimate based on the mean of the bootstrap replications

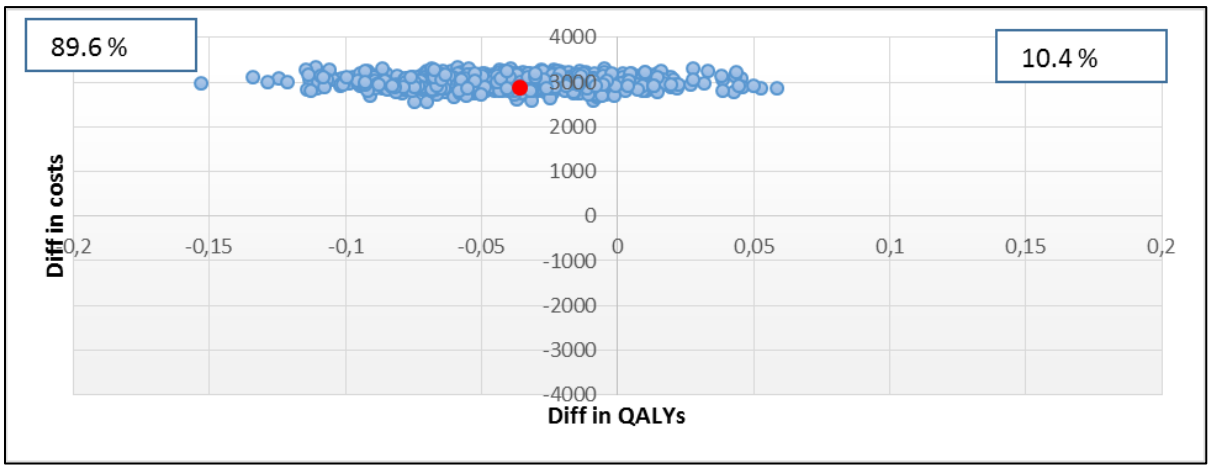
Figure 8 One-year CE-plane of costs per QALY (based on EQ-5D) from the societal perspective



The red dot is the point estimate based on the mean of the bootstrap replications

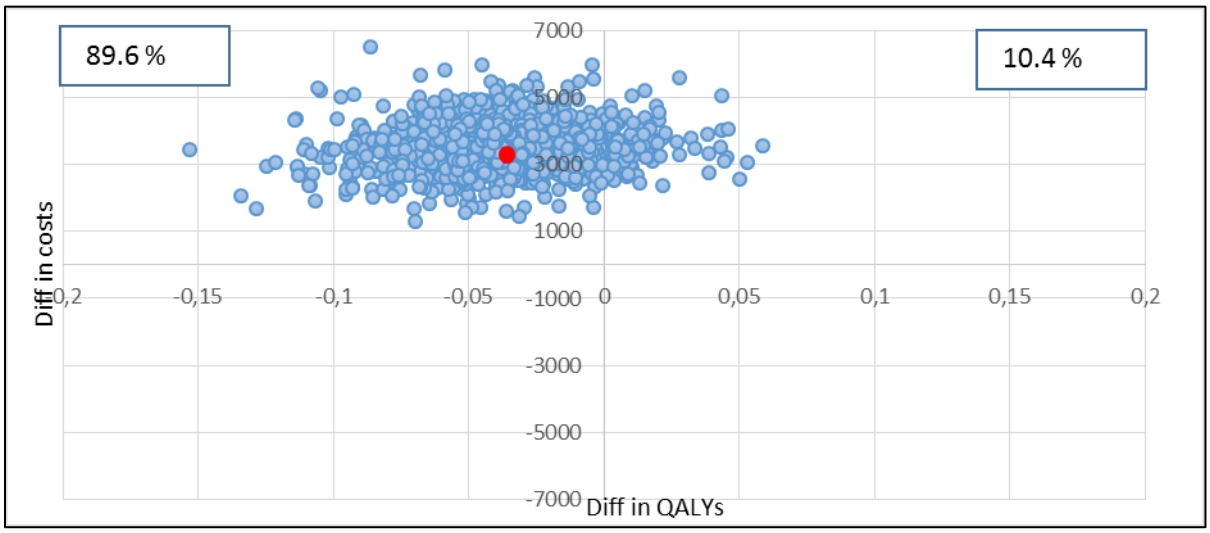
The two-year CE-planes of the costs per QALY, with QALYs based on EQ-5D utilities, are shown in Figure 9, for the healthcare perspective, and Figure 10, for the societal perspective. All bootstrap replications are located in the Northern quadrants, with almost 90% of the replications in the North West quadrant. The CE-planes of the costs per QALY based on SF-6D utilities are similar with 87% of bootstrap replications in the North West quadrant and 13% of bootstrap replications in the North East quadrant.

Figure 9 Two-year CE-plane of costs per QALY (based on EQ-5D) from the healthcare perspective



The red dot is the point estimate based on the mean of the bootstrap replications

Figure 10 Two-year CE-plane of costs per QALY (based on EQ-5D) from the societal perspective



The red dot is the point estimate based on the mean of the bootstrap replications

Sensitivity analysis

We performed a sensitivity analysis in which we assumed that the very first measurement of the RUQ-R and the outcomes during the expected allergy season actually felt into the non-allergy season. We re-estimated the models and the adjusted differences in costs and outcomes. The results are shown in Table 47. The results of the base case analysis were robust; SCIT remained dominated by UC.

Table 47 Results from the sensitivity analysis in which the first measurements during the expected allergy season were counted as part of the non-allergy season

Health care perspective	Diff. in costs*	Diff. in QALYs**	ICER
Base case			
Year 1	€1,899 (95%CI: 128;3687)	-0.014 (95%CI: -0.071;0.038)	Dominated
Year 1+2	€2,877 (95%CI: 198;4178)	-0.036 (95%CI: -0.153;0.059)	Dominated
Sensitivity analysis			
Year 1	€1,863 (95%CI:1390;2261)	-0.02 (95%CI:-0.068;0.053)	Dominated
Year 1+2	€2,851 (95%CI:2312;3306)	-0.04 (95%CI:-0.145;0.080)	Dominated
Societal perspective			
Base case			
Year 1	€1,836 (95%CI: 219;3587)	-0.014 (95%CI: -0.071;0.038)	Dominated
Year 1+2	€3,291 (95%CI: 166;5986)	-0.036 (95%CI: -0.153;0.059)	Dominated
Sensitivity analysis			
Year 1	€1,733 (95%CI: -474;4052)	-0.02 (95%CI:-0.068;0.053)	Dominated
Year 1+2	€3,166 (95%CI:604;6024)	-0.04 (95%CI:-0.145;0.080)	Dominated

** including study medication; ** based on EQ-5D utilities*

The 2-year CE-planes of costs per QALY showed that, compared to the base-case where 10.4% of bootstrap replications were in the North East quadrant, in the sensitivity analysis 26.4% of bootstrap replications were in the North East quadrant (healthcare perspective: Figure 12; societal perspective: Figure 12).

