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Cost-effectiveness of grass pollen subcutaneous immunotherapy (SCIT) compared to sublingual immunotherapy (SLIT) and symptomatic treatment in Austria, Spain and Switzerland

Bernd Brüggenjürgen¹, Thomas Reinhold²

¹Institute for Health Economics, Steinbeis-Hochschule Berlin (SHB), Gürtelstraße 29, Berlin, Germany

²Institute for Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, Germany

Correspondence: Bernd Brüggenjürgen, Steinbeis-Hochschule Berlin GmbH, Steinbeis-Haus, Gürtelstraße 29A/30, 10247 Berlin, email: bernd.brueggenjuergen@stw.de

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ABSTRACT

Background: While specific immunotherapy (SIT) has been proven to be cost effective for the treatment of allergic rhinitis compared to symptomatic treatment, there is a lack of European studies in which sublingual (SLIT) and subcutaneous (SCIT) immunotherapy were compared. The present analysis is focused on the cost-effectiveness of SCIT compared to SLIT and symptomatic treatment of grass pollen allergy in Austria, Spain and Switzerland. It will address specific properties of the underlying healthcare systems.

Methods: The investigation is based on a previously published health economic model calculation. This was designed as a Markov model with predefined health stages and a duration of 9 years covering specific preparations for SCIT (Allergovit) and SLIT (Oralair). The effectiveness was assessed as symptom-score based quality-adjusted life years (QALYs). Additionally, total cost has been determined as well as the cost-effectiveness of SCIT. The robustness of model results was proved in further sensitivity analyses.

Results: With regard to the effectiveness of both SCIT and SLIT, preparations were dominant compared to pharmacological symptomatic therapy. Both strategies were associated with additional cost, but combined with the results on effectiveness, both have to be regarded as cost-effective. A direct comparison of the SCIT (Allergovit) and SLIT (Oralair) showed lower total costs of SCIT versus SLIT for Austria, Spain and Switzerland (1,368 € versus 2,012 €, 2,229 € versus 2,547 € and 1,901 € versus 2,220 €) and superior effectiveness (SCIT, 8.02 QALYs; SLIT, 7.98 QALYs; and symptomatic therapy, 7.90 QALYs).

Conclusion: In patients with allergic rhinitis, SIT offers cost-effective treatment options compared to symptomatic treatment. When comparing SCIT (Allergovit) and SLIT (Oralair), SCIT was dominant in terms of QALYs as well as costs, in particular due to a slightly higher patient compliance and lower drug costs.

Keywords: immunotherapy; cost effectiveness; allergic rhinitis; modeling

Introduction

Allergic Rhinitis (AR) is a frequent chronic disease with potentially serious impact on patient's functioning and quality of life (QOL)[1]. AR can be managed by avoidance of allergens or by symptomatic treatment applying pharmaceutical products such as antihistamines, corticosteroids and bronchodilators in case of asthma. Beyond these symptomatic treatment approaches the allergen-specific immunotherapy (SIT) is an effective and the only long-term therapeutic option for AR. SIT is administered by gradually increasing quantities of allergen extract in order to mitigate the symptoms associated with the subsequent exposure to grass pollen. SIT has traditionally been administered by subcutaneous injections (SCIT) of high-dose hypoallergenic pollen (e.g. Allergovit®). More recently sublingual preparations (SLIT) have been approved, such as 5-grass pollen sublingual tablets (e.g. Oralair®).

Efficacy and cost-effectiveness of SIT versus symptomatic treatment has been proven in several studies[2, 3]. In addition, a growing range of studies indicate that SCIT and SLIT may be very advantageous to the healthcare systems[4, 5, 6]. However, comparative evidence with regard to efficacy and cost-effectiveness of sublingual versus subcutaneous immunotherapy is less clear.

Economic cost effectiveness modelling is a well-accepted approach to investigate the long-term consequences of treatment approaches in the absence of longitudinal real-life data[7, 8]. Due to the discrepancies in clinical evidence both clinical guidelines as well as Health Technology Assessment (HTA) institutions like NICE (National Institute for Clinical Excellence) compare decision alternatives on a product level, i.e. using e.g. the gold standard or most effective comparator[9]. For SLIT vs. SCIT three comparative cost effectiveness analysis (CEA) modelling approaches have been published from a third-party-payer perspective so far[6, 10, 11]. Two publications compared SLIT and SCIT treatments on a product level[6, 10], whereas one publication combined heterogeneous efficacy data from several SCIT products with different evidence levels to one SLIT product[11]. Those comparing on a product level, when assessing cost effectiveness, were once in favor of SLIT and once in favor of SCIT with both approaches being cost-effective compared to symptomatic treatment alone. In addition, two budget impact analyses from a societal perspective in a Danish and Swedish setting have been published with positive results for the SLIT approach when assuming identical compliance both for SLIT and SCIT.

However, comparative data with regard to cost-effectiveness of the different application modalities in SIT incorporating real-life compliance information has not been published for Austria, Spain nor Switzerland. Hence, our objective is to compare two relevant SLITS vs. SCIT pre-seasonal treatments from a third-party-payer perspective addressing peculiarities of these different healthcare systems.

Methods

Our modelling framework is adapted from modelling approaches of previously published CEA analyses for Germany[6, 10, 11]. A product specific comparison was chosen as the basis for modeling, applying Oralair® for the SLIT modality and Allergovit® for the SCIT alternative.

Model framework

The Markov model is based on predefined disease stages and corresponding transition probabilities for all treatment modalities in order to predict the long-term course of disease in a specific patient cohort (Fig. 1). Treatment alternatives included: SCIT with Allergovit®, SLIT with Oralair®, and symptomatic treatment alone. The Markov model has a 1-year cycle length and a time horizon of 9 years. Additional symptomatic treatment was allowed in both SIT arms. SIT duration was assumed to be 3 years.

(Figure 1 near here)

At the start of the model calculation, patients had a mean age of 29 years and were affected by grass pollen-related AR or rhino-conjunctivitis, but not allergic asthma (AA). During the model duration,

patients could develop AA. For these incident AA patients, an increased mortality and reduced quality of life were assumed in the calculation. The model also assumed that incident asthmatics are suffering during the complete pollen season for the following cycles. A relative risk reduction for both SCIT and SLIT of annual AA incidence of 0.505 was assumed[12, 13]. For those patients who discontinued SIT before the end of the 3-year period, it was assumed that no quality of life changing impact or risk-reducing effects on AA incidence would be seen following SIT discontinuation.

The percentage of patients discontinuing SIT prematurely was determined based on most recent European studies covering SCIT and SLIT real-life observations on discontinuation events. When 3-year data was not available, they were logarithmically approximated[14, 15, 16, 17] (Table 1). Discontinuing patients were not allowed to re-initiate SIT following discontinuation. The grass pollen season lasts 4.5 months per year[18, 19, 20].
(Table 1 near here)

Costs and use of resources

Costs for all treatment arms of the model were determined from a health insurance perspective. Drug costs for 3 years Allergovit® were obtained on the basis of the required prescription quantities specified in the prescribing information[21, 22]. The number of packs required for the entire treatment period was then calculated according to the time period covered by each pack. Oralair® should be initiated 4 months prior to, and continued throughout the pollen season[23]. Hence, two packs à 90 tablets, as well as two packs à 31 tablets, were required per treatment year with an assumed pollen season treatment duration of 4 months. For Spain the commonly accepted cluster administration approach for Allergovit® was applied[24]. The number of required packs for both drugs was then multiplied by the pharmacy retail price and deducted by mandatory rebates. This resulted in SIT drug costs for Austria, Spain and Switzerland of 1,099 €, 645 € and 1,216 € for Allergovit® and 2,813 €, 1,523 € and 2,805 € for Oralair® for the entire 3-year treatment period, with costs being equally distributed over the 3 treatment years. For those patients who discontinued SIT, drug costs were reduced by 50% for the year in which treatment was discontinued.

The cost of additional symptomatic treatment was calculated for loratadine or budesonide being in line with previous economic SIT comparisons[6, 11]. The same applied to the costs of contact with medical specialists, SCIT injections, diagnostic costs, and treatment costs upon onset of AA (Table 2). In addition to this, seven injections, as well as seven related contacts with medical specialists, were annually assumed for patients under Allergovit® (pre-seasonal treatment) in Austria and Switzerland, whereas for Spain 3 visits based on the clusters administration approach were applied[22]. Contact with a medical specialist was assumed to take place on a quarterly basis among patients using Oralair®. As with Verheggen et al.[11], 1.9 annual contacts with medical specialists were assumed for all SIT patients for the time following the 3-year treatment period. Likewise, allergy diagnostic workup was performed in the first year in all SIT patients prior to treatment initiation.
(Table 2 near here)

Effectiveness parameters

The effectiveness was assessed as symptom-score based quality-adjusted life years (QALYs). Based on unified symptom scores, standard mean differences were generated [10, 11]. For Allergovit® Corrigan et al. was used as the underlying clinical study [25]. For Oralair® Didier et al. 2007, Wahn et al. 2009, Didier et al. 2011 as well as Cox et al. 2012 were selected [26, 27, 28, 29]. In order to transfer symptom scores to QALYs the Rhinitis Symptom Utility Index (RSUI) was applied. RSUI is a preference-based utility index for rhinitis symptoms using standard gamble and visual analogue scale [30]. Using this scoring index, symptom severity was converted to utility. Patients' QALYs were further determined by patient's age and co-existing asthma during the pollen season [31, 32]. It was assumed that symptoms were not present outside the pollen season. In addition, the number of new-onset cases of AA was determined. All prognosed effects and costs were discounted at a rate of 3%.