Figure 11 Sensitivity Analysis: Two-year CE-plane of costs per QALY (based on EQ-5D) from the healthcare perspective

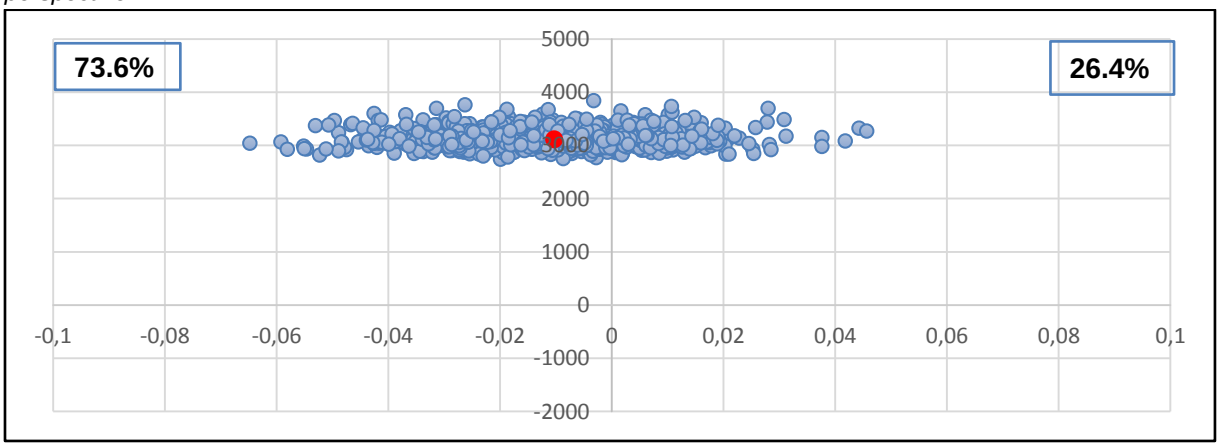
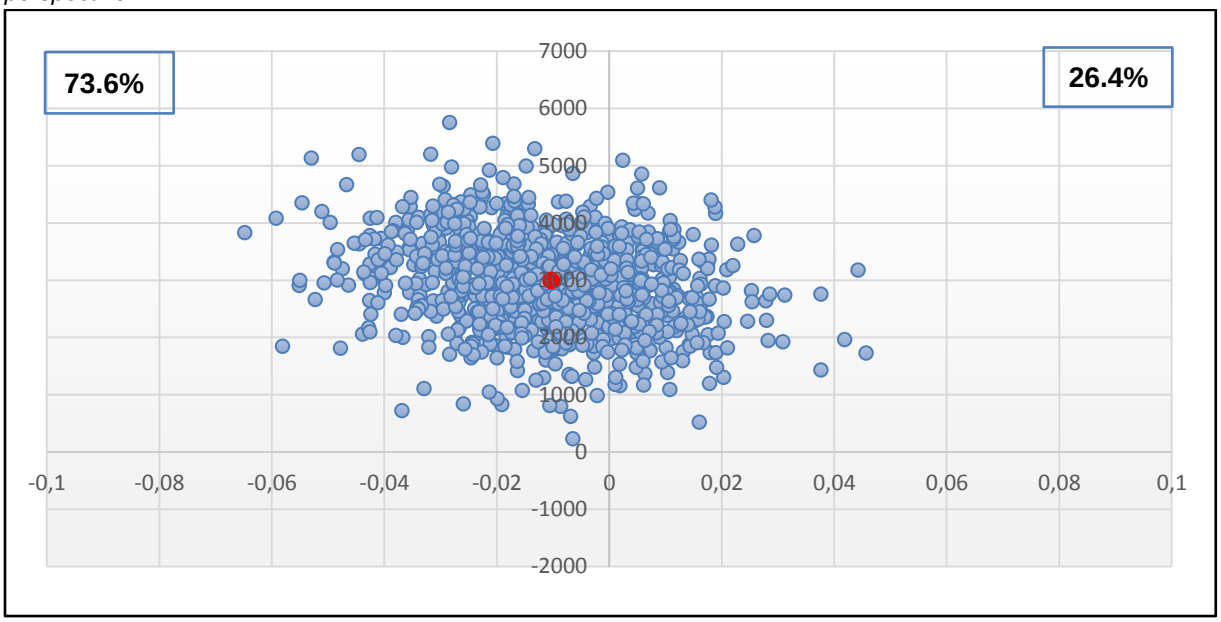


Figure 12 Sensitivity Analysis: Two-year CE-plane of costs per QALY (based on EQ-5D) from the societal perspective



The red dot is the point estimate based on the mean of the bootstrap replications

Subgroup analysis

The results of the subgroup analysis are shown below. The subgroup of patients with a tree pollen allergy included all patients with a tree pollen allergy with or without another allergy. Similarly, for the other subgroups. In all subgroup analysis, UC was dominant, except for the subgroup house dust mite, where the ICERs during the first year were €156,500 and €82,400 from the healthcare and the societal perspective, respectively.

Table 48 Results from the sensitivity analysis in which the first measurements during the expected allergy season were counted as part of the non-allergy season

Health care perspective	**Diff. in costs***	**Diff. in QALYs****	**ICER**
Base case			
Year 1	€1,899	-0.014	Dominated
Year 1+2	€2,877	-0.036	Dominated
Tree pollen			
Year 1	€1,813	-0.02	Dominated
Year 1+2	€2,820	-0.05	Dominated
Grass pollen			
Year 1	€1,944	-0.01	Dominated
Year 1+2	€2,887	-0.01	Dominated
HDM			
Year 1	€1,565	+0.01	€156,500
Year 1+2	€2,371	-0.02	Dominated

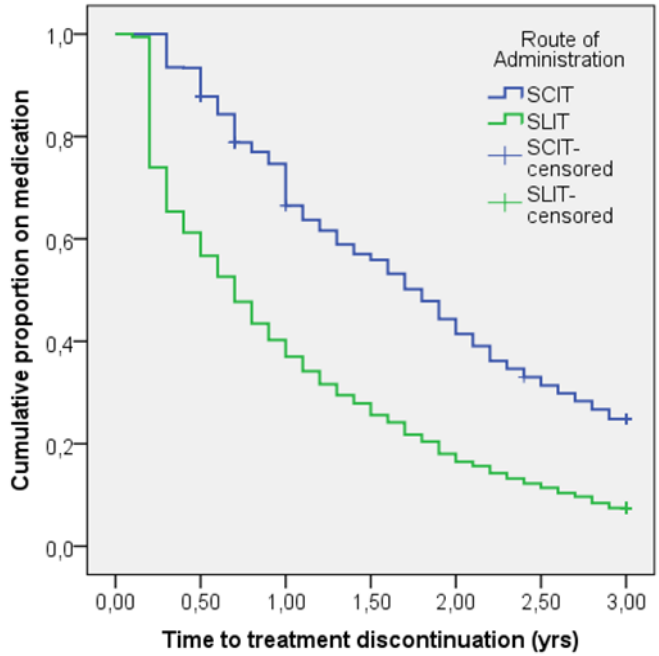
Societal perspective	Diff. in costs*	Diff. in QALYs**	ICER
Base case			
Year 1	€1,836	-0.014	Dominated
Year 1+2	€3,291	-0.036	Dominated
Tree pollen			
Year 1	€607	-0.02	Dominated
Year 1+2	€3,235	-0.05	Dominated
Grass pollen			
Year 1	€1,387	-0.01	Dominated
Year 1+2	€2,764	-0.01	Dominated
HDM			
Year 1	€824	+0.01	€82,400
Year 1+2	€2,138	-0.02	Dominated

** including study medication; ** based on EQ-5D utilities*

Adherence to SCIT in every-day clinical practice

Overall only 18% of users reached the minimally required duration of treatment of three years (SCIT: 23%, SLIT 7%). Median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively (P<0.001). See Figure 13 and Table 49.

Figure 13 Kaplan-Meier curves and summaries of time to treatment discontinuation by route of administration



P values of predictor level distribution equality are less than .001
(right censored for deceased and relocated cases)

Table 49 Summaries of univariable time to treatment discontinuation, persistence rates, and P values

Variable	Median time to treatment discont. (y)	Time to treatment discont.: Q1(y)	Time to treatment discont.: Q3(yrs)	Patients (n)	1-year persis-tence rate (%)	3-year persis-tence rate (%)	P-value
Route of administration							<.001
SCIT	1.70	2.90	1.00	2796	80	23	
SLIT	0.60	1.50	0.20	3690	38	7	
Allergen type							<.001
GP	1.00	2.00	0.60	2082	62	14	
TP	1.00	2.40	0.50	1154	61	16	
HDM	0.70	1.70	0.30	831	44	11	
any combi-nation	1.00	2.10	0.40	2398	53	14	
Prescriber							<.001
General practitioner	1.00	2.10	0.40	4801	59	14	
Allergologist	1.20	2.40	0.60	420	59	19	
Other prescriber	0.70	1.80	0.30	1045	43	12	
Age							<.001
Quartile I: ≤34y	0.90	1.70	0.30	1422	48	9	
Quartile II: 35 to 43y	1.00	2.00	0.40	1570	55	12	
Quartile III: 44 to 51y	1.00	2.20	0.40	1571	57	14	
Quartile IV: ≥52y	1.10	2.60	0.50	1923	63	19	
SES[*]							.001
Quartile I	1.00	2.00	0.40	1705	56	13	
Quartile II	1.00	2.20	0.50	1634	59	16	
Quartile III	1.00	2.10	0.50	1511	57	14	
Quartile IV	1.00	2.00	0.30	1542	53	13	
Geographic location							<.001
West	1.00	2.30	0.50	2157	59	17	
East	1.00	2.10	0.50	2810	53	12	
South	1.00	2.00	0.30	398	65	14	
North	1.00	2.00	0.50	1115	58	13	
Sex							.693
Male	1.00	2.10	0.50	2820	58	14	
Female	1.00	2.10	0.40	3666	55	14	

Truncated times to discontinuation, median, and first and third quartiles are shown.
**SES quartiles around median sample factor score. Lower SES quartiles indicate a higher status than the population mean, and higher SES quartiles indicate a lower status than the population mean.*

Predictors of premature discontinuation

A Cox proportional hazards model revealed that - besides route of administration - other independent predictors of premature discontinuation were found to be: prescriber, with general practitioner patients demonstrating longer persistence than those of allergologists and other medical specialists, single-allergen immunotherapy, lower socioeconomic status, and younger age. See Table 50.

Table 50 Premature discontinuation: Cox regression model

Variable	HR year 1	95% CI	P- value	HR year 2-3	95% CI	P- value	P value HR comparison*
Route of administration (SLIT vs SCIT [reference])	2.60	2.41-2.81	<.001	1.82	1.66-2.01	<.001	<.001
Prescriber (overall)			*<.001*			*.007*	
Prescriber (allergologist vs general practitioner [reference])	1.37	1.17-1.61	<.001	1.31	1.09-1.57	.004	.697
Prescriber (other specialist vs general practitioner [reference])	1.43	1.31-1.56	<.001	1.13	0.99-1.28	.078	.003
Allergen (overall)			*<.001*			*.717*	
Allergen (TP vs GP [reference])	.90	0.81-1.00	.044	0.99	0.86-1.14	.898	.258
Allergen (HDM vs GP [reference])	.96	0.86-1.07	.443	1.08	0.93-1.27	.305	.200
Allergen (combination therapy vs GP [reference])	.82	0.75-0.89	<.001	1.02	0.91-1.14	.726	.002
Patient sex (F vs M [reference])	1.03	0.96-1.10	.458	0.94	0.86-1.03	.192	.137
Age (overall)			*<.001*			*<.001*	
Age, quartile II vs I (reference)	.91	0.83-1.00	.041	0.89	0.78-1.01	.069	.787
Age, quartile III vs I (reference)	.83	0.75-0.91	<.001	0.79	0.70-.90	<.001	.567
Age, quartile IV vs I (reference)	.77	0.70-0.85	<.001	0.70	0.62-.80	<.001	.299
SES (overall)			*.006*			*.072*	
SES, quartile II vs I (reference)	1.00	0.91-1.11	.952	0.87	0.77-.99	.033	.089
SES, quartile III vs I (reference)	.95	0.86-1.05	.308	0.87	0.77-.99	.028	.279
SES, quartile IV vs I (reference)	1.12	1.02-1.24	.017	0.87	0.77-1.00	0.42	.002