Model calculation outcomes

Total costs per treatment group, QALYs, and the expected number of AA cases were simulated over the time period of 9 years. Incremental cost-effectiveness results are reported (costs per QALY gained) in the case of additional costs—but greater therapeutic benefit—compared with the comparative treatments.

Sensitivity analysis

Both probabilistic and deterministic sensitivity analyses were performed in order to estimate impact of inaccuracy of assumptions. Probabilistic sensitivity analysis was repeated 1000 times drawing value for all variables at random (from the value ranges listed in Table 2). In contrast, the deterministic sensitivity analysis consecutively varied individual influencing factors in the model with minimum and maximum values and documented the main analysis result after each variation.

Results

Costs

Over the 9-year time period, the total per-patient cost of treatment for Austria, Spain and Switzerland with Allergovit® was 1,368 €, 2,229 € and 1,901 € resp. The average total per-patient cost with Oralair® was 2,012 €, 2,547 € and 2,220 € resp. (Table 3) and total costs per symptomatic patient treatment for Austria, Spain and Switzerland were 441 €, 1,376 € and 681 € resp. Based on average real-life SIT discontinuation rates used in the model, only 381 of the 1,000 patients initially treated completed the entire 3-year treatment period with Allergovit® and 301 out of 1,000 patients treated with Oralair®. Average 3-year SIT costs (including discontinued patients) in Austria, Spain and Switzerland accrued to 710 €, 417 € and 786 € for Allergovit® and to 1,506 €, 816 € and 1,502 € for Oralair®. Treatment costs for AA were comparatively modest due to the low AA incidence of 0.46% per year.

(Table 3 near here)

Effectiveness

Both SIT groups showed superior QALY effects compared to symptomatic treatment. Patients receiving symptomatic treatment alone accumulated 7.90 QALYs over the modeling period, whereas Allergovit® and Oralair® achieved 8.02 and 7.98 QALYs, resp. While AA occurred in 39 of 1,000 patients receiving symptomatic treatment only, the number of incident asthmatics is lower at 28 cases (Allergovit®) and 30 cases (Oralair®).

Cost-effectiveness

When comparing Allergovit® with Oralair® in Austria, Spain and Switzerland SCIT resulted in a saving of 646 €, 318 € and 319 € resp. (1,368 € vs. 2,012 €, 2,229 € vs. 2,547 €, and 1,901 € vs. 2,220 € resp.). Since Allergovit® also showed better effectiveness in terms of QALYs gained and the number of asthmatics, it is both cost-effective and dominates SLIT in these countries. When comparing SIT with symptomatic treatment alone incremental cost per QALY gained (ICER, discounted) in Austria, Spain and Switzerland were 8,779 €, 8,069 € and 11,544 € resp. for Allergovit® and 22,710 €, 16,923 € and 22,228 € resp. for Oralair®

Sensitivity analysis

Cost and effectiveness results were robust in probabilistic sensitivity analyses. Allergovit® compared to Oralair® shows superior effectiveness in virtually all cases, both in terms of additional QALYs determined and Allergovit®-related savings in Austria, Spain and Switzerland (Fig. 2a-c).

The deterministic sensitivity analysis identified the variables discontinuation rates, as well as the calculated SIT drug costs as those items causing the greatest degree of uncertainty in terms of difference of costs. With regard to QALYs gained in the treatment groups, the variables assumptions on symptom scores and pollen season duration were most influential.

(Figure 2 a-c near here)

Discussion

Our Markov cost-effectiveness analyses for Austria, Spain and Switzerland suggest that the treatment of patients with pollen-induced rhino-conjunctivitis or AR using SCIT with Allergovit® is both effective and cost-effective compared with SLIT using Oralair® or purely symptomatic treatment. In Austria, Spain and Switzerland SCIT resulted in a saving of 646 €, 318 € and 319 € resp. compared to Oralair®.