*Multivariable Cox regression results regarding premature discontinuation separately for the period of the first year and the period 2 to 3 years after start of treatment are shown. Data shown are HRs with 95% CIs and P values. Predictors of premature discontinuation of treatment with reference categories are also shown. Age quartile I (≤34 years of age [reference]) is compared with quartiles II (35-43 years), III (44-51 years), and IV (≥52 years). SES quartile I (reference) is compared with quartiles II, III, and IV. SES quartiles are around the median sample factor score of -1.64. The lower quartiles have the highest status, and the higher quartiles have the lowest status. This model also included a significant (P < .005), although non–time-dependent, interaction effect between route of administration and allergen group: the HR of SLIT versus SCIT was 2.50 for users of GP immunotherapy, 2.14 for users of TP immunotherapy, 2.52 for users of HDM immunotherapy, and 3.17 for users of combination immunotherapy. *Comparison of HRs in year 1 versus HRs in years 2 to 3.*

Costs of premature discontinuation

Of the persistent patients, 56% were never late in picking up their medication from the pharmacy. Direct medication costs per nonpersistent patient discontinuing in the third year of treatment were 3,800 euros, an amount which was largely misspent. See Table 51.

Table 51 Immunotherapy: Cost of nonpersistence

Year of treatment discontinuation	Annual total costs (€)	Cumulative total costs (€)	Cumulative mean costs per nonpersistent patient (€)
1	2.88M	2.88M	1015
2	3.74M	6.62M	2069
3	3.42M	10.04M	3824

M = million

2.5. Conclusions

In this study we aimed to address the following research questions:

Clinical effectiveness

Is subcutaneous immunotherapy (SCIT) with tree pollen (TP), grass pollen (GP), house dust mites (HDM) or combinations effective compared to usual care (UC) only?

In the AIRFORCE study population of 183 patients with moderate to severe allergic rhinitis due to one (43%) or more (57%) allergies no statistically significant difference in daily symptom score between SCIT as add-on to UC and UC for either tree pollen, grass pollen and house dust mites was observed. Multivariate analysis with mean daily symptom scores as primary outcome did not reveal any effect of SCIT or concomitant allergies. Also, mixed models using all available data (individual total symptom scores for each day and each patient and all available pollen counts for each day) did not demonstrate any effect from SCIT. In addition, both groups did not differ in symptom and medication free days, well days, VAS, disease specific quality of life (RQLQ) and global assessment for each allergen separately. Patients' Global assessment of the change in allergy symptoms yielded a significant difference in favour of SCIT after the second year of treatment.

The unexpected lack of clinical efficacy is very relevant for clinical practice. Although all allergens used for SCIT have proven efficacy as demonstrated in double-blind placebo controlled randomized trials and meta-analyses, the outcome of the AIRFORCE study suggests that clinical efficacy may be less in average daily practice. The discrepancy between results from previous placebo controlled randomized trials and the AIRFORCE might call for a revision of the criteria for patients selected for treatment with subcutaneous immunotherapy. It is conceivable that patients with severe persistent rhinitis, not sufficiently responsive to maximum symptomatic therapy are more suitable for treatment with SCIT. This issue as well as possible limitations and sources of bias in the AIRFORCE study will be further addressed in the discussion below.

Cost-effectiveness

Is subcutaneous immunotherapy (SCIT) with tree pollen (TP), grass pollen (GP) or house dust mites (HDM) or combinations cost-effective compared to usual care (UC) only?

The main conclusion from the economic evaluation was that SCIT was dominated by UC. We have not found a statistically significant difference in costs between SCIT and Usual care, neither during the allergy season nor outside of the allergy season. This conclusion was the same regardless of whether we adopted a healthcare perspective (excluding costs of study medication) or a societal perspective. The numerical reduction in the costs of symptomatic medication and in the total health care costs when excluding the costs of study medication did not offset the cost increase due to SCIT. As expected, given the results on the clinical outcome measures, we have not found a statistically significant difference in utilities between SCIT and UC. This conclusion was reached regardless of whether we used the EQ-5D or the SF-6D to measure utilities. Patients with a house dust mite allergy had statistically significantly higher healthcare costs than patients without a house dust mite allergy, but the numerical difference was small. In line with this was the finding that patients with a house dust mite allergy has significantly lower SF-6D utility values than patients without this allergy.

Adherence

What is the adherence to SCIT using retrospective data from the project group, trial based data and data obtained from the PHARMO database?

In recent years, specialists adopted the policy to refer patients to GPs for carrying out maintenance immunotherapy after the phase of up-dosing in the practice of the specialist. This policy hampers an accurate registration of adherence to SCIT, however the results obtained from the PHARMO database may be representative for the project group.
No significant interaction between dropout and treatment was demonstrated. Real-life persistence is better in SCIT users than in SLIT users, though is low overall. There is an urgent need for further identification of potential barriers and measures that will enhance persistence and compliance.

2.6. Discussion

Clinical efficacy

At the level of individual allergens (tree pollen, grass pollen, house dust mites) it appeared that the mean differences between SCIT and UC for all outcome variables were small and not statistically significant. The direction of the effects was generally in favor of the treatment with SCIT. Comparing SCIT and UC, a non-significant tendency was observed in mean symptom scores and VAS (lower in the SCIT group), the number of symptom free days, medication free days and well days (higher in the SCIT group), rhinitis related quality of life (lower scores/less impaired in the SCIT group) and global assessment of improvement after each relevant season (higher scores/more improvement in the SCIT group).

MLR of the mean daily total nasal and eye symptom score - the primary outcome - did not reveal a statistically significant effect of SCIT treatment on the symptoms. Also no influence from gender, age, referral (from either general practitioner or specialist), year of inclusion or treatment with other allergens was observed.

To utilize all available data (all individual total symptom scores for each day and each patient and all available pollen counts for each day) linear mixed models were used with total symptom score (nose, eye, lung) as dependent variable, grass and birch pollen count, subgroup (mono-allergy and combinations of allergies) and treatment with SCIT as fixed effect and individual patient and date of assessment as random effect. An effect from SCIT could not be observed. As the efficacy of SCIT in HDM allergy is less well established(40), separate analyses were made in patients with or without HDM allergy. Again, no effect from SCIT could be seen.

After 2 years of treatment patients undergoing SCIT reported a slightly better improvement than subjects having UC. This difference was statistically significant.

Results and the state of the art
The European Agency of Medicine (EMA) states that the main aim of specific immunotherapy is a persistent effect due to changes in the immune system which can only be demonstrated in long-term studies.(41) However different claims for efficacy are possible: 1) Treatment of allergic symptoms demonstrated by short term clinical trials, 2) sustained clinical effect (i.e. maintenance of efficacy during two to three treatment years, 3) long-term efficacy and disease modifying effect (sustained efficacy in post treatment years) and 4) cure.(41) These claims have to be addressed when manufacturers aim to register new immunotherapy products. The short-term efficacy of SCIT with pollen has been established in several studies.(7) Sustained clinical effects have been studied mostly in studies of 1 year and 2 years duration. Only one study convincingly shows long-term efficacy (12) up to 3 years after ending immunotherapy. Other studies suggest a disease modifying effect (prevention of the development of asthma or new sensitizations).(42-44)

The outcome of the AIRFORCE study is in contrast with the findings of randomized clinical trials focusing on pollen or house dust mites with Alutard SQ® - registered products in the Netherlands - and a meta-analysis on subcutaneous immunotherapy with pollen. Treatment effect and sustained clinical effect during 2 years cannot be demonstrated for SCIT with UC as comparator. Before discussing possible explanations, we first summarize the evidence from the placebo-controlled and active-treatment-controlled studies.

Placebo controlled studies

In a randomized placebo controlled study with the same grass pollen allergenic extract (Alutard 100,000 SQ®-U) as used in the AIRFORCE study 203 subjects receiving SCIT were compared with 104 subjects receiving placebo and symptomatic treatment. Across the whole pollen season, mean symptom and medication scores were 29% and 32% lower, respectively, in the 100,000-SQ-U group compared with those in the placebo group (both P < .001).(26) Over the peak pollen season, mean symptom and medication scores were 32% and 41% lower, respectively, than those in the placebo group. Quality-of-life measures confirmed the superiority of this dose to placebo.(45) A smaller and older study, but also carried out with Alutard SQ® grass pollen comprised 40 adults.(46) There was a highly significant decrease in total symptom scores (p=0.001) in the Alutard SQ® treated group. The decrease in symptoms was 2.6 fold higher in the immunotherapy group than in the placebo group. Significant differences were also found in total drug use (p=0.002). Visual analogue symptom scores were also reduced in the active group (p=0.02, 2.2 v 5.5 (-4.8 to -0.5)). The post-seasonal assessment, by either the doctor or the patients, showed a large improvement (p less than 0.001) in favour of Alutard SQ®. The study differed from the AIRFORCE study, as a baseline year was included, thus change in both treatment arms could be compared.

A meta-analysis with 51 included studies and 2871 participants showed a significant reduction of symptom and medication scores, combined symptom and medication scores, nasal symptom scores and ocular symptom scores following subcutaneous immunotherapy(7).

Few studies with HDM immunotherapy have been published. In the Netherlands, for HDM allergy Alutard SQ® is the only registered product. In a small study RCT comprising 36 patients with house dust mite allergy patients treated with Alutard SQ® HDM showed a 58% reduction in diary card symptom scores (P<0.002) and a 20% reduction in the use of rescue medication.(27) The placebo group had a 32% reduction in symptom scores (P=NS), but no reduction in rescue medication requirements. Although SCIT with house dust mites has been acknowledged as an effective therapy in contrast to sublingual immunotherapy with HDM(47), there is a need for rigorous, long-term, double-blind, placebo-controlled randomized clinical trials with an efficacy criterion that reflects the particular features of HDM-induced allergic disease(40).

Comparison between SCIT and pharmacotherapy

An indirect comparison of RCTs with SCIT and RCTs using antihistamines, nasal steroids or leukotriene antagonists derived from meta-analyses demonstrated that SCIT was at least as effective as standard pharmacotherapy.(48) A disadvantage of this study is the lack of a head to head comparison. The analysis was done by comparing the differences between the effect-size of SCIT and pharmacotherapy over placebo treatment.

4 small trials have directly compared SCIT and pharmacotherapy in patients with pollen allergy. In a randomized, double-blind study comparing birch pollen SCIT and nasal corticosteroids (n=41) nasal steroid was more effective. (49) SCIT was used as pre-seasonal treatment only. The same was true for another study, a double-blind, parallel-group trial in 60 ragweed-sensitive adults. Pre-seasonal SCIT was more effective than steroid spray.(50) In an open study with 30 pollen-allergic patients SCIT was more effective in the first year of treatment than cetirizine, mometasone furoate, and levocabastine eye drops.(51) In a randomized study of 48 patients with allergic to pollen short-term SCIT was more effective than the standard treatment.(52)

In sum, based on the available literature a statistically significant difference between SCIT and UC was to be expected in favour of SCIT. For the individual allergens a much smaller difference was observed between the treatment groups than expected.

Potential limitations of the AIRFORCE study
When interpreting the results the impact of many different factors, such as the characteristics of the patients, the design of the study, the amount of pollen counted etc. have to be taken into consideration, as we do below.

1. *Are patients included according to international guidelines?*

All patients were characterized by moderate to severe persistent allergic rhinitis according to the ARIA guideline.(6) Selection criteria comprised sensitization to the relevant allergens, sufficient symptoms during the relevant season according to a retrospective symptom score (≥4 out of 12) and impairment of daily life activities. Sensitization to allergens is a prerequisite for allergen induced symptoms, however the degree of sensitization is not a predictor for severity of symptoms. A potential bias could be that the retrospective symptom score overestimates the real level of symptoms in the previous period. In fact, in a recent study we showed weak correlations between retrospective scores after the season and actual scores measured during the season.(53)
All patients fit into the ARIA criteria for considering immunotherapy:

- Patients with symptoms induced predominantly by allergen exposure
- Patients with a prolonged season or with symptoms induced by succeeding pollen seasons
- Patients with rhinitis and symptoms from the lower airways during peak allergen exposure
- Patients in whom antihistamines and moderate dose topical glucocorticoids insufficiently control symptoms
- Patients who do not want to be on constant or long-term pharmacotherapy
- Patients in whom pharmacotherapy induces undesirable side effects

2. *Do patients have sufficient symptoms to discriminate between SCIT as add-on to UC and UC alone?*

The mean total symptom scores varied from 3.5 – 7.7 (range 0-12). In addition, the RQLQ ranged from 1.3-2.0 on a 0-6 scale (0= no impairment, 6=maximal impairment). These data are in line with the observations in the large grass pollen study performed by Frew(26, 45).
However, the patients in the AIRFORCE study reported a remarkably high percentage of medication free days and well days. Thus, in spite of the retrospective score and a history of moderate to severe rhinitis the need for medication appeared to be less than expected, also in the group not undergoing SCIT.
Several explanations are possible:

- The most severe patients might not have been included, because those that were specifically referred to get immunotherapy because of the severity of their symptoms were not invited. This was a potential selection bias, resulting from the fact that SCIT has been a registered and reimbursed treatment for a long time. The possibility of being randomized to already documented insufficient standard therapy was considered as not feasible.
- Low pollen counts might have influenced the severity. This is true for the tree pollen season in 2012 and the grass pollen season in 2010. These seasons were taken out of the analysis because of the low pollen counts. However, other seasons were eligible for analysis. When days with sufficient pollen exposure only were taken into account, no substantial difference between both treatment groups were observed.