Patient relevant outcomes differences in QALYs could be identified as follows: patients receiving symptomatic treatment alone accumulated 7.90 QALYs over 9 years, whereas Allergovit® and Oralair® achieved 8.02 and 7.98 QALYs, resp. While the difference between SIT and symptomatic treatment is substantial, the increment in QALYs between SLIT and SCIT only just reaches clinical significance[33]. These differences in QALYs are primarily due to a varying number of AA cases occurring in the SIT treatment groups and the differences in the percentage of patients that completed the entire 3-year SIT treatment period, and thereby profited from the quality of life-enhancing and AA incidence-lowering effects of SIT[34]. As 39 AA incident cases in the symptomatic treatment group compared to SIT with 28 cases (Allergovit®) and SLIT with 30 cases (Oralair®) were observed, the reduction in quality of life associated with the presence of AA becomes more relevant in the symptomatic treatment group and results in fewer QALYs.

Our findings are based on country adaptations of existing health economic model calculations previously published by Reinhold et al. [6], who based the modeling framework on earlier versions of Verheggen et al. [11] and Westerhout et al.[10]. Comparable to Reinhold et al. we applied a product based comparison for Austria, Spain and Switzerland instead of a SCIT treatment mix, which appears a less reliable comparison given the heterogeneity of individual SCIT preparations available on the market. Based on most recent data from country specific pollen season information databases we could also adopt the length of the pollen season of Reinhold et al. at 4.5 months[6, 18, 19, 20]. However, we conservatively assumed that the need for Oralair® would last only for 4 months in the pollen season.

Adherence, characterized by wide variation in discontinuation rates, represents the most critical issue for the success of SIT as a treatment modality for allergic rhinitis [14, 35, 36]. As for Austria, Spain and Switzerland no real-life based data were available we estimated average discontinuation rates based on all available European real-life data based studies, including Italy, Germany, Sweden, and the Netherlands[14, 15, 17, 37, 38]. Missing observation years were approximated via log function and resulted in discontinuation rates for year 1 to 3 for Allergovit® of 22%, 34% and 26% and for Oralair® of 42%, 29% and 27%.

Effects of SIT with regard to risk reduction of AA were assumed to be comparable between SCIT and SLIT[39, 40]. Results from a meta-analysis comparison provided indirect evidence that SCIT is more effective than SLIT in controlling AA symptoms[41]. However, no studies directly comparing SLIT and SCIT in large patient cohorts have been published so far. Hence, assuming an equal SIT effect might represent a possible detriment to Allergovit®. Furthermore, total number of adverse events were reported to be higher in SLIT compared to SCIT[41]. Costs attached to these events were not incorporated in our model and might put a further disadvantage to SCIT from an economic modeling point of view.

Data on risk reduction of AA as a consequence of SIT are scarce. Prospective data for SLIT is spanning a few years[42], whereas Allergovit® could demonstrate a sustained clinical effect even at 12 years following the completion of treatment in childhood[43]. Two German retrospective sick fund database analyses confirmed the long-term effect of SIT also for adult AR treatment. Furthermore, our assumption of AA risk reduction of 50.5% is conservative as the risk reduction observed in these two real life database studies was between 60.0% and 69.6%.[44, 45] Of note is the fact that a 50.5%

AA risk reduction would be the ideal outcome whereas in the model a diminished decrease in AA incidence due to treatment discontinuation and death was observed.

When comparing results for Austria and Switzerland with Spain, a difference with regard to unit costs related to healthcare resource use could be observed. Where Austria and Switzerland apply activity-based remuneration schemes, the Spanish costing is based on statutory service fee schedules and hence more realistically reflecting institution-related costs. For Spain our analysis seems to be conservative as a study in house dust mite immunotherapy generated even a cost-saving of 64% when compared to standard symptomatic treatment, being driven by a substantial reduction of urgent care visits and allergologists visits[46].

Our results are based both on a deterministic and probabilistic economic model and have not been collected alongside clinical trials. Based on conservative assumptions our CEA results of SIT vs. symptomatic treatment alone with a range of 8,069 € to 11,544 € for Allergovit® and 16,923 € to 22,710 € for Oralair® are in the range considered as cost-effective when evaluating cost per QALYs (according to internationally accepted threshold values of maximally 50,000 € per QALY gained). Since the SIT treatment costs account for a high proportion of total patient costs, they strongly influence the cost results of the analysis. Therefore, a future price change could result in a reevaluation of costs and cost-effectiveness.

Conclusions

When comparing SCIT (Allergovit®) and SLIT (Oralair®) in an economic model, SCIT was dominant in terms of QALYs as well as costs in Austria, Spain and Switzerland. SCIT and SLIT were shown to be cost-effective in the treatment of patients with AR compared to symptomatic treatment alone. While SCIT and SLIT treatments exhibit similar effectiveness in terms of AA incidence, this 3-European country-analysis identified a cost saving potential related to SCIT over SLIT, particular due to a slightly higher patient compliance and lower drug costs.