3. *Are differences between the study design of the AIRFORCE study and previously published placebo controlled randomized trials responsible for the discrepancies in efficacy of SCIT observed in the AIRFORCE study and previous studies?*

- In the AIRFORCE study patients with multiple allergies were invited and treated with SCIT. In placebo controlled trials with Alutard SQ® grass pollen or house dust mites patients with other clinically relevant allergies were excluded (26, 27, 46). The AIRFORCE study clearly differs in this respect.
- In the placebo-controlled trials (26, 27, 46) patients were included with severe rhinitis uncontrolled by standard treatment. As stated above, the most severe patients might not have been included in the AIRFORCE study. Moreover, the ARIA guidelines allow for selection of patients who do not want to be on constant or long-term pharmacotherapy or subjects in whom pharmacotherapy induces undesirable side effects. In daily practice these patients are eligible for SCIT, whereas they might have sufficiently been controlled with standard treatment. It is conceivable that these patients have less benefit from SCIT as add-on therapy. The AIRFORCE study is however not designed to differentiate between patient who are resistant to standard treatment and patients who are sufficiently controlled by pharmacotherapy.

4. *Are data obtained from patients in the AIRFORCE study reliable?*

Data collection was designed very carefully. All questionnaires were web-based. Participant received reminders by SMS to fill in the questionnaires. Whenever a patient started with filling in the questionnaire, the system did not allow for missing data. Consequently, the number of missing questionnaires was low. Mean diary compliance, expressed as the ratio between submitted and available diaries was 74%.
In the mixed model analysis a significant dose response relation between symptoms and relevant pollen counts could be demonstrated which underwrites the quality of the data.
One may criticize the self-reported nature of the resource utilization data. However, we tried to reduce the recall bias by using a recall period of only two-weeks. During the allergy season, the resource utilization questionnaire was administered every two week, such that the entire allergy season was covered.

5. *Is there any immunological effect?*

IgG_4 levels were measured as a marker of an immunological response to treatment. Indeed, IgG_4 levels increased for all allergens in the SCIT group, whereas no change was seen in the UC group.

6. *Was the power of the AIRFORCE study sufficient?*

The study was powered for 240 patients with a dropout of 20%. The number of randomized patients was lower than expected: 183 out of 832 assessed subjects, with a dropout of 31 (16.9%). Therefore, it was not possible to perform subgroup analyses with the 7 different subgroups. However with this number of patients, the mixed models and the GEE models should have revealed a difference between SCIT and UC if there was any.

The costs of SCIT are relatively high. The study medication itself and administering the study medication through injections at the clinic cost on average €1949 in year one and €997 in year two. The costs of symptomatic medication are much lower, i.e. a few hundred euros per patient per year at maximum. The slight numerical reduction in costs of symptomatic medication did not compensate the costs of SCIT. Even if SCIT would reduce the need for symptomatic medication to zero, this would never be sufficient to offset the costs of SCIT. From a societal perspective, SCIT could lead to greater savings when it reduces productivity loss from absence of paid work (absenteeism) or productivity loss from the fact that work is hindered by rhinitis symptoms (presenteeism). That is why we asked detailed questions about absenteeism as well as presenteeism. However, we have not found reductions in productivity loss, which might in part be because patients may need to take time off work for the frequent clinic visits.
The aim of SCIT is not to reduce total costs but to reduce symptoms and improve quality of life. If quality of life is sufficiently improved this might well justify a substantial increase in total costs.

Unfortunately, we have no indications of substantial improvements in quality of life, not when measured with a disease-specific quality of life questionnaire nor when measured with a generic quality of life questionnaire.

2.7. Recommendations

As the AIRFORCE study did not show superiority of SCIT over UC in this study, we recommend accentuating the indications of immunotherapy. To achieve the efficacy of SCIT as demonstrated in randomized placebo controlled trials, adult patients with severe persistent rhinitis symptoms insufficiently or uncontrolled by standard pharmacotherapy might be offered immunotherapy.
Guidelines should be adapted accordingly.

The lack of efficacy does not permit any conclusions on a potential differential efficacy of tree pollen, grass pollen or house dust mite. Thus specific recommendations on this topic are not possible.

The early immune response in childhood is weaker and probably more susceptible to immunological intervention.(54) In more advanced diseases stages the immune response is highly complex and molecularly heterogeneous.(55) It has been suggested that early childhood offers a window of opportunity with a higher chance to affect the natural history of disease.(56) The AIRFORCE study however does not address the efficacy of SCIT in children. Recommendations are restricted to the adult population only.

As the AIRFORCE study was not designed to address long-term efficacy(12), prevention of asthma in patients with rhinitis(42, 43) or prevention of new sensitizations(44) it is not recommended to discard immunotherapy as a therapeutic modality. Immunotherapy may be still indicated especially as a last step in a stepwise approach of treating patients with allergic rhinitis.

We demonstrated that adherence to immunotherapy (either subcutaneously or sublingually administered) is strikingly low in the Netherlands. It is recommended to implement measures to enhance adherence (information, education, achieving feedback from patients and regular patient contact). The lack of adherence further underpins the proposal to restrict immunotherapy to motivated patients, who are insufficiently controlled by other medication. Although the analysis of adherence to immunotherapy is descriptive, not providing explanations, it is conceivable that unrestricted selection of patients for immunotherapy treatment will contribute to problems in adherence.

In the Netherlands SCIT is currently reimbursed by healthcare insurers as it is part of the basic benefit package. This study has questioned the rather broad target population for SCIT that is described in the current clinical guidelines. Perhaps, if the target population was restricted to patients with severe symptoms that persist despite optimal symptomatic therapy, the cost-effectiveness of SCIT could be improved.

3. Rapportage proces

Zijn in één of meer onderdelen van de door ZonMw goedgekeurde subsidieaanvraag wijzigingen opgetreden? Ja/~~Nee~~

Let wel! Op grond van de subsidievoorwaarden dient een voornemen tot wijziging van de goedgekeurde subsidieaanvraag zo spoedig mogelijk schriftelijk ter goedkeuring aan ZonMw te worden voorgelegd.