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Table 1. European SIT Discontinuation Rates

Source	Data Origin	N	Country	Year 1	Year 2	Year 3
SLIT						
Senna et al. 2010	Rx data	*)	I	47%	18%	40%
Sieber et al. 2011	Rx data	112	D	29%	28%	18% ‡)
Andreasen et al. 2012	Rx data	636	SE	28%	24% #)	7%
Kiel et al. 2013	Rx data	3,690	NL	62%	53%	61%
Egert-Schmidt et al. 2014	Market data	706	D	47%	51%	38%
Lemberg et al. 2017	PMS data	123	D	37%	3%	0%
Mean				42%	29%	27%
SCIT						
Sieber et al. 2011	Rx data	602	D	41%	34%	33% ‡)
Andreasen et al. 2012	Rx data	354	SE	27%	22%	7%
Kiel et al. 2013	Rx data	2,796	NL	20%	49%	44%
Egert-Schmidt et al. 2014	Rx data	85,241	D	0%	52%	44%
Lemberg et al. 2017	Market data	207	D	21%	15%	0%
Mean				22%	34%	26%

Discontinuation rates of follow-up years were based on remaining patients at the end of the prior period. If discontinuation was not reported, rates either have been calculated based on provided adherence data or derived from published survival functions;

Notes: *) not specified - sales data from 2 major companies in Italy from 2006 to 2009, #) Year 2 approximated via log-function, ‡) Year 3 approximated via log-function;

Abbreviations: D – Germany, I – Italy, NL – Netherlands, Rx - prescription, PMS - patient management system, SE – Sweden.

Table 2. Model calculation input data

	Country	Austria		Spain	Switzerland Conversion rate €/CHF:	Min-max variation in sensitivity analyses
Model assumptions	Mortality rate for allergic asthma p.a. [11]	0.069 %		0.069 %	0.069 %	
	Background mortality rate p.a. [47]	0.048%		0.035%	0.035%	±30%
	Dropout rate for SCIT Allergovit® [14, 15, 16, 17, 37, 38]	Year 1	22%	22%	22%	±30%
		Year 2	34%	34%	34%	±30%
		Year 3	26%	26%	26%	±30%
	Dropout rate for SLIT Oralair® [14, 15, 16, 17, 37, 38]	Year 1	42%	42%	42%	±30%
		Year 2	29%	29%	29%	±30%
		Year 2	27%	27%	27%	±30%
	Asthma incidence p. a. [11]	0.46%		0.46%	0.46%	±30%
Cost and resource assumptions	Relative risk reduction in asthma incidence with SIT [11]	50.5%		50.5%	50.5%	±30%
	Pollen season duration (months) [18, 19, 20]	4.5		4.5	4.5	±30%
	Costs for SCIT with Allergovit® over 3 years	1,098.90 €		645.12 €	1,215.56 €	±10%
	Costs for SLIT with Oralair® over 3 years	2,813.10 €		1,523.47 €	2,805.42 €	±10%
	Costs for loratadine per season [48, 49, 50]	SIT	6.14 €	4.76 €	22.45 €	±10%
		ST	9.01 €	6.99 €	32.93 €	±10%
	Costs for budesonide per season [48, 49, 50]	SIT	2.39 €	1.10 €	2.46 €	±10%
		ST	4.18 €	1.92 €	4.30 €	±10%
	Costs per contact with a medical specialist [51, 52, 53, 54, 55]	18.82 €		79.90 €	17.51 €	±10%
	Costs per SCIT injection [51, 52, 53, 54, 55]	2.71 €		13.89 €	22.26 €	±10%
	Diagnostic work-up [51, 52, 53, 54, 55]	29.49 €		120.00 €	47.87 €	±10%
	Costs attributable to allergic asthma p.a. [5, 56, 57]	753.00 €		1,355.00 €	1,779.00 €	±50%
	Number of annual physician contacts for SCIT with Allergovit® [21, 24]	7		3	7	±30%
	Number of injections p.a. for SCIT with Allergovit® [21]	7		7	7	±30%
	Discount rate p.a.	3%		3%	3%	±30%

SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; ST, symptomatic treatment

Table 3a. Per-patient costs over 9 years (discounted) according to treatment type taking into account all patients in a treatment arm (including those that dropped out from SIT) - Austria

Type of cost	Allergovit®	Oralair®	Symptomatic treatment
SIT	710 €	1,506€	-
Symptomatic treatment	87 €	91 €	106 €
Asthma costs	32 €	36 €	49 €
Visits to a medical specialist	472 €	350 €	286 €
Injections	37 €	-	-
Allergy diagnostic work-up	29 €	29 €	-
Total costs per patient	1,368 €	2,012 €	441 €

Table 3b. Spain

Type of cost	Allergovit®	Oralair®	Symptomatic treatment
SIT	417 €	816 €	-
Symptomatic treatment	59 €	62 €	71 €
Asthma costs	57 €	65 €	89 €
Visits to a medical specialist	1,386 €	1,485 €	1,216 €
Injections	189 €	-	-
Allergy diagnostic work-up	120 €	120 €	-
Total costs per patient	2,229 €	2,547 €	1,376 €

Table 3c. Switzerland

Type of cost Conversion rate CHF/€: 0,93	Allergovit®	Oralair®	Symptomatic treatment
SIT	786 €	1,502 €	-
Symptomatic treatment	250 €	259 €	298 €
Asthma costs	75 €	85 €	116 €
Visits to a medical specialist	440 €	326 €	266 €
Injections	302 €	-	-
Allergy diagnostic work-up	48 €	48 €	-
Total costs per patient	1,901 €	2,220 €	681 €

SIT, specific immunotherapy

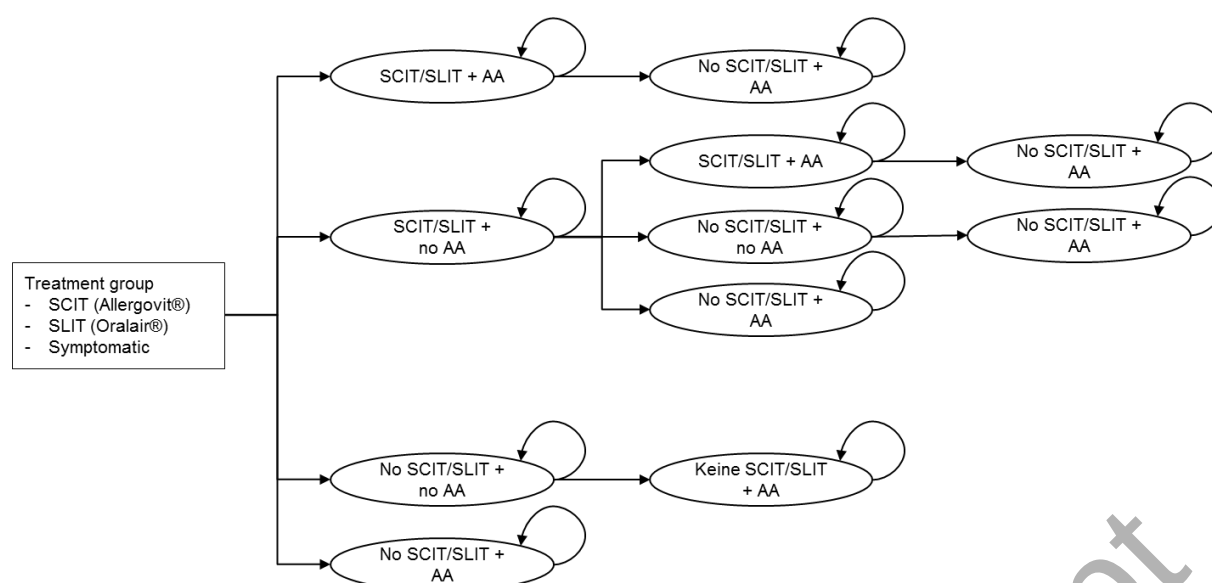


Fig. 1. Basic structure of the underlying Markov model (all patients are at risk of death. This is not shown in order to simplify representation)