INDIEN JA Geef aan voor welke van de volgende onderdelen de wijziging(en) consequenties hebben:	
x	Tijdsplanning
☐	Goedgekeurde begroting
☐	Vraagstelling / taakstelling
x	Geplande activiteiten, plan van aanpak [1]
☐	Beoogde resultaten
x	Samenwerking
☐	Anders, nl

INDIEN NEE
Het niet vermelden van wijzigingen betekent volgens ZonMw dat de uitvoering plaatsvindt zoals is beschreven in de goedgekeurde subsidieaanvraag (of een door ZonMw goedgekeurde wijziging daarvan).

Laat u in geval van wijzigingen het rapporteren achterwege, dan kan ZonMw op grond van de subsidievoorwaarden consequenties verbinden aan de subsidieverlening. Het is daarom van essentieel belang dat u inzichtelijk maakt of op de genoemde onderdelen de werkelijke uitvoering overeenkomt met de goedgekeurde.

[1] (denk hierbij o.a. aan studieopzet, interventies, uitkomstmaten, dataverzameling, instroom respondenten/patiënten)

Toelichting op wijzigingen

The study was extended with one year.
The recruitment of participants was severely hampered in 2009. Most importantly, the pandemic Influenza A (H1N1) infection and the subsequent vaccination program rolled out over the Netherlands made involvement of general practitioners impossible. In addition, delays in medical ethical committee procedures in other centres than Rotterdam delayed the recruitment process beyond the appropriate time period for recruitment. As the start of immunotherapy needed to be scheduled in a narrow time frame from September- mid December, 12 months extension was required to recruit patients for two years treatment.

The original statistical plan was extended with mixed modelling analysis to capture all available data (all patients, all available daily symptom scores, all daily pollen counts).

Some changes in the study group: LUMC was not able to participate. Instead, the ENT-department of the AMC entered the study group.

3.1. Methodologie en uitvoeringsproces

Beschrijf de methodologie van het project
Beschrijf zowel de kansen/succesfactoren als de problemen/belemmeringen die u bij uitvoering van het project bent tegengekomen.

Heeft u tips voor collega's die een soortgelijk project (gaan) uitvoeren. Denk hierbij bijvoorbeeld aan hoe u eventuele knelpunten heeft opgelost bij bijvoorbeeld: voorbereiding, uitvoering, samenwerking, draagvlak, tijd, financiën, etc.

Advantages of the study design

- The AIRFORCE study has been designed as randomised controlled study to evaluate the efficacy and cost-effectivenesss of SCIT as add-on to usual care. The study better represents daily clinical practice, as placebo controlled studies are more strictly regulated in terms of using rescue medication and scheduled visits to physicians and investigators. The frequency of visits to physicians are similar for both placebo and actively treated patients due to the nature of the injection therapy.
- In immunotherapy large amounts of data are being collected. Basic statistical methods (univariable analysis, MLR, ANCOVA) do not utilize all these data. In addition, observations on days with low pollen counts have to be discarded. The statistical approach of linear mixed modelling enabled us to use all available data.

We encountered several problems:

- Delay in recruitment. This was solved by extending the study. This extension had a substantial financial impact. Costs of personnel had to be covered by the dept. of Allergology, ErasmusMC and the IMTA, EUR.
- Patients referred to specialist for immunotherapy or patients not responding to pharmacotherapy might not have been included in this study. It is difficult to overcome this bias as immunotherapy is a registered and well established treatment modality for many years in the Netherlands. The lesson to be learned is that these kind of studies should be carried out at a much earlier stage, for instance parallel to or just after registration of products
- In some seasons pollen counts were low. This is a problem inherent to studies including pollen allergic patients. It is however a matter of debate as to whether climate changes may increasingly hamper such studies. Also in 2013 (not a part of this study) pollen counts in the birch pollen season were low, whereas the grass pollen season was much later than usual. There is a discussion about using environmental pollen chambers with controlled pollen exposure.(57) However, these procedures cannot replace the evaluation of daily clinical practice.

3.2. Diversiteit

Is er aandacht besteed aan relevante verschillen binnen de doelgroep naar sekse, etnische achtergrond, leeftijd en andere relevante kenmerken? Ja/~~Nee~~

Indien ja, beschrijf de belangrijkste leerpunten:

Multivariate analyses took age and gender into account. Effects were not consistent. Females scored significantly higher in the ITT analysis for tree pollen and house dust mites, lower in the analysis for grass pollen. This was not confirmed in the PP analyses. An effect from age was not observed.

3.3. Samenwerking met eindgebruikers

Is er rekening gehouden met wensen en behoeften van eindgebruikers (bijvoorbeeld patiënten(organisaties), consumenten, commerciële bedrijven en publieksgroepen enz.)? ~~Ja~~/Nee

Is er inbreng geweest van eindgebruikers (bijvoorbeeld patiënten(organisaties), consumenten, commerciële bedrijven en publieksgroepen enz)? Ja/Nee

Indien ja, beschrijf hieronder hoe dat is gebeurd.

We received a grant from ALK-Abello to measure IgG4 (not budgeted in the original proposal). ALK did not have any influence on the study.

3.4. Samenwerking met intermediaire doelgroepen

Is er inbreng geweest van (vertegenwoordigers van) intermediaire doelgroepen (bijvoorbeeld zorgverleners, beleidsmakers, beroeps- en brancheorganisaties enz.) . ~~Ja~~/Nee

Indien ja, beschrijf hieronder de belangrijkste leerpunten.

4. Rapportage vervolg

U wordt gevraagd hieronder inzicht te geven in hoe u de eindresultaten een stap verder brengt.
U kunt van ZonMw een extra impuls ontvangen. Indien uw antwoorden hiervoor aanleiding geven, dan vraagt ZonMw u om een aanvraag in te dienen voor het verspreiden en implementeren van de eindresultaten. Deze impuls bestaat uit een subsidiebedrag van maximaal € 50.000,-.

4.1. Welke resultaten/eindproducten heeft uw project/onderzoek opgeleverd?

One paper published in the Journal of Allergy and Clinical Immunology.(58) See also 5. Publicaties en producten below.

4.2. Zijn de resultaten van het project bekend gemaakt bij relevante databanken?

~~Ja~~/Nee
Indien ja, welke?

4.3. Voor welke doelgroepen zijn deze resultaten van belang?

In particular physicians who have to select patients for immunotherapy. Organisations, responsible for guidelines in the field of immunotherapy (in the Netherlands: NHG, NVvA, International: EAACI and WAO)

4.4. Welke activiteiten voor welke doelgroepen heeft u al verricht en gaat u nog uitvoeren om goede verspreiding en implementatie van de resultaten te bevorderen?

The results from the study (apart from the paper on adherence (58)) are recently known. Thus, attempts to spread and implement the results have not been carried out yet. The results of the analysis of clinical effectiveness of subcutaneous immunotherapy using Alutard SQ® will be submitted to a major clinical journal, such as the Journal of Allergy and Clinical Immunology (JACI) or Allergy. The professional community involved in the practice of allergen immunotherapy will be informed of the results of this analysis by means of a poster or podium presentation at the upcoming congress of the European Association of Allergy and Clinical Immunology (EAACI), to be held 7-11 June in Copenhagen (Denmark). Furthermore, the cost-effectiveness analysis will be submitted for publication to a major health-economic journal, such as Health Economics or Value in Health.

4.5. Neemt een persoon of organisatie de nieuwe kennis, innovatie of werkwijze over, of gaat deze verder met de resultaten van het project?

Nee/Misschien/Ja, zeker
Indien Misschien of Ja, zeker: beantwoord ook de volgende drie vragen:

4.6. Vindt het vervolg plaats binnen of buiten ZonMw?

☐ Binnen ZonMw, bij het programma:…
☐ Buiten ZonMw, de volgende partijen of organisaties:

4.7. Vindt het vervolg plaats in een andere fase van de kennisketen2?

☐ Nee, het vervolg blijft in deze fase van de kennisketen:
☐ Fundamenteel onderzoek
☐ Strategisch onderzoek
☐ Toegepast onderzoek
☐ Ontwikkelprojecten
☐ Implementatieprojecten

☐ Ja, het vervolg vindt plaats in deze fase van de kennisketen:
☐ Fundamenteel onderzoek
☐ Strategisch onderzoek
☐ Toegepast onderzoek
☐ Ontwikkelprojecten
☐ Implementatieprojecten

Toelichting
Kunt u de antwoorden toelichten cq. onderbouwen:
At this stage, there will be no follow-up research. As the results are not in line with the current literature, it is most important to spread the results by publications and subsequently, trying to include the results into guidelines.

4.8. Bijdrage aan maatschappelijke ontwikkelingen

Krijgt dit projectresultaat een toepassing in de praktijk? Denk hierbij aan:

- Gebruik in richtlijnen, protocollen, standaarden, etc
- Gebruik in inhoud, kwaliteit of doelmatigheid van de zorg of preventie
- Gebruik in verandering van professionele handelen of organisatorische verandering
- Verandering in keuze van zorg of leefstijl van patiënt, consument, burger
- Gebruik in handleidingen, onderwijsmodules, leerboeken, etc
- Gebruik in technologische ontwikkelingen, instrumentenontwikkeling, etc
- Gebruik in grootschalige verbeterprogramma's zoals doorbraakprojecten, LAK, etc

~~Ja~~/Nog niet, maar dat kan nog/ ~~Nee~~

Krijgt dit projectresultaat een toepassing in beleid? Denk hierbij aan:

- Gebruik bij besluitvorming over DBC ontwikkeling, verstrekkingsregels basispakket, verzekerde pakketten, etc.
- Gebruik in adviesrapporten, signalementen van raden, colleges, RIVM, NIVEL, CvZ, etc
- Gebruik in beleidsnotities VWS of NWO, intern of extern, of in beleidsbrieven aan tweede kamer
- Gebruik in beleidsnotities van landelijke koepels en organisaties
- Andere bijdrage aan zorg- of preventiebeleid, namelijk…

[2] ZonMw bestrijkt alle vijf fasen van de kennisketen: fundamenteel onderzoek, strategisch onderzoek, toegepast onderzoek, ontwikkelprojecten en implementatieprojecten.

~~Ja~~/Nog niet, maar dat kan nog/ ~~Nee~~

Krijgt dit projectresultaat een commerciële toepassing? Denk hierbij aan:

- Gebruik van projectresultaat als te vermarkten intellectueel eigendom
- Octrooien, royalty regeling of andere overeenkomst mbt intelectueel eigendom
- hoe
- Nieuwe onderneming als gevolg van projectresultaat of overgang van direct bij het project betrokken personen naar zo'n nieuwe onderneming

Ja/Nog niet, maar dat kan nog/ Nee

Toelichting
Kunt u de antwoorden toelichten cq. onderbouwen:

The AIRFORCE study demonstrates that SCIT is not cost-effective in this study population. Moreover, treatment is being hampered by low adherence. Stricter indications for SCIT are required. It is conceivable that SCIT should be used as last-resort-treatment in patients who have proven treatment failure to usual care.
R. Gerth van Wijk is member of a series of international guideline committees. He will communicate the results with these committees and will try to include the conclusions and recommendations in guidelines. In addition, we will reach out to national organisations for guideline implementation (Netherlands Society of Allergology, NHG). As a number of allergologists have been participated in this study, we expect that this study will have an important impact on the clinical practice of allergolgists.

5. Publicaties en producten

Podium presentation:	Assessing the compliance & persistence of allergen immunotherapy in allergic rhinitis using a retrospective pharmacy database from The Netherlands
Congress:	14th Annual European congress, International Society for Pharmacoeconomics & Outcomes Research (ISPOR)
Date & Location:	July 11th, 2011, Madrid (Spain)
Award received:	Best new investigator podium presentation

Podium presentation:	Premature discontinuation of treatment among allergen immunotherapy users in allergic rhinitis
Congress:	31st Congress, European Association of Allergy & Clinical Immunology (EAACI))
Date & Location:	June 19th, 2012, Geneva (Switzerland)

Poster presentation:	Premature discontinuation of treatment among allergen immunotherapy users in allergic rhinitis
Congress:	European Respiratory Society (ERS) 2012 congress
Date & Location:	September 1st-5th, Vienna (Austria)

Article:	Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy
Authors:	Menno A. Kiel, MD, MSc, Esther Röder, MD, PhD, Roy Gerth van

	Wijk, MD, PhD, Maiwenn J. Al, PhD, Wim C.J. Hop, PhD, Maureen P.M.H. Rutten-van Mölken, PhD
Journal:	Journal of Allergy & Clinical Immunology (JACI)
Issue number / Pages:	132: 353-36
Year of publication:	2013

6. Algemene opmerkingen

Ruimte om zaken te vermelden waarvan u vindt dat die voor ZonMw en/of het programma van belang kunnen zijn.

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