AA, allergic asthma; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy

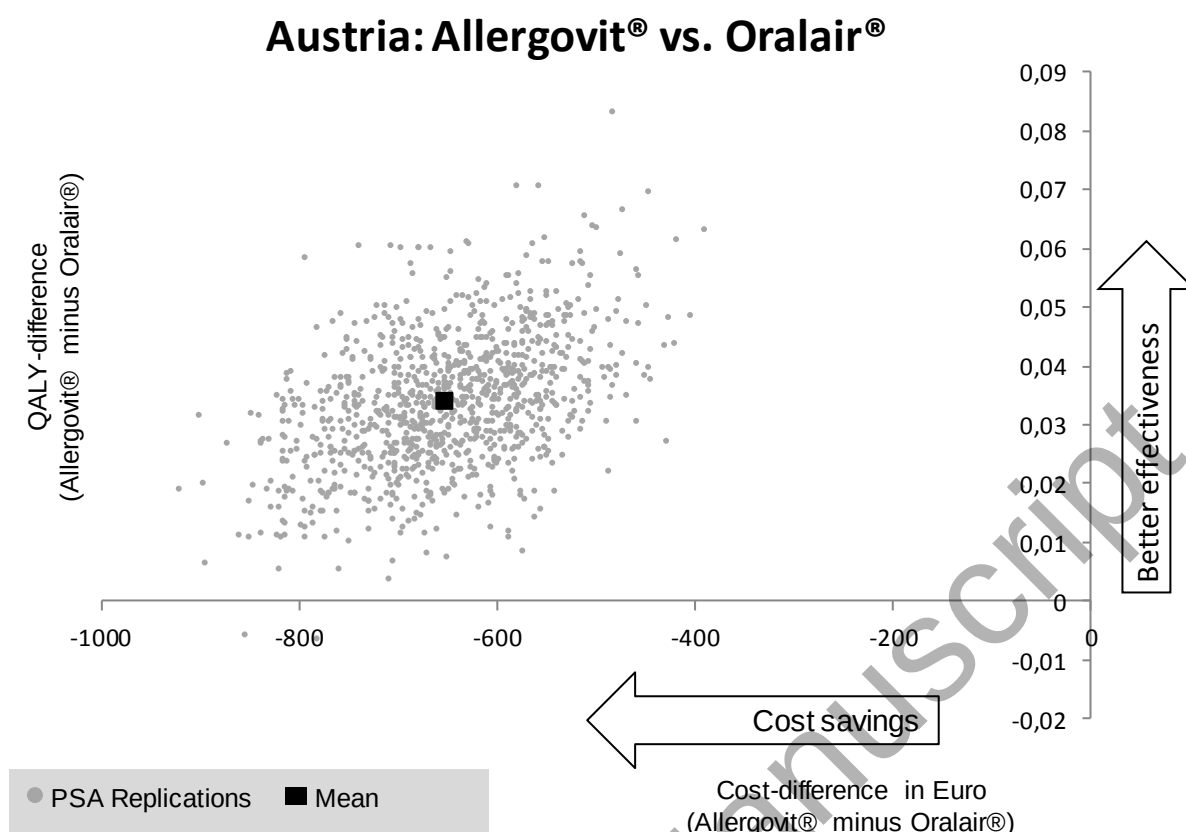


Fig. 2a. Results of the probabilistic sensitivity analysis (PSA) on the cost-effectiveness of SCIT versus SLIT for Austria

QALY, quality-adjusted life year; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy

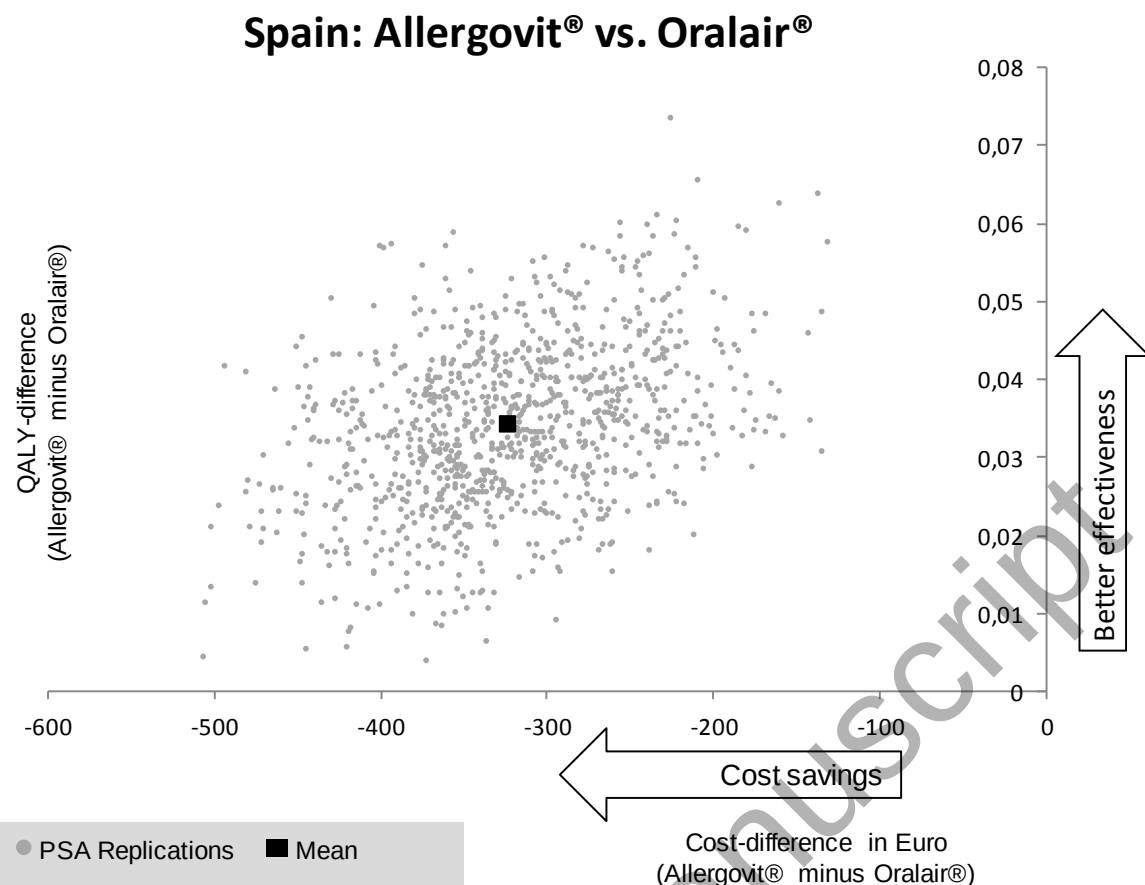


Fig. 2b. Results of the probabilistic sensitivity analysis (PSA) on the cost-effectiveness of SCIT versus SLIT for Spain
 QALY, quality-adjusted life year; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy

Switzerland: Allergovit® vs. Oralair®

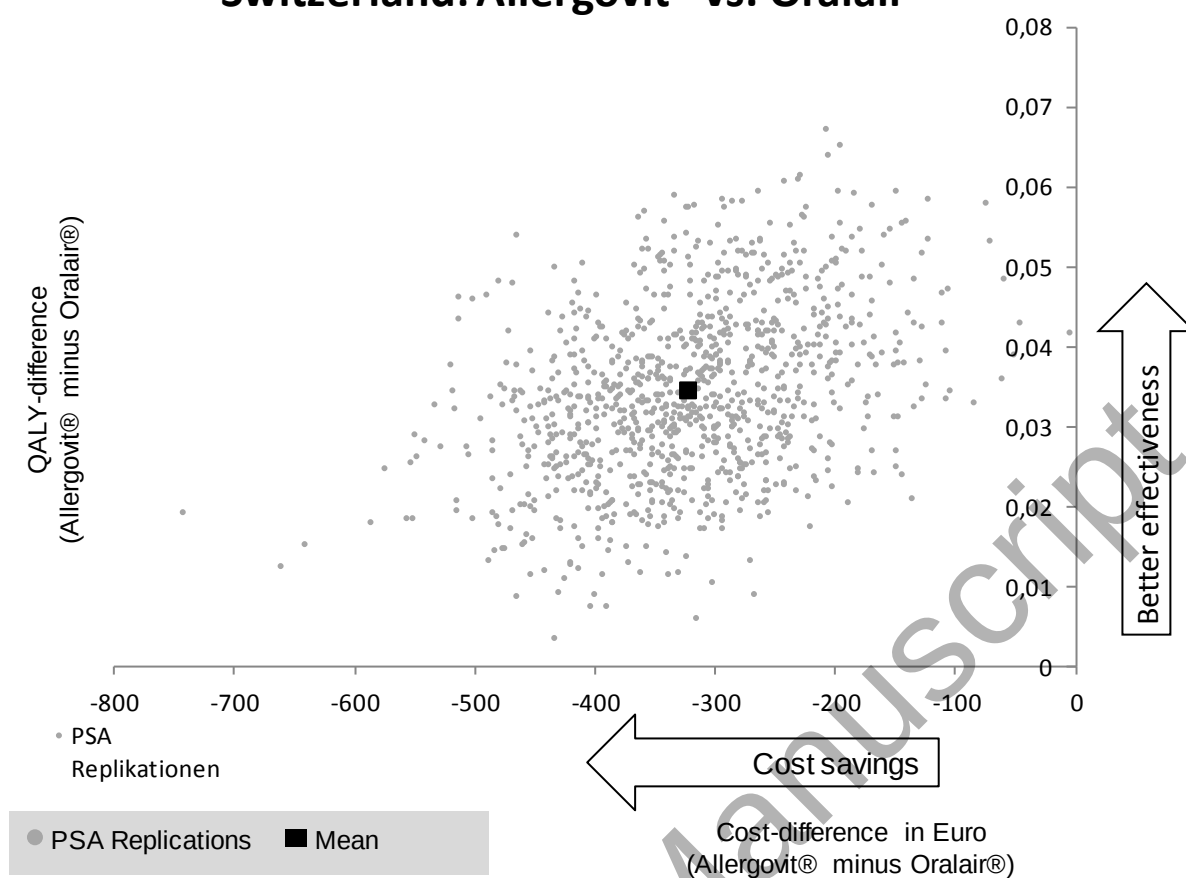


Fig. 2c. Results of the probabilistic sensitivity analysis (PSA) on the cost-effectiveness of SCIT versus SLIT for Switzerland

QALY, quality-adjusted life year; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy